Bring hypertension guidelines into play

Guideline-based decision support system for drug treatment of hypertension and epidemiological aspects of hypertension guidelines

Mats Persson

Umeå 2003
Family Medicine, Department of Public Health and Clinical Medicine
Umeå University
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Allmänmedicin, Institutionen för folkhälsa och klinisk medicin.
Umeå Universitet
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Examinator: Professor Lars H Lindholm

Fakultetsopportent: Docent Hans Ibsen, Department of Internal Medicine M, Glostrup Hospital, DK-2600 Glostrup, Denmark.
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Mats Persson
Family Medicine, Department of Public Health and Clinical Medicine, Umeå University, S-901 87 Umeå
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ABSTRACT
Arterial hypertension is one of the main risk factors for cardiovascular disease. Furthermore, large randomised controlled trials have established that drug treatment is effective, not only in reducing blood pressure, but also in alleviating its complications. However, physicians face several problems in the management of hypertension. Among the most important are cardiovascular risk estimation and antihypertensive drug treatment. The aim of paper I was to help physicians apply evidence-based recommendations concerning antihypertensive drug treatment to individual patients by constructing a clinical decision support system (CDSS) based on hypertension guidelines. The principles for a guideline-based CDSS for drug treatment of hypertension were specified in paper I. In paper II the CDSS was evaluated against 338 actual antihypertensive drug treatments in primary health care. This comparison showed a great potential for improvement, and merely by complying with guidelines drug costs could be reduced by 40% while at the same time keeping the quality of antihypertensive drug treatment. The study also showed poor control of high blood pressure, and the drug treatment was confined to one or two drugs for most patients. In paper III, the 1999 WHO/ISH Hypertension Guidelines method for risk stratification was applied to a 1999 MONICA sample (n=5,997) from Northern Sweden. Each subject was risk-classified using a CDSS, according to the 1999 WHO/ISH scheme. Only one fifth of the drug-treated hypertensives were well controlled, and the incidence of newly detected blood pressure elevation was high. The majority of subjects with high blood pressure had medium or higher risk, and in poorly controlled drug treated hypertensives 87% had medium or higher risk. In paper IV treated but poorly controlled hypertensives had increased risk of stroke (odds ratio 6.1 CI 2.4–15.3). Only one of the 129 individuals who suffered stroke had treated and adequately controlled hypertension. It was concluded that the “rule of halves” still exists and the high remaining risk in poorly treated hypertensives is remarkable, requiring attention from the medical profession. In paper V, risk estimation by risk equations was compared to risk classification by the 1999 WHO/ISH risk stratification scheme. It was concluded that the risk assessment obtained in the medium risk group by guidelines was not accurate enough for clinical use.

A majority of the hypertensive population have increased risk of cardiovascular disease. Treatment goals stated in major guidelines are far from being attained, and especially among poorly treated hypertensives the risk of stroke is high. A guideline-based CDSS for antihypertensive drug treatment could, if followed, reduce drug cost by 40% and enhance the quality of hypertension drug treatment. Better management of hypertension by complying with guidelines is urgent given the extent of high BP, its high risks and the poor control of drug-treated hypertensives.

Key words: Arterial hypertension, cardiovascular risk, clinical decision support system, drug treatment, guidelines.
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Illustration; the key link between the evidence-based knowledge and the desired medical decision is the patient's medical profile consisting exactly of the medical factors needed to take a high-quality evidence-based decision.
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Arterial hypertension is one of the main risk factors for cardiovascular disease. Furthermore, large randomised controlled trials have established that drug treatment is effective, not only in reducing blood pressure, but also in alleviating its complications. However, physicians face several problems in the management of hypertension. Among the most important are cardiovascular risk estimation and antihypertensive drug treatment. The aim of paper I was to help physicians apply evidence-based recommendations concerning antihypertensive drug treatment to individual patients by constructing a clinical decision support system (CDSS) based on hypertension guidelines. The principles for a guideline-based CDSS for drug treatment of hypertension were specified in paper I. In paper II the CDSS was evaluated against 338 actual antihypertensive drug treatments in primary health care. This comparison showed a great potential for improvement, and merely by complying with guidelines drug costs could be reduced by 40% while at the same time keeping the quality of antihypertensive drug treatment. The study also showed poor control of high blood pressure, and the drug treatment was confined to one or two drugs for most patients. In paper III, the 1999 WHO/ISH Hypertension Guidelines method for risk stratification was applied to a 1999 MONICA sample (n=5,997) from Northern Sweden. Each subject was risk-classified using a CDSS, according to the 1999 WHO/ISH scheme. Only one fifth of the drug-treated hypertensives were well controlled, and the incidence of newly detected blood pressure elevation was high. The majority of subjects with high blood pressure had medium or higher risk, and in poorly controlled drug treated hypertensives 87% had medium or higher risk. In paper IV treated but poorly controlled hypertensives had increased risk of stroke (odds ratio 6.1 CI 2.4 – 15.3). Only one of the 129 individuals who suffered stroke had treated and adequately controlled hypertension. It was concluded that the “rule of halves” still exists and the high remaining risk in poorly treated hypertensives is remarkable, requiring attention from the medical profession. In paper V, risk estimation by risk equations was compared to risk classification by the 1999 WHO/ISH risk stratification scheme. It was concluded that the risk assessment obtained in the medium risk group by guidelines was not accurate enough for clinical use.

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Key words: Arterial hypertension, cardiovascular risk, clinical decision support system, drug treatment, guidelines
ORIGINAL PAPERS

The thesis is based on the following papers:


V. Mats Persson, Bo Carlberg, Lars Weinhall, Leif Nilsson, Birgitta Stegmayr, Lars H Lindholm. Risk stratification by guidelines compared to risk assessment by risk equations applied to a MONICA sample. (Accepted in Journal of Hypertension)

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CDSS</td>
<td>Clinical decision support system</td>
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<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DSS</td>
<td>Decision support system</td>
</tr>
<tr>
<td>EBM</td>
<td>Evidence-based medicine</td>
</tr>
<tr>
<td>HCC</td>
<td>Health care centre</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>HTML</td>
<td>Hypertext markup language</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems, tenth revision</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>IMT</td>
<td>Intima-media thickness</td>
</tr>
<tr>
<td>JNC VI</td>
<td>The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>LVH</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MONICA</td>
<td>Multinational Monitoring of Trends and Determinants in Cardiovascular Disease</td>
</tr>
<tr>
<td>MRFIT</td>
<td>Multiple Risk Factor Intervention Trial</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NSW</td>
<td>Northern Sweden</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PAR</td>
<td>Population-attributable risk</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SEK</td>
<td>Swedish crowns</td>
</tr>
<tr>
<td>TOD</td>
<td>Target Organ Damage</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VIP</td>
<td>Västerbotten Intervention Programme</td>
</tr>
<tr>
<td>WHO/ISH</td>
<td>World Health Organisation/International Society of Hypertension</td>
</tr>
<tr>
<td>WHR</td>
<td>Waist to hip ratio</td>
</tr>
<tr>
<td>XML</td>
<td>Extensible markup language</td>
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</table>
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PAPERS I-V
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INTRODUCTION

1. Hypertension and this thesis
Various aspects of hypertension guidelines have been evaluated in this thesis. Guideline recommendations concerning antihypertensive drug treatment were considered first, and the research question dealt with was how to apply evidence-based knowledge to individual patients, in a situation where the amount of information is overwhelming. My viewpoint was that of the practising physician, anxious to make a high-quality decision based on evidence but constrained by available time and knowledge. Was it possible to construct a clinical decision support system that made it easier to follow guidelines concerning antihypertensive drug treatment, and what would the consequences be for cost and quality if recommendations were followed?

Decisions concerning drug therapy and other interventions are based not only on blood pressure, but also rely on an estimate of cardiovascular risk, simply because the benefit resulting from an intervention increases with increased risk. The risk stratification scheme proposed by the 1999 WHO/ISH Hypertension Guidelines was applied to a hypertensive population and the consequences were evaluated in terms of hypertension treatment, blood pressure control and cardiovascular risk. The association between poorly treated hypertension and stroke was studied, as well as blood pressure control in the county of Västerbotten. Finally, the risk stratification scheme proposed by the 1999 WHO/ISH Hypertension Guidelines was compared to risk estimation by risk equations.

Applying evidence-based knowledge to the medical profile of the hypertensive patient is the core aim of this thesis, but this does not imply that other factors concerning the doctor–patient relationship are less important. Also, this thesis has no more to do with computers and technology than the content of written guidelines has to do with the manufacture of paper or printing technology.

2. Hypertension
Arterial hypertension (hypertension) in adults, irrespective of age, is defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg, definitions are shown in Table 1 (1, 2). The distribution of blood pressure (BP) in the population is continuous and approximately normally distributed, and there is no natural cut-point that distinguishes hypertensives from normotensives (3). In most hypertensives (92–94%) the aetiological cause is unknown and the condition is classified as “Essential hypertension 110.9” according to International Statistical Classification of Diseases and Related Health Problems, tenth edition (ICD-10) (4, 5). Those with a known cause of elevated blood pressure (BP), usually kidney disease, are diagnosed
Table 1. Blood pressure definition and classification in adults in the 1999 WHO/ISH and JNC VI hypertension guidelines from 1997. When the systolic and diastolic blood pressure are in different categories, the highest category is used.

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;130</td>
<td>&lt;85</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Hypertension (mild&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Hypertension (moderate&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Hypertension (severe&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>&gt;180</td>
<td>&gt;110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>&gt;140</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure, DBP = diastolic blood pressure. <sup>1</sup>Grade 1 (WHO/ISH), stage 1 (JNC VI). <sup>2</sup>Grade 2 (WHO/ISH), stage 2 (JNC VI). <sup>3</sup>Grade 3 (WHO/ISH), stage 3 (JNC VI).

as having secondary hypertension (4, 5). Except in cases of extreme BP values, hypertension is virtually free from symptoms and the diagnosis cannot be made without measuring the BP (4). Since the intra-individual variation in BP is large it is of great importance to measure BP repeatedly under standardised conditions and over a sufficient period of time, at least 3 months in mild hypertension (6). Data from national surveys show a prevalence of hypertension for adults aged 18–74 years of 21.1% in the United States, data from NHANES III (7). The prevalence increased with age, data from US 1988–91, age 18–29 (4%), 30–39 (11%), 40–49 (21%), 50–59 (44%), 60–69 (54%), 70–79 (64%), ≥80 years (65%) (8).

Hypertension is a leading risk factor for atherosclerotic disease and its main manifestations are: ischaemic heart disease (IHD), stroke, heart failure and end-stage renal disease (1, 2). The two leading causes of death worldwide in 1990 were ischaemic heart disease and cerebrovascular disease, together about one fifth of all deaths (9). SBP over 115 mm Hg is the leading contributor to death worldwide, ahead of such factors as tobacco, high cholesterol, underweight, overweight and unsafe sex (10). IHD death rates vary between countries from about 350/100,000 individuals yearly in countries with high incidence rates to about 160/100,000 in Italy and 60/100,000 in Japan (9). IHD and stroke account for about 80% of all cardiovascular disease (11). The incidence of IHD in Western Europe and North America has declined during the last few decades, while the decline in stroke has been less impressive (2).

The clinical management of hypertension aims to prevent IHD, stroke, chronic renal failure and heart failure (1, 2). Antihypertensive drug treatment is effective and well tolerated, and a reduction in SBP of about 10–12 mm Hg or in DBP of 5–6 mm Hg reduces IHD by about 20% and stroke by about 40% (12).
In younger (<65 years) subjects diastolic hypertension is more common, but in the age group 65–74 years isolated systolic hypertension (SBP ≥140 and DBP <90 mm Hg) dominates (7). SBP increases successively with age, while DBP increases up to about 50–55 years and decreases thereafter (7). Poor blood pressure control is overwhelmingly due to lack of systolic pressure control, and this also applies to drug-treated individuals (13). The ratio of hypertension prevalence between women and men at 30 years of age is about 0.6–0.7 (women/men) and rises to 1.1–1.2 at the age of 65 (4). Blood pressure control in the community is far from satisfactory; only about one third or less of drug-treated hypertensives reach blood pressure targets recommended in major guidelines (7).

3. Hypertension and risk

3.1 Blood pressure and risk
The relationship between blood pressure and cardiovascular risk is strong, graded, continuous, consistent, independent and highly predictive for adult men and women of all ages, at least up to 89 years (14). This is so for different ethnic and racial groups and for different countries, and it applies to BP levels from at least 115/75 mm Hg, with no threshold level where the risk suddenly increases (14). This relationship exists for those without established cardiovascular disease, as well as for those with coronary heart disease, previous stroke, heart failure or end-stage renal disease (14-18). Controlling for total cholesterol, HDL, diabetes, weight, smoking, and alcohol consumption does not alter risk associated with BP (14).

In a meta-analysis of 61 prospective observational studies including one million adults with a total of 12.7 million person-years and 56,000 vascular deaths, each increase of 20 mm Hg SBP (or 10 mm Hg in DBP) from 115/75 mm Hg was associated with a twofold increase in risk of death from stroke and ischaemic heart disease in both sexes and in ages between 40 and 69 years; the relative risk was about half as large in the age group 80–89 years compared to those aged 40–49 (14). Elevated BP gives a somewhat more pronounced risk of stroke than of IHD and other vascular events, and the risk increase is steeper in younger than in older ages (14). The absolute annual difference in stroke death, associated with a given difference in BP, increases with age because of the rapid increase of absolute risk in elderly and despite the reduction in relative risk with age (14).

Randomised trials have shown that BP lowering can produce rapid reductions in vascular disease risk, and the meta-analysis by the Prospective Studies Collaboration provides complementary evidence that even greater differences in risk are likely to be produced by prolonged differences, beyond 4–5 years, in BP (14). If the high risk associated with pre-existing CV disease is considered, many could benefit from BP-
lowering therapy, largely irrespective of their current BP or even if they currently are classified as normotensive (14).

3.2 Lifetime risk
The lifetime risk of developing hypertension has been estimated at 90% and for antihypertensive drug treatment at 60% (19, 20). The lifetime risk, estimated in the Framingham Heart Study, for a 40-year-old man developing coronary heart disease (angina pectoris, unstable angina, myocardial infarction or death from coronary heart disease), one of the main manifestations of hypertension, was 48.6% (excluding angina pectoris 42.4%) and for women 31.7%. For a 70-year-old the corresponding figures were 34.9% and 24.2%. Lifetime risk remains high even in old age, but it is lower because competing causes of death increase and because of the shorter life expectancy (19).

The greater life expectancy for a young or middle-aged woman or man with a low risk profile compared to others in the same age group has been estimated at 5.8–9.5 years, but only 4.8–9.9% of the cohorts belonged to the low risk group (21). Myocardial infarction developed 8.3, 12.4 and 11.5 years earlier in men if hypertension, high cholesterol or smoking were present, respectively (22).

3.3 Attributable fraction
The population-attributable fraction is a measure of how much of the population burden of disease could be eliminated if a specific risk factor was removed from the population (23). The attributable fraction is heavily dependent on the prevalence of the risk factor, e.g. if a risk factor causes a fivefold increase in risk but exists only in 2% of the population that develop the disease, then the attributable risk would be about 1.6% (5 (relative risk for exposed) – 1/5 (risk for exposed) × 0.02 (prevalence of the risk factor) = 0.016 (attributable fraction)). That is, almost 98.4% of the disease would still be left if the risk factor were totally eliminated. Hence, it is of interest to know the extent of a certain risk factor in the population.

In the cohort of men screened for the Multiple Risk Factor Intervention Trial (n=361,662, aged 35–57) and followed for 11.6 years, it was estimated that 49% of all CHD deaths were excess deaths attributable to SBP above optimal level (<120 mm Hg) (15, 24). Furthermore, in the follow-up of the screenees of the MRFIT trial, values above low risk (<120/<80 mm Hg, cholesterol <5.0 mmol/L, non-smoker, no diabetes) for these risk factors were able to explain up to 90% of the excess risk of CHD (25). Elevated blood pressure has been estimated to account for about 57% of all stroke death and for about 24% of all coronary heart disease death in Eastern Asian populations (26).
The distribution of disease cases over the BP scale from about 120 mm Hg shows that the increased burden of CHD caused by high BP cannot be solved solely by treatment of those with the highest BP levels. About 70–80% of all adults have BP levels above optimal (<120/<80 mm Hg) and are accordingly at increased risk due to their BP. Of all these excess CHD deaths in the follow-up of the MRFIT study, 31.9% were attributable to BP levels of 120–140 mm Hg, 42.9% to levels of 140–159 mm Hg and 24.1% to SBP levels of 160 mm Hg or above (15, 24).

A small change in the distribution of SBP in the population is likely to give a substantial decrease in cardiovascular disease. A reduction of SBP by only 2 mm Hg on the population level would correspond to a reduced stroke mortality by 6%, CHD mortality by 4% and total mortality by 3% (17, 27, 28).

Similarly the Framingham Heart Study data indicate that a 2 mm Hg reduction in the population average of diastolic BP for white US residents, 35–64 years of age, would result in a 17% decline in the prevalence of hypertension, a 14% risk reduction of stroke and a 6% reduction in risk of IHD (29).

4. Assessment of cardiovascular risk in hypertensive patients

4.1 Assessment of risk in guidelines

The ability to substantially reduce cardiovascular mortality and morbidity through treatment of blood pressure, blood lipids and smoking cessation has raised the important issue of how to identify those who are candidates for treatment. Global (total) risk estimate, that is, considering the combined effect of all risk factors, is now adopted by most guidelines as the preferred way of selecting whom to treat, e.g. 1999 WHO/ISH Hypertension Guidelines, JNC VI. Likewise many guidelines have adopted the concept that intensity of management of risk factors should be proportional to the absolute risk of a future event (2, 30-34).

Hence, assessment of future cardiovascular risk is a fundamental and necessary step to achieve a cost-effective and high-quality treatment decision, especially in primary prevention. The assessment requires not only knowledge of which factors are involved, how they are defined and their precise value for each individual but also knowledge of how these factors interact to give an accurate risk estimate. Risk factors, target organ damage and established CV disease are the factors to combine in order to get an accurate estimate of risk.

4.2 Risk factors

The major independent risk factors for coronary heart disease are sex, age, blood pressure, elevated cholesterol levels (particularly elevated LDL and decreased HDL
Bring hypertension guidelines into play

levels), smoking, and diabetes (30). Predisposing risk factors, which worsen the independent risk factors, are genetic disposition (which can be estimated by family history of cardiovascular disease), obesity, physical inactivity, food intake, and ethnic and psychosocial factors. Finally, we have an increasing number of conditional risk factors. These are associated with increased risk of cardiovascular disease, although their causative, independent and quantitative effect is not yet fully confirmed, e.g. fibrinogen, C-reactive protein, and insulin resistance (30, 35).

4.3 Target Organ Damage
In addition, target organ damage (TOD) partly caused by the above risk factors, is important to consider when assessing cardiovascular risk. The most important target organ damage is left ventricular hypertrophy, kidney damage (proteinuria or slight elevation of plasma creatinine) and atherosclerotic plaque (1). Age is the most powerful predictor of CVD and is thought to represent the accumulation of atherosclerotic plaques (36). Using ultrasound for finding intima-media thickness (IMT) and plaque in the carotid artery can improve the ability to predict risk (37-39), but there are methodological problems (40), and others have found that predictive power increases only marginally when IMT is used (40, 41). This could also be a way to find subclinical atherosclerosis in those with low predicted cardiovascular risk (42).

4.4 Established cardiovascular disease
The most important cardiovascular diseases to consider are ischaemic stroke, cerebral haemorrhage, transient ischaemic attack, myocardial infarction, angina pectoris, coronary revascularisation, congestive heart failure, diabetic nephropathy, renal failure and peripheral vascular disease (1). Those with already established atherosclerotic disease are considered to have high risk of further CV diseases, and active intervention is advocated (1, 2).

4.5 Risk factor clustering
Hypertension seems to be associated with increased levels of other risk factors such as dyslipidemia and impaired glucose tolerance (43). Hypertensives on drug treatment continue to have increased risk of cardiovascular disease (44). Many studies have reported the impact of risk factor clustering, with increased risk as the level and number of risk factors increases (45-47) with further risk exposition for hypertensive subjects.

One special type of risk clustering is defined as the metabolic syndrome, including type II diabetes, impaired glucose tolerance and/or insulin resistance together with at least two of the following factors: hypertension (≥140 and/or ≥90 mm Hg), obesity (BMI ≥30 or waist-hip ratio (WHR) >0.90 for men and WHR >0.85 for women),
microalbuminuria (≥20 μg/min) and hypertriglyceridemia (≥1.7 mmol/L or HDL <0.9 mmol/L for men and <1.0 mmol/L for women) (48).

4.6 Risk equations
Guidelines are used to judge CV risk, but risk equations derived from statistical models (logistic regression, Cox regression) can also be used to describe how risk factors are associated with risk of various outcomes such as stroke, IHD or all-cause mortality. These models represent the impact of various risk factors on the specified outcome.

To be able to calculate an absolute risk, i.e. the probability of getting a certain disease within a specific time, you must also estimate the baseline hazard function (Cox regression). This baseline hazard function together with the sum of all risk factors for an individual gives the total risk for the individual. In logistic regression the same type of problem exists. The baseline hazard function can be calculated from the sample from which the risk coefficients for each risk factor were estimated or the baseline risk function can be represented by the use of incidence data from the population.

The propensity to develop CV disease given a certain risk profile varies among different populations, but the relative impact on CV disease of changes in risk factor levels seems to be surprisingly consistent between populations despite great differences in incidence (23, 49-53). This propensity for CV disease, baseline incidence, for a given set of risk factors varies between populations and is called the population baseline absolute risk (23).

This is important to keep in mind, because if the risk function is derived from a population with high incidence of CHD and then applied to a population with low or medium incidence of CHD, then the risk will be over-estimated for the low-incidence population (49, 54). It is an advantage if the risk equation is estimated from a population that is representative of the population that the risk equation is intended to be used on and this was the main reason for estimating our own risk function based on the NSW MONICA samples.

The first and most widely used risk equations concerning cardiovascular risk are those from the Framingham Heart Study (55, 56). It is important to be aware of some other properties of risk equations.

A risk function can be used to identify those with moderate elevations of several risk factors as high-risk patients, while simply counting risk factors above a certain level can miss individuals with several risk factors but each one only moderately elevated (57). The projection time is also very important; a person with a 15% ten-year risk will have approximately 30% risk in 20 years (57). On the other hand, risk can be underestimated if there is only one risk factor but it is extremely high (57).
The estimated risk is not necessarily correct for each individual with that collection of risk factor values; rather, it is the average risk for a group with these characteristics, and the exact probability for an individual is not known.

The relative effect of increased risk factor levels decrease with age, especially for lipid risk factors (58), whereas high BP and diabetes continue to be strong risk factors. As the relative effect of risk factors declines with age the absolute risk increases even more, thereby maintaining the importance of raised risk factor levels (14).

4.7 Absolute and relative risk
Absolute risk is the number of subjects getting a disease during a specified time divided by the number of disease-free subjects at the beginning of the period (59). Relative risk is best understood and interpreted if compared to some basic and easily understood level of risk, e.g. low risk (cholesterol <5.0 mmol/L, BP <120/<80, non-smoking and no diabetes) or average risk for that sex and age, i.e. the absolute risk for a certain person is divided by the absolute risk for the low or average risk state. It is crucial to understand that since relative risk is derived from a ratio it tells nothing about the level of absolute risk, e.g. if ten-year relative risk is reduced by 50% it can be based on an absolute benefit of 1% over ten years if the absolute risk is reduced from 2% to 1% during the period (the chance of avoiding disease increases from 98% to 99%).

Due to the slowly progression of CV disease short/medium-term absolute risk is low in young people, regardless of the number or level of risk factors, whereas in old people absolute risk is high, even if risk factor levels are moderate. This is the reason why relative risk could be a better indicator of risk in younger and maybe also in older people. A three-fold increase in relative risk from the lowest level has been designated moderately high risk, while a fourfold increase is called high risk in a joint statement from AHA and ACC (57).

The precise level of high short-term (10 years) absolute risk varies. The joint European Societies have identified high short-term absolute risk as a risk giving a >20% probability of developing CHD in the next ten years (33), and it is recommended that when a patient reaches this threshold the treatment should correspond to that given in secondary prevention (33). This threshold was derived with total CHD as end-point according to the wide Framingham definition. The definition of high absolute risk in the 1999 WHO/ISH Hypertension Guidelines is >20% risk of fatal and non-fatal CHD and stroke in ten years.
4.8 Problems with risk assessment

Guideline algorithms and risk equations are two different methods used to assist physicians' estimate of cardiovascular risk. These two methods can be based on exactly the same calculations of risk, but often have different levels of accuracy. The guideline approach can also be based on combinations of risk factors, but put together in a way that seems sensible and logical rather than based on actual calculations based on data. The guideline approach divides patients into different categories, while risk equation, derived by statistical methods, can take into account variations in the exact level of each included risk factor variable (if implemented in the equation), e.g. age, blood pressure. The risk stratification scheme proposed by the 1999 WHO/ISH Hypertension Guidelines is shown in Table 2. Generally speaking, guideline algorithms do not need advanced mathematical calculation, while risk equations need computations. This need for computer assistance hampers the use of risk equations in clinical practice; instead multi-coloured charts showing different levels of risk have been used.

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>Other risk factors and disease history</th>
<th>Grade 1 (mild hypertension)</th>
<th>Grade 2 (moderate hypertension)</th>
<th>Grade 3 (severe hypertension)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low risk</td>
<td>Medium risk</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>l. No other risk factors SBP 140–159 or DBP 90–99</td>
<td>Medium risk</td>
<td>Medium risk</td>
<td>Very high risk</td>
<td></td>
</tr>
<tr>
<td>II. 1–2 risk factors</td>
<td>High risk</td>
<td>High risk</td>
<td>Very high risk</td>
<td></td>
</tr>
<tr>
<td>III. 3 or more risk factors or TOD or diabetes</td>
<td>Very high risk</td>
<td>Very high risk</td>
<td>Very high risk</td>
<td></td>
</tr>
<tr>
<td>IV. ACC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOD, Target organ damage (e.g. left ventricular hypertrophy, proteinuria); ACC, associated clinical conditions (e.g. myocardial infarcation, stroke); SBP, systolic blood pressure; DBP, diastolic blood pressure.

An algorithm, although easily explained on paper, can nevertheless become very complex and difficult to apply to individual patients' medical profiles. Furthermore, the algorithm can at the same time be too crude, with huge categories and a poor ability to separate individuals with different risks. Simplification intended to increase usability tends to reduce the accuracy of the guideline algorithm and the balance here is delicate. In paper V the risk stratification algorithm proposed in the 1999 WHO/ISH Guidelines was compared with risk equations and the aim was to evaluate the accuracy of the guideline method.

Moreover, the physician does most risk estimations in clinical practice without the aid of guidelines or computing devices. However, physicians have difficulties assessing
CV risk, especially estimation of absolute risk (60). Risk assessments are not consistent between doctors, often only one parameter is considered, and deviations from guidelines are great (61-64). CDSS based on risk equations can help the physician to do more accurate risk estimations (65).

5. Effects of treatment

A number of large RCTs during the last two decades have proved the efficacy of antihypertensive drug treatment with thiazide diuretics, β-blockers, ACE-inhibitors, calcium antagonists and angiotensin-II receptor antagonists in preventing cardiovascular disease up to at least the age of 80 years (66-80).

In an overview of 14 randomised placebo-controlled trials (n=37,000) of antihypertensive drug treatment (mainly diuretics or beta-blockers) without other risk factor interventions, a mean difference in diastolic blood pressure of 5–6 mm Hg for 5 years was found to reduce stroke by 42% (95% CI 33–50%) and coronary heart disease by 14% (95% CI 4–22%). It was concluded that almost all the epidemiologically expected stroke reduction occurs, within 2–3 years, but only about half of the expected reduction in coronary heart disease (12). An update published in 2000 compared treatment effects on mortality and major cardiovascular morbidity of various antihypertensive drug classes (diuretics, beta-blockers, ACE-inhibitors, calcium antagonists). In four placebo-controlled trials of ACE inhibitors the reduction in stroke was 30% (95% CI 15–43%), and CHD 20% (95% CI 11–28%) for a weighted average difference of 3/1 mm Hg in BP, and patient selection criteria were predominantly history of cardiovascular disease or diabetes (81). In two placebo-controlled trials of calcium antagonist treatment, mean follow-up 3.8 years, the reduction of stroke was 39% (95% CI 15–56%), and CHD 21% (95% CI 6–41%) for a weighted average difference of 9/5 mm Hg and patient selection criteria were isolated systolic hypertension and previous CHD (81).

In another meta-analysis of nine trials including 27,743 subjects, where calcium antagonists were compared with other antihypertensive drugs (diuretics, beta-blockers, ACE-inhibitors or clonidine) it was found that calcium antagonists had less effect on myocardial infarction and heart failure than other antihypertensive drug treatment regimes but a tendency to a better effect on stroke (81). When less intensive antihypertensive drug treatment was compared to more intensive treatment, three studies, mean follow-up 4.2 years, the reduction in stroke was found to be 20% (95% CI 2–35%), and CHD 19% (95% CI 2–33%), for an average difference of 3/3 mm Hg (81). In a meta-analysis of BP an average reduction of SBP by 12–13 mm Hg over 4 years of follow-up was associated with a 21% reduction in CHD, a 37% reduction in stroke, a 25% reduction in total cardiovascular mortality, and a 13% reduction in all-cause mortality (82).
The effect of drug treatment of hypertension in everyday clinical practice is comparable to the risk reduction achieved in randomised clinical trials (83). Hypertensives seem to have higher risk than the general population even though the blood pressure is controlled by drug treatment (84, 85). Antihypertensive drug treatment does not fully reduce the risk associated with hypertension, but the reasons for this are not clear. Two possible causes are poorly treated hypertension and short trials; up to five years may be too short to show the full benefit of treatment (14). Metabolically adverse effect of thiazides and beta-blockers have also been proposed, although no support for this hypothesis can be found in large randomised controlled trials (33, 69, 72, 78). In a study to assess the association between first ever ischaemic stroke and use of antihypertensive drugs, it was found that drug regimes that did not include a thiazide were associated with an increased risk of stroke (86).

Neither sex nor age usually affects responsiveness to various antihypertensive agents (87), but there are race differences; blacks respond more favourably to thiazide-diuretics and calcium-antagonists (2). Although antihypertensive drug treatment may induce side effects in some patients, quality of life is maintained and possibly improved by any of the drugs recommended for initial therapy (88).

6. Blood pressure control

6.1 Awareness, treatment and control

The gap between recommendations given in recent hypertension guidelines and clinical practice is huge concerning BP control in most drug-treated hypertensives (89-97). The status of BP control in the community is often expressed in scientific reports in terms of prevalence, awareness, treatment and control of hypertension (2, 98). Prevalence of hypertension is the proportion of the adult population having high blood pressure at a given time, often judged by BP measurement on one occasion. Awareness is the proportion with high blood pressure at the screening who are aware of having high blood pressure before the screening. Treatment is the proportion of hypertensives treated (usually with drugs) for high BP, and finally, control refers to those who are treated and have attained target blood pressure (usually defined as below 140/90 mm Hg or in older publications below 160/95 mm Hg).

Neglect to measure BP does not seem to be a major cause of poor BP control. Almost two thirds of the unaware had their BP measured during the last year (99), 87.4% had their BP measured during the previous year (100), and in a Canadian study had more than half (51%) had their BP measured in the last 6 months and 75% within the last year (101). The majority of hypertensives reported not being treated at all (61%), drug treatment alone (16%), drugs and non-pharmacological treatments combined (15%), and non-pharmacological treatment alone (6%) (101).
Unawareness correlated to being male, working full-time, more than two years since the last BP measurement, and having public health insurance (compared to private) (99), while in another study persons (>55 years) living without a partner and men living in a home for elderly had a higher risk of being unaware and without antihypertensive treatment (102). Awareness correlated to higher education, visiting a physician in the previous year and being female (103). Better BP control correlated to BP measurement within the last year, part-time employment, male gender, and resident in urban areas (104).

Ambulatory BP monitoring also showed inadequate BP control, ruling out the white-coat effect as an explanation for poor BP control among drug-treated hypertensives (105). Unawareness is also common concerning other cardiovascular risk factors; in an Italian study 60% were aware of hypertension, 77% aware of diabetes and 65% aware of dyslipidemia (106).

### 6.2 Antihypertensive drugs and uncontrolled blood pressure

The majority of inadequately controlled drug-treated hypertensives have mild or moderate hypertension. Among drug-treated hypertensives in Italy (≥65 years, mean 75 years) 17.6% were controlled (<140/<90), 50.5% had a BP of 140–159/90–99 mm Hg and 31.9% had BP at or above 160/100 mm Hg (100). In a Spanish study of hypertensives, aged 35–64 years, 66% had BP within the range of mild hypertension (140–159/90–99 mm Hg) (107).

In a Canadian study the use of calcium antagonists and ACE-inhibitors increased during the period 1985 to 1995, from 2.1% to 19.7% and 5.2% to 25.4%, respectively, while combination therapy decreased from 39.6% to 15.6% and therapies using diuretics decreased from 31.3 to 17.2%. At the same time the proportion of controlled hypertension decreased from 67.4% in 1985 to 42.6% in 1995 in men, and in women from 62% to 57.4%, at an additional cost of 79% (108).

In a US study of people ≥65 years the average number of antihypertensive drugs was 1.5 in 1989 and 1.7 in 1999 (95). In another study of antihypertensive drug treatment 78.7% received one drug, 18.7% two and 2.6% received three or more (104). Between 1977 and 1987 the physicians' attitude towards initiating drug treatment changed, as they advocated earlier treatment at lower BP levels and this was evident for different age groups (98). The willingness to give drug treatment for a certain BP level declines with the age of the patient (98).

An extremely poor control rate was found in China, where in urban areas about 4% of all hypertensives were controlled down to <140/<90 mm Hg and in rural areas about
1%. In 1991 the estimated number of hypertensives in China was 90 million (93). A study of Type I diabetic patients (mean age 33 years) from 31 diabetes clinics in 16 European countries found that 81% of drug-treated hypertensives had one drug and 11.3% were controlled to target blood pressure <130/<85 mm Hg (109).

Table 3 (page 22) contains a summary of some large prospective population studies around the globe concerning prevalence, awareness, treatment and control of hypertension during the 90s. Despite improvements in the management of hypertensive patients, far from all are adequately controlled. Both in the NSW MONICA sample from 1999 and in the Västerbotten Intervention Programme, conducted during the 90s, hypertension control is poor.

While awareness and treatment have consistently improved, the control rate among drug-treated hypertensives has not improved at the same pace. Many researchers in this field have concluded that it is time to improve hypertension treatment in order to improve outcome (1, 2, 110). In a Finnish study the authors concluded that “the biggest problem in hypertension care has shifted from detection to adequate treatment of high BP” (96), and authors from France have come to the same conclusion (97).

7. Guidelines and clinical decision support systems

7.1 Evidence-based medicine

Evidence-based medicine (EBM) is an important concept in medicine, defined in an editorial in BMJ as “conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (111). The practice of EBM means integrating evidence from research with one’s own clinical knowledge and with consideration of the individual patient’s predicament and preferences (111). Furthermore, the concept of EBM has been especially stressed in areas concerning medical therapy and diagnoses (111). EBM used in clinical practice will enhance quality and other outcome measures (112).

Sackett emphasises in his book *Evidence-based Medicine* (113) the following important reasons for practising EBM: (i) new evidence should lead to major changes in patient care; (ii) practising physicians often fail to obtain and use available new evidence; (iii) medical knowledge deteriorates with time and must be updated; (iv) traditional continuing medical education is insufficient to bring about important changes in practice; and (v) it is a way to keep the physician up to date with current and important knowledge. The usefulness equation (usefulness = validity × relevance/work), states that the information must be relevant for the decision at hand, should be based on scientific evidence and must be retrieved and used with a minimum of effort in order to be useful for the busy clinician (114).
<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Age/sex/number</th>
<th>Hypertension prevalence (%)</th>
<th>Awareness (%)</th>
<th>Control (%) Treatment</th>
<th>Control (%) Drug-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>1997-99</td>
<td>25-64 Y, M/F, n=482</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>US</td>
<td>1998-99</td>
<td>25-64 Y, M/F, n=1695</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>US</td>
<td>1999-00</td>
<td>25-64 Y, M/F, n=1326</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>England</td>
<td>1994</td>
<td>25-64 Y, M/F, n=12116</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Finland</td>
<td>1994</td>
<td>25-64 Y, M/F, n=11592</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>NSW Monika</td>
<td>1995-99</td>
<td>25-60 Y, M/F, n=59973</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>VIP Sweden</td>
<td>1995-96</td>
<td>25-60 Y, M/F, n=248</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>France</td>
<td>1992</td>
<td>15-64 Y, M/F, n=13183</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>South Africa</td>
<td>1999-2000</td>
<td>15-64 Y, M/F, n=96226</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Korea</td>
<td>1999-2000</td>
<td>15-64 Y, M/F, n=950356</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>China</td>
<td>1999-2000</td>
<td>15-64 Y, M/F, n=9300</td>
<td>140/90</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
</tbody>
</table>
7.2 Clinical decision support systems

A clinical decision support system (CDSS) is any computer program that can help health care professionals to make clinical decisions (115) and influence medical decisions at the time and place decisions are made (116). Such systems have been used since the late 1950s. CDSSs use a number of problem-solving strategies: Bayesian theory, decision tree, sensitivity analysis, statistical models, pattern recognition, rule base and hybrid systems (117).

Basic features of CDSSs should be: to support clinicians, not replace them, to improve patient care, to be updatable, to have an acceptable response time, and to be easy to use (115, 118). CDSS should be considered as support systems and not as decision-makers (115). Development of a powerful CDSS for correct prescription is badly needed, because prescribing errors, of various kinds, are numerous and dangerous and costly (119). Delivering information “just in time” is important (120). User-friendliness and avoidance of time-consuming tasks have also been emphasised as important properties of CDSSs (121). Physicians' attitude to CDSSs can influence the implementation process (122, 123).

CDSSs have been evaluated, and many have shown effects on physicians' behaviour, but few studies have demonstrated effects on patient outcome (124). A review of computer-based CDSSs' effects on physicians' performance and patient outcome showed that they can enhance clinical performance but effects on patient outcome were insufficiently studied (124). A systematic review of randomised controlled trials on the effect of computers and computer-based CDSSs on the management of hypertension showed that computers had a favourable effect on the management and follow up of patients (125). However, many studies fail to show any change in behaviour (126). CDSSs are difficult to implement in a busy primary care setting, and availability and simplicity are thought to be crucial requirements (127).

7.3 Guideline implementation

The very idea of guidelines is to transfer evidence-based knowledge derived from clinical research into manageable recommendations, but these recommendations have not materialised into appropriate clinical implementation (128-131). The statement “Words without action”, issued by Jonathan Lomas, is still relevant (128). Active dissemination of guidelines does not always have any impact on behaviour (132).

The implementation of guidelines in clinical practice faces many difficulties. Lack of time for basic health care work, the logarithmic increase in the amount of medical information, the increasing complexity of management and increasing demands are some of the pitfalls in the implementation of good evidence (133). All of these obstacles
apply also to hypertension guidelines (134). It is of great importance that the implementation of EBM is targeted against the issues where the evidence is strong and can be strongly backed by a respected clinical body (135).

Physicians who knew most about guideline content also felt that they were the most qualified to override the guidelines when they believed they did not apply. It was easier to encourage physicians to do more rather than less for the patients (136). Guideline implementation occurs in the context of conflicting pressures for clinical autonomy, professional standardisation and quality improvement (137). Factors influencing the implementation of guideline were: non-controversial advice was followed better than controversial advice, clearly written better than vague recommendations, evidence-based better than those not based on evidence, recommendations that demanded a change in existing practice routines were followed less than those that did not require a change (138). Far more energy has been put into the development of guidelines than into their implementation (139).

Too few recognise the true dimension of the information problem, and acknowledge the need for assistance in retrieval and use of knowledge (140). In the late 1990s approximately 30,000 citations were added each month to MEDLINE (133). Medicine lacks an efficient connection between those who produce and archive medical knowledge and those who must apply it (140).

Six important obstacles, from a total of 59, were recognised in a study of physicians' search for evidence-based answers to medical questions. These obstacles were: the excessive time required, difficulty modifying a vague original question, difficulty finding an optimal strategy for search, failure to find sources covering the whole topic, uncertainty about how to know when all relevant information was found, and inadequate synthesis of multiple bits of evidence into a clinical useful statement (141).

While solid evidence exists that BP therapy is effective, it is obvious that BP control among hypertensives is poor (Table 3), and many factors contribute to the gap between guidelines and practice (132). Prescribing practices for older hypertensive patients are not consistent with evidence-based guidelines, and interventions are called for to encourage evidence-driven prescribing practices for the treatment of hypertension (129). Strong evidence supports the need for better blood pressure control, with an emphasis on the elderly and other populations that are difficult to treat (118). This evidence has been incorporated in hypertension guidelines but implementation in clinical practice has been weak.

8. Hypertension guidelines

New knowledge has to be summarised and interpreted, in order to be usable in clinical practice. This process is often done by different societies and authorities and issued as
recommendations or medical guidelines intended for the medical profession. As guidelines are produced at different times and the evidence on which guidelines are based evolves, it is evident that they will not be exactly alike. However, the basic views of hypertension, its epidemiology, risks and treatment are quite similar between major guidelines. In detail they are of course not replicas of each other, and some parts of the proposed recommendations are, as always, open to discussion.

While blood pressure definitions, given in Table 1, are the same between guidelines, they do differ in recommendations concerning when to initiate drug treatment and in recommended target blood pressure, see Table 4 (1, 2, 33, 142-144).

It is well established that hypertension is a risk factor for cardiovascular disease, and this applies to virtually all imaginable subgroups and to an incredible amount of diseases (14). Furthermore, the risk increases from at least 115/75 mm Hg with no obvious cut-off level, which makes it difficult to establish a BP level where drug treatment should be initiated (14). However, the effect of lowering BP (measured as avoided number of myocardial infarctions, strokes and deaths during a certain time, e.g. 5–10 years) is heavily dependent on the prevalence of other major risk factors for cardiovascular disease such as age, sex, smoking, cholesterol, diabetes, target organ damage and already established CV disease (1, 2, 45, 47).

<table>
<thead>
<tr>
<th>Table 4</th>
<th>WHO/ISH¹</th>
<th>JNC VI²</th>
<th>BHS³</th>
<th>European task force⁴</th>
<th>Canada⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Published</td>
<td>1999</td>
<td>1997</td>
<td>1999</td>
<td>1998</td>
<td>2002</td>
</tr>
<tr>
<td>Definition of hypertension</td>
<td>≥140/&gt;90</td>
<td>≥140/&gt;90</td>
<td>≥140/&gt;90</td>
<td>≥140/&gt;90</td>
<td>≥140/&gt;90</td>
</tr>
<tr>
<td>Indication for drug treatment, no risk factors</td>
<td>≥150/&gt;95</td>
<td>≥140/&gt;90 (12 month expectancy)</td>
<td>≥160/&gt;100</td>
<td>≥160/&gt;95</td>
<td>≥160/&gt;100</td>
</tr>
<tr>
<td>Risk factors, diabetes, TOD or established CVD</td>
<td>≥140/&gt;90 (&lt;130/&gt;85⁴)</td>
<td>≥140/&gt;90 (&lt;130/&gt;85⁴)</td>
<td>≥140/&gt;90⁶</td>
<td>≥140/&gt;90⁶</td>
<td>≥140/&gt;90</td>
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<tr>
<td>Target BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>&lt;140</td>
<td>&lt;140</td>
<td>&lt;150 (&lt;140⁰)</td>
<td>&lt;140</td>
<td>&lt;140 (&lt;160⁰)</td>
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<tr>
<td>Diastolic BP</td>
<td>&lt;90</td>
<td>&lt;90</td>
<td>&lt;90 (&lt;85⁰)</td>
<td>&lt;90</td>
<td>&lt;90</td>
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<tr>
<td>Diabetes</td>
<td>&lt;130/&gt;85</td>
<td>&lt;130/&gt;85</td>
<td>&lt;140/&gt;90 (&lt;80⁰)</td>
<td>&lt;130/&gt;80</td>
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<tr>
<td>Younger (&lt;65 y)</td>
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<td>&lt;130/&gt;85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>&lt;130/&gt;85 (&lt;125/&gt;75⁰)</td>
<td>&lt;130/&gt;85 (&lt;125/&gt;75⁰)</td>
<td>&lt;130/&gt;85 (&lt;125/&gt;75⁰)</td>
<td>&lt;130/&gt;80 (&lt;125/&gt;75⁰)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Blood pressure levels (mm Hg) at which drug therapy should be initiated and target blood pressure according to five different guidelines. BP = blood pressure, TOD = target organ damage, CVD = cardiovascular disease; a diabetes or renal insufficiency; b Heart failure, renal insufficiency or diabetes; c or a predicted ten-year risk of CHD of >=15%; d absolute CHD risk >= 20% or TOD; e optimal <140/>85 (<140/>80 if diabetes); f for patients treated for isolated systolic hypertension the goal is below 160 mm Hg, or a reduction of 20 mm Hg from baseline if initial SBP is less than 180 mm Hg; g Renal insufficiency and proteinuria >1 g/d. ¹WHO/ISH Hypertension Guidelines; ²JNC VI Guidelines on prevention, detection, evaluation, and treatment of high blood pressure; ³British Hypertension Guidelines; ⁴Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention; ⁵Canadian recommendations for management of hypertension.
Accurate evaluation of risk is crucial for targeting limited resources towards those individuals that will benefit most from treatment. But this requires an accurate and easy to use method for risk categorisation. The risk stratification method proposed in the 1999 WHO/ISH Hypertension Guidelines, see table 2, is scrutinised and evaluated in this thesis. A similar method for risk assessment is advocated in JNC VI.

The common trends put forward by authors of hypertension guidelines during the 1990s are the following: (i) hypertension is defined as $\geq 140/\geq 90$ mm Hg in adults independent of age; (ii) consensus about target blood pressure of $<140/<90$ mm Hg, and $<130/<80-85$ in those with diabetes and renal insufficiency; (iii) recognition of both systolic and diastolic BP as risk factors and thus important to treat; (iv) the concept of total cardiovascular risk estimation; (v) the use of absolute risk for guiding the intensity of interventions and when to start drug treatment; (vi) the need to combine several different antihypertensive drugs to obtain target BP; and (vii) the importance of lowering the blood pressure per se (1, 2, 33, 142-144).
AIMS

The overall aim of this thesis is to contribute to improved management of hypertension by: assessment of blood pressure treatment and control in the community, estimation of risk associated with high blood pressure, particularly stroke risk in poorly treated hypertensives, and development of a clinical decision support system for drug treatment of hypertension. The specific aims were:

- To develop a clinical decision support system (CDSS) for antihypertensive drug treatment, capable of implementing evidence-based rules extracted from accepted medical guidelines.
- To evaluate cost and drug use if guidelines for antihypertensive drug treatment were followed compared to current treatment.
- To study cardiovascular risk among people with high blood pressure.
- To study stroke risk associated with poorly treated hypertension.
- To study the status of hypertension treatment and control.
- To assess different risk prediction methods in hypertensive subjects.

The specific aims for each paper were as follows:

Paper I
- To build a computer-based decision support system capable of applying the evidence-based rules extracted from guidelines to any patient's medical profile.
- To develop a formal method for transforming guideline rules into formal rules, capable of implementation as a computer-based clinical decision support system by a professional programmer.
- To test a general-purpose programming language, Visual Basic, as a development tool for decision support systems in health care.

Paper II
- To evaluate a computerised clinical decision support system for drug treatment of hypertension, regarding quality, safety, drug use, and cost compared to actual antihypertensive drug treatment.

Paper III
- To study the consequences of applying the 1999 WHO/ISH risk stratification scheme to a MONICA sample, regarding blood pressure control, indications for treatment, target blood pressure and risk distribution.

Paper IV
- To assess risk factors for stroke, associations between stroke and blood pressure control and to assess the proportion of these categories in a geographically defined population in Northern Sweden.
Paper V

- To compare the distribution of cardiovascular risk in hypertensives when different risk assessment methods were used on the same set of individuals. Cardiovascular risk assessed by the algorithm described in 1999 WHO/ISH Hypertension Guidelines was compared with risk estimated by risk equations from the Framingham Heart Study and the Northern Sweden MONICA Study (NSW MONICA).
MATERIAL AND METHODS

9. Paper I

9.1 Development of decision support system for antihypertensive drug treatment

The target group for the clinical decision support system (CDSS) was physicians, especially general practitioners, managing hypertensive patients. In order to be usable in clinical practice the CDSS had to be fast, easy to use and readily accessible from the computer on the physician's own desk. Also very important was its capacity to give patient-specific support and continuous medical education. For the software development, a regular programming language was preferred to an expert system shell or the like. Visual Basic 4.0 from Microsoft was selected for the software development.

9.2 User interface

The input was obtained from a three-tabbed dialog-box, where the user with a mouse-click checks the current patient's medical profile. The medical profile consists of 41 diseases and factors considered important when choosing drug class. Ongoing antihypertensive drug therapy and drugs with side effects excluding their use were fed to the DSS by another dialog-box.

In order to understand, learn from and, perhaps most important also trust the recommendation given by the DSS, the feedback was not only given as the name of the generic drug class proposed but also as a statement including the medical profile of the patient, side effects, ongoing therapy, if any, and finally the considerations taken by the DSS and additional comments depending on recommended drug class.

9.3 The problem of antihypertensive drug treatment

Hypertension treatment is complex from the medical point of view. More than half of the hypertensive population needs more than one drug to achieve target blood pressure (2), and in these cases drug interaction must be considered. What drug or drug combination to prefer is influenced by many factors. Many experts advocate individualised drug treatment in hypertension, and it is up to the physician to review the properties and interactions of each drug. Furthermore, the physician must choose the most suitable drug with regard to the characteristics of the patient and also do this in a consistent, cost-effective way based on scientific evidence (2, 145).

In Sweden there are nine main pharmacological classes given against hypertension in primary health care. These classes are thiazides (2 drugs), beta-blockers (8 drugs), ACE-inhibitors (8 drugs), calcium antagonists (9 drugs), alpha-blockers (2 drugs), combined alpha- and beta-blockers (2 drugs), loop diuretics (1 drug), spironolactone
Bring hypertension guidelines into play

(1 drug) and angiotensin-II antagonists (5 drugs). Every class contains one to nine different formulations, all of them with different pharmacological properties, prices and dose regimes. It is not possible to freely combine these drugs due to unfavourable interactions or insufficient effect.

The rule-base must be extracted from guidelines, randomised controlled trials and experts. A great number of factors influence the choice of pharmacological class in various ways (2). For each possible medical profile each pharmacological class may have both positive and negative effects and these have to be judged against each other in every situation. A drug may have a negative effect but should nonetheless be used because of a more important positive effect due to another concomitant disease. In some situations where several drugs are not available because of side effects, being already in use or having contra-indications, the remaining drugs may have possible negative effects but must nonetheless be given.

In total, 41 factors were chosen. These factors were selected to represent the best proven and most important to consider before initiating or adding pharmacological treatment. These factors in combination with possible experienced side effects and ongoing drug treatment constituted the patient profile. With 41 dichotomic variables, the number of possible profiles is almost astronomical – \(2^{41} (2,199,023,255,552)\) – to match with 15,120 possible drug combinations (up to five different drugs out of nine possible ones). Furthermore, these are only some of the necessary factors the physician has to take into consideration before choosing a drug. Other circumstances are costs, patient’s preferences, compliance issues and up to nine different brands in one single pharmacological class. The complexity of hypertension treatment should not be underestimated, and it would be pointless to try to force every facet of the domain into the rule-base. So the most important step is to pinpoint evidence-based rules derived from generally applicable knowledge and, on the other hand, to define what must be left to the judgement of the physician. The responsible clinician’s judgement of the needs of the individual patient is the most important (2) and overarching principle in health care. The DSS should provide, in an understandable way, the recommendations obtained from current guidelines, defined as above, when strictly applied to the patient’s medical profile.

9.4 Comparison of classes
The ranking of the nine pharmacological classes, used in paper I and II, is done according to available documentation, experience gained with the drug class and therapy tradition. It must be stressed that the ranking is in no way based on therapy cost. However, it should be noted that the two first-line drugs cost only about 1/5 to 1/10 of what the calcium antagonists, ACE-inhibitors and angiotensin-II antagonists cost.
Apart from the ranking in the list, each group is considered equivalent regarding quality of life (146), efficiency in lowering blood pressure (6), effects on CV disease prevention and the total number of side effects in a large group of patients. This basic order of drug class is also updated if changes in guidelines indicate that this ranking should be changed.

9.5 Medical advantages and disadvantages

A drug may have compelling and well-documented benefits in certain medical conditions and a drug can also be disadvantageous in certain situations (2). Most drugs, however, have an average blood pressure lowering effect with a certain probability of expected effect on the blood pressure and also a certain probability of side effects.

It is crucial to extract only the best-documented advantages and disadvantages and limit the total number to consider. A large number of factors increase input and output, decrease usability, and poorly documented factors would be impossible to rank. However, the exact number of factors to take into account cannot be exactly determined and may vary from time to time depending on the results and interpretations of clinical trials.

Sparsely documented theoretical advantages, not confirmed in hard end-point trials, tend to favour the newer and more expensive drugs. Proposed advantages, when based only on theoretical considerations, are not implemented, because hypothetical advantages cannot be allowed to compete with proven ones.

9.6 Pharmaceutical class list

This list is based upon the assumption that all of these nine pharmacological classes can be placed in order from a first-line drug to a last-line drug. A patient with uncomplicated hypertension and with no previous experience of pharmacological treatment should be offered the first-line drug. If this does not work or there is need for further treatment, the second-line drug is offered and so on, until one has a combination which is well tolerated by the patient and reaches the target blood pressure. Because many patients need two or more different drugs, we created five levels of treatment. Level one consisted of one drug in order from first-line to last-line drug, level two with different combinations of two drugs starting with the combination of the first-line drugs (thiazide and beta-blockers) and so on. Preferable combinations were listed ahead of less favourable ones, so that the best combination possible could always be obtained. This list of combinations is the total amount of combinations that the program can propose. The list is cleared of less efficient and contra-indicated alternatives, and more commonly used and better-documented combinations lie ahead of less documented alternatives. The program only selects less-documented alternatives
if the alternatives above have been ruled out, because of side effects, contra-indications, or if they have certain benefits considering the patient’s medical profile.

The pharmaceutical class list is an ordinary text-file, which is read by the program at the start. This approach makes it possible to use several lists, each list reflecting different therapy traditions, but the rule-base of the program is left unaffected. It is even possible to create a list optimised for cost-reduction.

9.7 Working scheme
Since it is impossible to implement a direct mapping from the patient profile and recommended drug treatment, the DSS needs a working scheme that is reliable, unambiguous and easy to understand and evaluate. The system strives to achieve this by using a straightforward rule-base to arrange the antihypertensive drug classes into four basic categories: contra-indicated, non-suitable, neutral and suitable. Due to a strict priority order, a single drug class can only be added in one of the above categories. All categories except contra-indicated are ordered. The suitable and non-suitable categories are ordered by the rule-base whilst the neutral category inherits the order from the pharmaceutical class list described above. When this procedure is carried out, the system tries to find a valid combination using the ordering above, i.e. trying to select the best antihypertensive drug class from the suitable category and then adding this to the ongoing treatment (if any). If the suitable category is empty, or the system is unable to add any drug class in the suitable category, the system then checks the neutral category. If this fails, the system finally checks the non-suitable category, starting with the least unsuitable. A contra-indicated drug (or a drug specified by the user as giving important side effects) is never recommended.

The basic steps in this working scheme are, see paper I figure 5.

1. Inspect and modify the list of drugs which the user specified as giving side effects (s-e). For example, if the user selects Ca(Verapamil), the system automatically adds Ca(Diltiazem) to the list.

2. Determine (from the patient’s medical profile) which drug classes are contra-indicated (c-i).

3. Evaluate which antihypertensive drug classes are suitable or non-suitable in relation to medical factors (ranking). Order the drug classes (position) within the same ranking, if there is more than one suitable class for a medical factor.

4. Inspect the ongoing treatment and give warnings if any drug is considered non-suitable. Contra-indicating drugs or drugs with user-specified side effects are removed.
5. Select the best drug (position) from the most important medical factor (ranking) and verify (validate) that it exists as a valid combination in the pharmaceutical group list.

6. If validation failed, try the second best from position and ranking, with ranking always in precedence over position.

Even though the steps above are easy and intuitive, the real implementation is rather complex and hard to evaluate by inspection. Therefore, we have translated the detailed rule-base into a formal syntax in order to minimise the semantic gap between the rules expressed by the guideline and the final implementation. The syntax is based upon sets and sequences using symbols commonly known in natural sciences and operators such as union, interaction, concatenation etc. The total rule-base includes approximately 150 rules.

9.8 Dichotomic variables
The DSS is rule-based and requires dichotomic variables. Most of the input variables can be only true or false, which is both advantageous and disadvantageous. It is not possible, for instance, to specify an advantage of 0.65 for a beta-blocker in a patient
Bring hypertension guidelines into play with moderate migraine. At first sight it seems obvious that this possibility should give a more accurate result. This is, however, based on the assumption that the physician’s diagnosis and calibration of each disease is very exact. Especially in heart failure this could be advantageous, but there is considerable clinical difficulty in the accuracy of diagnosing heart failure, and gradation of heart failure at various levels can be very uncertain (147). This is also true for many other diagnoses. In clinical practice the physician has to decide either way, because it is not possible to give a fraction of a drug. As the DSS gives the ranking for each advantage and disadvantage, it is easy for the physician to give priority, for instance, to a beta-blocker in a patient with severe migraine if the DSS ranked the beta-blocker as disadvantageous because of mild claudiocatio intermittens, just as is done in usual practice, with the difference that the factors now are easily recognised.

10. Paper II

10.1 Evaluation of clinical decision support system

Three health centres in the city of Umeå and one in the municipality of Robertsfors were selected for the study. The chief physicians at these units agreed to provide comparison material for the study. Hypertensive patients from each of the four health centres were classified according to age, and data from every fifth of these patients were collected from the medical record. The following data were recorded: age (in years), sex, antihypertensive drug(s), dose prescribed, and the most recently obtained blood pressure reading. Moreover, any of 41 different variables (see below) requested by the DSS were noted if present, as were also side effects of such a degree that the drug had been changed. For each drug, brand name and dose were noted and the cost was calculated according to current prices in the Swedish Drug Compendium 1997.

Thus, the medical profile of each patient was assessed by the DSS. Diseases and other complicating factors which influence drug treatment of hypertension were used as input data. Drugs that could not be used, due to previous side effects, were also fed into the system. Age, sex and blood pressure were not used by the system with the exception of “age over 70 years”.

The DSS was requested to propose the same number of drugs that the patient was actually taking, i.e. if the patient was taking one drug the system proposed only one drug, if the patient was taking three drugs the DSS proposed three drugs and so on. The DSS did not recommend brand names, it only recommended one of the following generic classes: thiazide diuretics with potassium-sparing agent (if potassium-sparing agent was not suitable or contra-indicated only thiazide diuretics were used), beta-blockers, ACE-inhibitors, calcium antagonists, alpha-blockers, combined alpha- and beta-receptor-blockers, loop diuretics, spironolactone, or angiotensin-II antagonists.
The CDSS could recommend combinations of up to five generic classes. If the patient was treated with a combination preparation such as Synerpril® (enalapril and hydrochlorothiazide) the system would propose two generic classes, except for thiazide combined with a potassium-sparing agent which was handled as one drug.

10.2 Drug cost
The cost of actual drug treatment was calculated for three months for the exact brand and dose used for each patient. The cost of the treatment proposed by the DSS was calculated in the following way. If a generic class was the same in the two alternatives (actual treatment and the one proposed by the DSS), the drug cost for the DSS was set to the same amount as actual treatment, no matter what dose or brand was used by the physician. This ensured that there would be no difference in total cost when the same generic classes were used.

However, if the program proposed a generic class not used by the patient, the drug cost for three months was calculated according to recommended drug by the pharmaceutical committee of the county. Doses were selected to be equipotent with those used in Swedish Trial of Old Patients with Hypertension (STOP-Hypertension-2) (148), except for Renitec® (enalapril) doses, which were chosen both according to STOP-Hypertension-2 (20 mg o.d.) and according to the average doses used in actual treatment, which was 10 mg o.d.

11. Paper III

11.1 The Northern Sweden MONICA Study
The Northern Sweden MONICA (NSW MONICA) screening from 1999 was used in paper III to illustrate the application, on the population level, of the risk stratification scheme proposed in the 1999 WHO/ISH Hypertension Guidelines. Hypertensives without established CV disease, aged 30–74 years, from the NSW MONICA sample, were also used in paper V to compare two different risk assessment methods.

Screenings in the WHO MONICA Project were also conducted in 1986, 1990 and 1994. Data from these screenings were used in paper IV to obtain baseline values of major risk factors for individuals with incident stroke during follow-up and also to obtain baseline values for controls. These MONICA screenings were also used in paper V for estimation of cardiovascular risk functions applicable to Northern Sweden. An overview is given in figure 1 (next page).

The WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project was initiated during the early 1980s (149). The main
The aim of the study is to explore to what extent changes in cardiovascular morbidity and mortality over time may be explained by changes in population levels of classical cardiovascular risk factors (150, 151). The project has been implemented in 39 populations in 26 countries. The counties of Västerbotten and Norrbotten in Northern Sweden comprise one of the MONICA populations with 510,000 inhabitants, 291,000 in the 25–64 age group. A representative sample of this population, stratified for sex and age (25–34, 35–44, 45–54, and 55–64 years), was examined in 1986, 1990, and 1994. These examinations included blood pressure measurements, laboratory tests and a comprehensive questionnaire; for details see (152). Nurses conducted the interviews and the blood sampling. In 1999, the cohorts examined in 1984 (n=1,320), 1990 (n=1,266), and 1994 (n=1,591) were re-examined, together with a new random sample from 1999 (n=1,823) aged 25–74 years. Out of 8,359 invited, a total of 6,000 patients attended (72%), 5,997 with blood pressure values recorded.

### 11.2 Recorded data

The accuracy of the risk stratification of hypertensives relies on a comprehensive set of information about each patient. Data available and used in this MONICA material were age, sex, SBP, DBP, smoking, total cholesterol, diabetes mellitus, family history...
of premature cardiovascular disease, stroke, transient ischaemic attack, angina pectoris and myocardial infarction. Data on TOD were not available. Data on associated clinical conditions were based on questionnaire responses. Information on myocardial infarction and stroke was based on the following two questions: “Have you been hospitalised for a verified myocardial infarction?” and “Have you had a stroke (clot or haemorrhage)?” The diagnosis of heart failure relied on a combination of the following: presence of dyspnoea, taking diuretics and/or ACE-inhibitors and not taking drugs against hypertension. Presence of angina pectoris was based on responses to the Rose questionnaire (153). Blood pressure was measured twice by a random zero sphygmomanometer in the sitting position after a 5-minute rest (152). The mean of the two measurements was recorded. The random zero method was used to reduce observer bias and terminal digit preference (154), but the method has been found to underestimate BP (155, 156).

11.3 WHO/ISH risk assessment method

The 1999 WHO/ISH Hypertension Guidelines risk stratification scheme, shown in Table 2 (page 17), was designed to estimate the absolute risk of hypertensive patients as a basis for management decisions. The three levels of hypertension were: Grade 1 (140–159/90–99 mm Hg), Grade 2 (160–179/100–109 mm Hg), and Grade 3 (>180/>110 mm Hg). In Table 2, the blood pressure grades are presented on the horizontal axis.

On the vertical axis the presence of different risk factors is shown: (men >55 years/ women >65 years, current smoking, total cholesterol >6.5 mmol/L, diabetes, and a positive family history of cardiovascular disease before the age of 65), diabetes, TOD, and ACC. TOD includes: left ventricular hypertrophy (LVH), proteinuria, elevation of plasma creatinine, and atherosclerotic manifestations verified by ultrasound or X-ray. Associated clinical conditions includes: ischaemic heart disease, and cerebrovascular disease (including transitory ischaemic attacks), renal failure and peripheral arterial insufficiency.

Four categories of cardiovascular risk were defined: low, medium, high and very high risk. Each category represents a range of absolute risks of CVD. Within each range, the risk of any one individual will be determined by the severity and number of risk factors present as well as blood pressure level, calculated from Framingham data (55). The low risk group includes men below 55 and women below 65 years of age with Grade 1 hypertension and no other risk factors. Medium risk was defined as Grade 2 hypertension and no other risk factors as well as Grade 1 or Grade 2 hypertension with one or two risk factors. High risk includes patients with three or more risk factors, diabetes or TOD combined with Grade 1 or 2 hypertension, as well as Grade 3
hypertension without other risk factors. Patients with Grade 3 hypertension and one or more risk factors and all patients with clinical cardiovascular disease carried the highest risk of cardiovascular events, defined as 30% or more over 10 years.

11.4 Computer program for risk categorisation
In order to stratify patients according to the WHO/ISH risk assessment method, a computer decision support program was used. The program was adapted for this project, through facilities for database access, which made it possible to read MONICA data and put each subject into the right “risk cell” according to the WHO/ISH risk stratification scheme. The output was an ordinary Microsoft Excel file, which was further analysed in the Microsoft Excel 2000 program. This DSS was constructed using the same basic principles as the DSS for antihypertensive drug treatment. First the rules for BP categorisation were formalised using the method described for the drug treatment system. Secondly, rules specifying impact of risk factors, target organ damage and established CV disease were specified according to the description of the WHO/ISH risk stratification method given above. The version intended to be used by physicians was somewhat different from that used in the project. One major difference was the possibility to give as input several blood pressures taken at different dates in the clinical version. The DSS could then compute average BP and give recommendations depending on the number of BP measurements and on whether observation time was considered sufficient according to the WHO/ISH Guidelines. Another major difference was the implementation of written recommendations according to the WHO/ISH Guidelines in the clinical version. The physician specified the patient’s medical profile and received in response the estimated risk, whether drug treatment was indicated, target blood pressure and comments.

12. Paper IV
12.1 The Västerbotten Intervention Programme
In the county of Västerbotten in Northern Sweden a community-based programme for the prevention of cardiovascular disease (CVD) and diabetes, the Västerbotten Intervention Programme (VIP), was launched in 1985 (157). This programme combined a population-oriented and an individually oriented strategy. As one part of VIP all men and women in Västerbotten County were invited to a health screening and individual health counselling at their primary health care centre, at 30, 40, 50 and 60 years of age. By 1999, almost 60,000 individuals had participated, representing a participation rate of 60% of those invited. In a previous study, differences in social characteristics between participants and non-participants were explored. According to this, the social selection bias was small, indicating the Swedish primary health care service to be a rather unbiased base for educational health counselling (158).
12.2 The case-referent study
The case finding of stroke among participants in the MONICA and VIP screening was based mainly on three sources: discharge records from hospitals, reports from general practitioners, and death certificates. All cases with acute stroke (age group 25–74 years) and acute myocardial infarction (AMI) (age group 25–64 years) from the MONICA area have been included in the Northern Sweden MONICA registries since 1985. A nested case-referent design was used in which the incident cases were definite first-ever stroke events, classified according to MONICA criteria and identified during the period 1 January 1985 to 31 August 1996. We identified 166 individuals, who after participation in either the MONICA or VIP health surveys, suffered from a first-ever ischaemic or haemorrhage stroke before the age of 75. In order to avoid secondary behavioural effects, individuals with a previous AMI (n=15), or cancer diagnosis according to the Regional Cancer registry (n=13) were excluded. Also, 9 cases with a previous stroke event were excluded. Thus, 129 cases (107 ischaemic and 22 haemorrhagic; 83 men and 46 women) remained. Potential referents for each case were randomly selected among participants in the MONICA or the VIP surveys. They were matched for sex, age (± 2 years), type of survey (MONICA or VIP) and date (± 1 year) of health survey, and geographical region. Individuals were excluded if they had died or had moved away from the Northern Sweden MONICA region before 31 August 1996. Referents were also excluded if they were known from the Northern Sweden MONICA incidence registry to have had AMI or stroke before the health survey. An additional questionnaire was sent to all referents to further ensure absence of stroke and/or AMI in their history. Finally, two referents for each case were selected. However, one of the patients had only one corresponding matched referent.

12.3 Measurements of biomedical variables in VIP
Smoking habits were defined as those reporting (i) daily smoking of cigarettes, cigarillos, cigars or a pipe, (ii) ex-smokers and (iii) non-smokers. Individuals who reported being "occasional smokers" were classified as non-smokers.

In the MONICA surveys BP was measured twice by a random zero sphygmomanometer in the sitting position after a 5-minute rest, and the mean of the two measurements was recorded. In the VIP survey the BP was recorded after 5 minutes' rest. For subjects with blood pressure measured only in a recumbent position, adjustment for sitting posture was based on comparisons between sitting and recumbent position in 1,850 subjects within the VIP health survey. Systolic blood pressure (SBP) was divided into three groups according to clinical relevance: less than 140, 140–159 and 160 mmHg or higher. Diastolic blood pressure (DBP) was grouped into less than 90, 90–99 and 100 mmHg or higher. BP status was categorised as: (a) normotensive (SBP<140 and DBP<90 mmHg), (b) treated and adequately controlled hypertension (SBP<140 and
DBP<90), (c) treated but poorly controlled hypertension (SBP ≥140 and/or DBP≥90), (d) untreated hypertension (SBP ≥140 and/or ≥90 and awareness of having high BP), and (e) newly detected elevated BP hypertension (SBP ≥140 and/or DBP≥90 and the patient not aware of previous elevated BP).

For total cholesterol, four groups were judged clinically relevant: below 5.2, 5.2–6.49, 6.5–7.79 and 7.8 mmol/L or more. Samples for lipid measurements were obtained after a minimum of four hours’ fasting. Total cholesterol was measured using a bench top analyser (Reflotron®, Boehringer Mannheim GmbH Diagnostica, Germany) or by an enzymatic method (Boehringer Mannheim GmbH Diagnostica, Germany). Body Mass Index (BMI) was calculated as weight (kg)/(height in m)². Weight was measured in light indoor clothing and recorded to the nearest 0.5 kilogram and height was measured to the nearest centimetre, without shoes. BMI was divided into four groups, below 23, 23–26.9, 27–29.9 and ≥30 kg/m². History of diabetes was classified from the answer to the question “Do you have diabetes?” in the health survey questionnaire.

12.4 The cross-sectional study

As a second step the case-referent study categorisation of patients with elevated blood pressure (BP) was used to estimate the proportion of these categories among the VIP participants until 31 December, 1999 (altogether 59,735 persons). The purpose of this praxis study was to explore the extent to which the 1999 WHO/ISH Hypertension Guidelines were followed in the different categories (1).

12.5 Statistical analysis

Means for baseline cardiovascular risk factors were calculated for cases and referents. To evaluate the mean differences in risk factors, Student's t-test was used for continuous variables and chi-squared testing for distributions. A p-value less than 5% was regarded as statistically significant. Missing values for categorical variables were treated in the analyses as a separate category (omitted from tables). The data were analysed by univariate and multivariate logistic regression using the conditional maximum likelihood routine designed for matched analysis to estimate odds ratios (OR) with 95% CI and trends in odds ratios. To test the relation between increasing levels of risk factors and the risk of stroke, we categorised the continuous variables in clinically defined levels. In the cross-sectional study, means between blood pressure control categories were compared after adjustment for age differences using a General Linear Model.
13. Paper V

13.1 End-point definition
The three MONICA cohorts from 1986, 1990 and 1994 were used for estimation of risk equations for MI (fatal and non-fatal) and stroke (fatal and non-fatal). Only hospitalised patients registered in the Swedish Hospital Discharge Register with a primary diagnosis of acute MI or stroke were included as end-points in this study. Non-fatal MI included the following diagnoses according to the “International Statistical Classification of Diseases and Health Problems” (ICD), ICD-8 (410*), ICD-9 (410*) or ICD-10 (I21*, I46.1), and non-fatal stroke comprised the following diagnoses: ICD-8 (431*, 433* and 436*), ICD-9 (431*, 434* and 436*) and ICD-10 (I61*, I63* and I64*), i.e. haemorrhagic, thrombotic and undefined stroke cases. All subarachnoid haemorrhage or transitory ischaemic attacks were excluded.

From the Swedish Cause of Death Register, those with one of the above diagnoses registered as the principal death cause were included as fatal MI or stroke. The end-points had to be preceded in time by the MONICA screening examination. In patients with multiple cardiovascular events, only the first event was considered in this study. End-point data were collected from screening date until 31 December 2000.

13.2 Statistical analysis
The Cox proportional hazards regression model (159) was used to estimate the NSW MONICA risk functions. One equation was estimated for MI (n=91) and one for stroke (n=118). The estimated probability of an event was calculated as $P = 1 - [S(t)]^\beta$, where $S(t)$ is the estimated baseline survival function for time $t$ and $\beta$ is the sum of the products of the risk factor levels and the estimated coefficients. The baseline survival function was determined for 10 years as 0.000119 for MI and 0.0000812 for stroke. The risk factors included in the models were age, sex, SBP, smoking, cholesterol and diabetes. They were chosen to match the 1999 WHO/ISH risk factors as closely as possible. Using different factors could give highly different risk estimates in individual subjects merely because of differences in selected factors, compared to guidelines, which we wanted to avoid. We also wanted to include the risk factors typically used by physicians. Continuous variables were age and systolic blood pressure; categorical variables were sex, smoking (smoker defined as daily smoking or stopped within the last year), diabetes (yes/no) and total cholesterol level ($\leqslant 6.5$ mmol/L or $>6.5$ mmol/L). The diagnosis of diabetes was based on the following question: “Do you have diabetes?”

13.3 Framingham risk function and risk comparison
The Framingham risk equations for ten-year risk of myocardial infarction or stroke were used (55). Since the high-density lipoprotein (HDL) value was not included as a
risk factor and data on HDL were not available for the MONICA sample, the value 1.0 was used for all subjects in the equation. Information on left ventricular hypertrophy (LVH) was not available in the NSW MONICA population, and this value was therefore set to negative for all subjects.

Each subject in the study population was classified by a computer-based decision support system, into the four risk categories (low, medium, high and very high) defined by 1999 WHO/ISH Hypertension Guidelines. Risk factors considered were age, sex, total cholesterol level, current smoking, systolic blood pressure, diastolic blood pressure, diabetes and family history of premature cardiovascular disease.

In the next step the ten-year risk of fatal/non-fatal MI or stroke was computed for each individual in each of the four risk groups by the Framingham risk equations and by the risk equations derived from the NSW MONICA samples. The spread of individual risk values in each risk group was then compared to the risk interval proposed for each risk group by 1999 WHO/ISH Hypertension Guidelines.
RESULTS

14. Paper I

A CDSS for antihypertensive drug treatment was developed and the following main characteristics were implemented. The input comprised the medical profile of the individual patient concerning factors relevant for the selection of the drug class. In addition, ongoing antihypertensive drug therapy and non-usable drugs could be specified. For instance, a drug tested by the patient but rejected due to side effects could be labelled as non-usable. If ongoing antihypertensive drug treatment was specified, the DSS was programmed to find the most suitable addition to current treatment. If ongoing treatment included a contra-indicated drug it was discarded by the DSS. If no ongoing therapy was specified, a recommendation was given explicitly from the patient’s medical profile.

The feedback to the physician consisted of the follow main items:

- Medical profile specified by the physician.
- Contra-indicated drugs (if any) due to the medical profile.
- Ranking list of advantages and/or disadvantages (if any) of different drug classes in relation to the medical profile.
- Recommended drug or validated combination of drug classes.
- General comments.

The user must obtain a full account of the decisions and rankings made by the CDSS, in order to judge what relevance the recommendation has to the needs of the individual patient. The feedback is built to give a clear and concise summary of the factors emphasised by the guidelines. Figure 7 from paper I (next page) shows a typical summary including input, contra-indicated drugs (if any), advantages and disadvantages in ranking order and the drug class recommendations given. There are also a number of appropriate comments, which are issued to give additional information and guidance to the physician. If needed the recommendation can be printed. The CDSS can suggest up to five antihypertensive drugs in combination.

If the CDSS is unable to find a combination on the specified level it responds with “No drug found”. This could be the case if the patient has several ongoing drugs, if several drugs are not tolerated or contra-indicated. If there is no suitable combination there is certainly a need for consultation with a specialist regarding pharmacological treatment.

*Validated combination means that the combination in itself is correct, i.e. the combination can be used as such.
Bring hypertension guidelines into play

Fig. 7. Program response for an older patient with aortic stenosis and previous myocardial infarction. He has experienced side-effects from Ca-antagonists and is taking a thiazide with potassium-sparing agent.

15. Paper II

The average cost for one year of antihypertensive drug therapy for all 338 patients was 1,804 SEK, which was in accordance with earlier Swedish estimates of 1,600 and 1,700 SEK per year (160, 161). The corresponding annual cost for treatment based on the DSS was, according to given premises, 1,076 SEK, a reduction of total costs by 40%.

The CDSS proposed only a fraction of calcium antagonists used, but several times more thiazide diuretics than prescribed by physicians on the HCCs. Since the CDSS only implemented recommendations obtained from guidelines, it was obvious that thiazide diuretics were given to patients instead of calcium antagonists if the patient did not have any specific medical advantage from the calcium antagonist, see figure 2 from paper II (next page).

The doses and brand of drug chosen for each generic class of antihypertensives directly reflected the total cost of treatment. The following example refers to recommendations of the CDSS. For example, if Seloken-ZOC® (metoprolol CR) 50 mg o.d. or 100 o.d. was chosen for the DSS instead of Atenolol NM Pharma® (atenolol) 50 mg o.d. this gave a 1.6% or 3.5% higher total cost. This illustrates the potential further gain in cost-efficiency if the most inexpensive generic is used. Renitec® (enalapril) 20 mg o.d.
Fig. 2 Distribution of generic classes for treatment of hypertension, actually used compared to the distribution proposed by the DSS (n = 338).

gave a 7.4% higher cost for the CDSS’s drug profile than Renitec® 10 mg o.d. The distribution of Renitec® doses per day for actual treatment was: 2.5 mg (n=1), 5 mg (n=12), 10 mg (n=17), and 20 mg (n=11).

The treatment cost varied among the four health centres studied, but there was no correlation to the patients’ ages, blood pressure levels or the number of registered complicating factors, except that the health centre with the most expensive treatment also had the oldest hypertensive population.

Treatment cost correlated to sex: Men had a somewhat more expensive treatment than women and the same was true for the CDSS’s recommendation. The expense for actual treatment of women was 83% of the expense for men’s treatment. The corresponding figure for CDSS’s recommendation was 89%.

Current guidelines recommend different treatment regimes in hypertensives with complicating diseases, as stated above. The CDSS was programmed accordingly. For example, the CDSS give priority to beta-blockers in patients with prior myocardial infarction, migraine or ischaemic heart disease. In contrast, beta-blockers were not suggested by the DSS if asthma was present. Actual treatment was compared with the CDSS’s recommendation in patients suffering from complicating diseases such as previous myocardial infarction, diabetes, migraine, left ventricular hypertrophy or asthma. Nothing in the proportion of given drugs in groups with complicating diseases indicated that the quality of given treatment deteriorated due to the shift between thiazide diuretics and calcium antagonists; on the contrary, diabetics received more ACE-inhibitors, and those suffering from IHD received more beta-blockers.
In this study only 21% of the patients had systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg, as shown, which parallels the result in paper III where BP control in the NSW MONICA sample from 1999 was examined.

16. Paper III
The MONICA sample from 1999 included 6,000 patients (49% men, 25–79 years, mean age 54.2 years). Only one fifth of drug-treated hypertensives had their blood pressure controlled to <140/<90 mm Hg. More than two-thirds of those with high blood pressure did not take antihypertensive drugs. Most of them were unaware that they had high blood pressure.

In the drug-treated hypertensives with remaining high blood pressure (n=737) almost all had a medium or higher risk; in fact, 35% had a very high risk, figure 2 from paper III. In the untreated subjects with high blood pressure (n=1,773) the risk group pattern was more benign. The risk increased successively with age both for drug-treated and non-drug-treated subjects.

Out of 917 drug-treated subjects, 278 were below the age of 60. When target blood pressure was shifted from below 140/90 to below 130/85 (in our computer model) for these drug-treated subjects under 60, as recently recommended by WHO/ISH, the number of inadequately treated subjects increased by 34 (12% increase of inadequately treated in ages below 60 years), 14 of whom were in the low risk group, while 15 had one or two risk factors and thus belonged to the medium risk group, and only five had a high or a very high risk.
The risk stratification was extended into the normotensive range, which made it possible to stratify the whole population. There was a considerable difference in age between different risk groups, in the low risk group, 12% were aged 60 or above. The corresponding figures for the other risk groups were: 42% (medium), 69% (high), and 85% (very high).

Out of 5,997 subjects, 3,431 were normotensives. The distribution of all subjects with high blood pressure (n=2,566), not divided into treated/not treated, was different when the WHO/ISH risk stratification approach was used, compared with the distribution when only blood pressure levels were used. The borderline group was smaller if risk factors were considered as well.

17. Paper IV

All persons in the case-referent study were participants in a prior health survey. The stroke events occurred on average 36 months after the health survey. In 78% of the cases an event of ischaemic stroke (60 males and 41 females) occurred, 17% had an intracerebral haemorrhage (18 males and 4 females), while the remaining 5% stroke events (5 males and 1 female) had an unspecified stroke diagnosis.

The univariate analyses revealed diabetes, smoking, obesity (BMI ≥ 30), systolic and diastolic blood pressure, and BP status (c) treated but poorly controlled hypertension, and (d) untreated hypertension, to be important in predicting risk of stroke.

In the multivariate regression model we used the factors that were significant in the univariate analysis. Due to multicolinearity, BP status, but not diastolic and systolic blood pressure was included in the model. In this combined model only history of diabetes and BP status (c), treated but poorly controlled hypertension, and (d), untreated hypertension, proved to be important in predicting stroke, while smoking and obesity could not be shown to be independent risk factors, Table 3 from paper IV (next page). The risk of stroke associated with treated but poorly controlled hypertension was six times higher than for normotensives and well-treated hypertensives.

When applying the five case-referent hypertension categories to praxis, more than two thirds (69%) of the 59,735 VIP participants were normotensive, and 3% had adequately controlled hypertension (8% of all hypertensives, corresponding well with the result from paper III with 7% controlled hypertensives). Among the remainder, 15% had newly detected elevated blood pressure, 6% had treated but poorly controlled hypertension, while 7% had known but untreated hypertension. Population-attributable risk (PAR) of poorly treated hypertension was 46%, i.e. non-controlled blood pressure among people with blood pressure >140/90 in the survey explained 59
Table 3 Multivariate conditional logistic regression

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomedical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history</td>
<td>110</td>
<td>226</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>14</td>
<td>3</td>
<td>21.4</td>
<td>2.6 to 177.3</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>60</td>
<td>141</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>31</td>
<td>67</td>
<td>1.2</td>
<td>0.7 to 2.3</td>
</tr>
<tr>
<td>Daily smoker</td>
<td>35</td>
<td>45</td>
<td>1.7</td>
<td>0.8 to 3.3</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25 kg/m²</td>
<td>40</td>
<td>99</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>25–26.9 kg/m²</td>
<td>29</td>
<td>58</td>
<td>1.0</td>
<td>0.5 to 1.9</td>
</tr>
<tr>
<td>27–29.9 kg/m²</td>
<td>31</td>
<td>58</td>
<td>1.4</td>
<td>0.7 to 2.8</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>26</td>
<td>32</td>
<td>1.8</td>
<td>0.8 to 3.9</td>
</tr>
<tr>
<td><strong>Hypertension treatment categories</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (SBP &lt; 140 mmHg, DBP &lt; 90 mmHg)</td>
<td>33</td>
<td>107</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Treated and adequately controlled hypertension (SBP &lt; 140 mmHg, DBP &lt; 90 mmHg)</td>
<td>1</td>
<td>9</td>
<td>0.3</td>
<td>0.1 to 3.1</td>
</tr>
<tr>
<td>Untreated hypertension</td>
<td>23</td>
<td>24</td>
<td>4.3</td>
<td>1.7 to 10.5</td>
</tr>
<tr>
<td>Treated but poorly controlled hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, or both)</td>
<td>30</td>
<td>27</td>
<td>6.1</td>
<td>2.4 to 15.3</td>
</tr>
<tr>
<td>Newly detected increased BP</td>
<td>37</td>
<td>88</td>
<td>1.9</td>
<td>0.9 to 3.6</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, confidence interval; SBP, DBP, systolic and diastolic blood pressures; BP, blood pressure.

out of 129 stroke cases in the population. This means that half of all stroke cases would be eliminated if all hypertensives were adequately controlled. The normotensive participants were younger than the other four categories. Women were over-represented in all categories but newly detected elevated BP. The normotensive category showed a more favourable risk factor pattern in all respects, except for daily smoking. However, when the possible interaction between smoking and BP status was analysed, daily smoking and poorly controlled hypertension combined indicated the highest risk of stroke. Again, these two factors are identified to be of key importance for development of stroke, and consequently priority should be given to interventions against them.

18. Paper V

Hypertensives (n=1,781) in the NSW MONICA sample from 1999 were categorised into four different risk groups defined by the 1999 WHO/ISH Hypertension Guidelines, and in the next step the Framingham risk equations and NSW MONICA risk equations were used to compute risk for each individual in the various groups. The agreement was good when the values from the Framingham risk equation were averaged for each WHO/ISH risk group. The mean values were somewhat higher than the median values due to outliers with high risk.

The risk obtained with the NSW MONICA risk equation and the Framingham risk equation for those belonging to the low risk group is shown in Figure 2 from paper V. The box plot shows the median value, first and third quartile, maximum and minimum
values and outliers. All had a risk below the cut-off value for low risk (15%) defined by the guidelines, and half of the subjects had risk values below 5.6% and 2.5% respectively, a well-defined low risk group, and no one exceeded 15% in risk.

The ten-year risk distribution, computed with risk equations, for the medium, high and very high risk groups from the WHO/ISH classification, are also shown in Figure 2 from paper IV. The average risk increases for each risk group, but if the predicted risk for each individual is considered the risk varies from low to high depending on variations in risk factor values within the limitations given by the 1999 WHO/ISH Hypertension Guidelines.

The distribution of risk for different age groups (30–39, 40–49, 50–59, 60–69 and 70–74 years) in the medium risk group was calculated. As expected, the risk increases with more advanced age, reflecting the dominating importance of the age variable in cardiovascular risk equations.
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DISCUSSION

19. EviBase HT clinical decision support system for drug treatment of hypertension

19.1 Complexity of antihypertensive drug treatment

The objective of hypertension guidelines and guidelines in other medical domains is to summarise relevant scientific facts, but it is not only a passive accounting of published scientific work. Instead different results are weighted against each other and the quality of evidence is assessed and ranked. Billions are spent on clinical trials to establish best treatment regimes, and guideline authors perform a tremendous amount of work gathering and compiling all this abundant quantity of scientific evidence. This is compiled into recommendations about management of patients in routine clinical practice and distributed to the medical profession.

The 1999 WHO/ISH Hypertension Guidelines (1) and JNC VI (2) are likewise based on a comprehensive review and interpretation of current cardiovascular research, with the aim of improving management of hypertension. Recommendations concerning antihypertensive drug treatment in routine clinical care are an important part of the guidelines. However, antihypertensive drug treatment is complex and this is true despite the fact that every single recommendation given seems simple and easy to carry out. Although guidelines have been produced in large numbers during the past 20 years, the clinical impact on blood pressure control has been far from satisfactory, and the complexity of antihypertensive drug treatment is one of the factors counteracting adequate BP control. The rationale for a CDSS for drug treatment of hypertension is discussed as well as its medical concept, technical aspects and limitations.

The huge expansion of evidence-based knowledge concerning antihypertensive drug treatment is impressive but has led to increased complexity. Large clinical trials have established that certain antihypertensive drugs are advantageous if certain complicating diseases are present, e.g. beta-blockers in patients with IHD, ACE-inhibitors and angiotensin-II antagonists in heart failure or diabetic nephropathy. On the other hand, drugs can also be unfavourable in certain conditions, e.g. certain calcium antagonists in heart failure, beta-blockers in asthma. Every antihypertensive drug class has its own set of absolute contra-indications, which the physician has to consider. Furthermore, it is not possible to combine antihypertensive drugs randomly, either due to contra-indications or because of less BP lowering effect with certain combinations of drugs. Side effects can likewise contribute to the complexity of treatment and limit the number of available drugs.

By aggressive forced step-up drug treatment regimes, several large treatment trials have accomplished better blood pressure control than seen in everyday clinical practice.
Bring hypertension guidelines into play (68, 72, 162, 163) and we have learnt that combinations of two or more drugs are needed for most hypertensives to achieve target blood pressure. Large observational studies have found that systolic blood pressure is as important for the development of cardiovascular disease as diastolic BP (14). Large treatment trials have established that drug treatment of systolic hypertension is effective in reducing CV disease (77, 164-166). Since systolic BP is more difficult to control than diastolic BP, the need to combine drugs has increased (99).

While the total cost of treatment and health care is more of a political and ethical issue, the cost-efficiency is much more a medical issue for which the medical profession should take responsibility. Given two equally effective therapies, it is imperative to abandon the more expensive one, in order to maximise health benefits from the limited resources allocated to health care. As the knowledge base of medical evidence increases, is it important to discard ineffective or unnecessarily expensive therapies and managements to improve health care outcome, but at the same time increasing the demands put upon practising physicians.

The first-line drug is the one to use if no drug class has any special advantage or disadvantage for a certain patient. The concept of first- and second-line antihypertensive drug classes is based on proven efficacy, safety and scientific documentation. Thiazide diuretics and beta-blockers are well documented as being as safe and effective as newer drugs such as ACE-inhibitors, calcium antagonists, and angiotensin-II receptor antagonists. As add-on therapy the drugs most often used are alpha-blockers, loop-diuretics and spironolactone. Despite the superior cost-efficiency of thiazide diuretics and beta-blockers and the fact that all guidelines include them among first-line drugs, the use of thiazides decreased during the 1990s (167, 168).

To complicate matters further, marketing activities from large pharmaceutical companies have been intensive, focusing on factors with proven or theoretical advantages for their own drug. The information about antihypertensive drug treatment is now so overwhelming that the basic treatment rules have been blurred. Unless one is a specialist in the field, one will need guidelines to be able to treat patients in accordance with all these medical factors and accompanying rules. Making guidelines universally available has been the preferred way to support the practising doctor, but it soon became evident that implementation and use of new knowledge for individual patients was still difficult, and making the guidelines widely accessible has not yet been sufficient to make their content applied to individual patients in a busy practice. An elaborate examination of the steps necessary to comprehend and apply recommendations typically given in guidelines formed the basis for the development of a clinical decision support system for drug treatment of hypertension described in paper I.
19.2 From guideline to an applied medical decision

19.2.1 Find significant medical factors

Antihypertensive drug treatment is complex and difficult, but there are also a number of obstacles when guidelines are used to support a complicated medical decision. Some of these obstacles are described below.

Each evidence-based medical decision, e.g. concerning selection of antihypertensive drug, is based on an essential set of medical factors which must be considered by the physician, before an evidence-based decision can be made. This subset of factors is highly specific and significant for the decision at hand, and is drawn from the much larger set of medical factors within the domain of arterial hypertension. This subset should influence the decision (select drug class) in order to get the optimal outcome (effect on health and cost). Neglecting important factors or ignorance about one or more indispensable items in the subset jeopardises the quality of the decision.

It is up to the physician to recognise these factors and apply them when decisions are to be made concerning individual patients. This subset must be looked for in hypertension guidelines. However, in the guideline each factor is often described in its own context, e.g. grouped according to the drug class to which it belongs, not according to medical decisions. The consequence is that the information needed is scattered within the guidelines, making it difficult to extract those factors that are essential for a particular medical decision. Furthermore, patients' medical profiles are often subdivided into different categories contributing to further fragmentation, which can make the link between the decision and factors governing the decision even more obscure and difficult to apprehend.

19.2.2. Dependencies and individual values

Once the subset is characterised, the value of each factor has to be set. This collection of several variables, specific for each patient, has to be remembered by the physician during the decision-making process. Moreover, guidelines contain many dependencies, i.e. what is stated in one place in the guidelines could be overruled by another statement concerning another factor in a different part of the guidelines, forcing the physician to have a working knowledge of the entire guideline text. When all possible dependencies are cleared and the collection of factors governing the medical decision is found and given a patient specific value, then the phase of applying the evidence-based knowledge to the individual case begins.

19.2.3 Find significant rules to apply

What rules should be applied to the collection of data in order to finally find the correct answer? This is often the most complex and time-consuming part. Although
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each isolated rule is very simple, the complexity arises when these rules are combined. Assume that each rule consists of three possibilities a, b and c, and that you have nine rules none more complicated than three possibilities; you then end up with 19,683 possible combinations from these nine simple rules, and all must be taken into consideration simultaneously – a daunting task in a busy doctor’s office.

It will not be possible to describe each typical patient because of the exponential increase in alternatives. Instead each rule is described and arranged in some hierarchical logical order, e.g. according to drug class and within each class according to different diseases. The tricky part is to figure out the combined result of all these simple rules scattered all over the guidelines, each with different ranking and priority information attached to it. These are, briefly, some of the difficulties encountered when applying complex knowledge in key medical areas.

The key link between the evidence-based knowledge and the desired recommendation is the patient’s medical profile consisting exactly of the medical factors needed to take a high-quality evidence-based decision.

19.3 The EviBase medical concept

19.3.1 Defining decision to support

Guideline-based CDSSs must have a technical architecture capable of implementing a dedicated kernel for presentation and execution of rules and for distributing the system to users. But the technical solution has to be based on a medical concept which describes the premises for guideline-based CDSSs. The guideline-based CDSSs explicitly address problems associated with the use of guidelines to support clinical decisions.

The development cycle does not begin by an exhaustive search of the MEDLINE to gather all available information on antihypertensive drug treatment and in the second step try to cram all evidence-based knowledge into the CDSS. The basic approach is instead to define what key medical decisions the physicians have to make in order to give cost-effective and high-quality care (high-quality care has many dimensions, we are here referring to core medical decisions, if possible based on EBM). Selecting which persons with high BP to treat with drugs is one fundamental question. The next question is which drug class should be used, alone or in combination, to obtain blood pressure control. This process of finding appropriate and important medical questions requires profound medical knowledge of the particular medical domain and also knowledge of the environment (mostly country-specific issues) where the evidence is about to be used. In short, the CDSS must focus on important issues and it must be possible to base its solutions on evidence.
19.3.2 Choose guidelines
The medical guidelines on which to base the solution must meet certain requirements. As the selected guideline will be the medical anchor of the CDSS, any deviation from the guideline must be clearly stated in the output. The guideline itself must be recognised and cleared by some trusted authority. The evidence used must also be of importance to the physician and recognised by the physician. The EviBase concept is that of evidence-based medicine, and the user must also acknowledge this broader concept. The CDSS is a tool for applying knowledge that the physician understands, acknowledges and wants to implement, but is too complex for him/her to consistently implement in an accurate way in a busy clinical practice.

19.3.3 Specification of medical factors
Factors of significant importance for the decision have to be specified. Even though the CDSS is based on a specified guideline and evidence-based factors, there will always be delimitation problems. The most important and best-proven evidence should be included, while that of doubtful significance should be ignored or implemented as comments. In this stage specialist knowledge is required to decide which factors to include and where to make delimitations. It is important to understand that the quality of the CDSS is based on the amount of proven evidence in the guideline, not on precisely which factors are judged to be too uncertain to be included. A large amount of factors are not only of practical concern; uncertain factors interfere with proven evidence and could lead to poorer recommendations. It is not crucial to include as many factors as possible in the CDSS; instead it is crucial not to leave out important evidence while taking in less valuable factors. The definition of each factor is also an important development step; the purpose of these definitions is to make sure that the input of the medical profile will be as correct as possible. Also, the arrangement of the visual elements in the input box is designed to support an intuitive and correct input of data to the CDSS.

19.3.4 Specification of rules
The rules needed to make a decision for the medical profile fed through the interface to the system by the physician are those rules and recommendations specified and retrieved within the chosen guideline. In this step too, specialist medical knowledge will be required since not all recommendations in the guideline are always specified as clear-cut logic rules. When rules are executed the system should provide feedback to the user, in order to give a full account of the rules that have been applied to the medical profile.

19.3.5 Doctor–patient relationship
Not all factors and circumstances should be forced into the CDSS, rather as few
factors as possible. These few factors are those based on evidence, which of course limits the decisions the system could support. Factors that are not evidence-based or based on facts should not be implemented in the CDSS as rules, since there is no way to predict the validity or reliability of the result. For instance, dose adjustment could be a question that is better left to the physician and patient to agree upon. Particularly factors that are important for the doctor-patient relationship should be left out of the CDSS. It is important to remember that even if a medical decision is based on evidence, it is also heavily dependent on the interaction between the doctor and the patient.

19.3.6 Guideline recommendation vs. medical decision
It is crucial for the understanding of the meaning of the CDSS's output to separate the medical decision made by the physician from the recommendation obtained from guidelines; although they may often be the same, they are not always so. The medical decision is made by the physician from all information available and in concordance with the patient, while the recommendation obtained from guidelines concerns the medical profile alone. The CDSS does not provide medical decisions. The CDSS is not a replacement for a physician, on the contrary. However, it supports the decision making by supplying the recommendation given by the guideline in response to the patient's medical profile. This guarantees that evidence-based factors will be considered or at least known by the physician in the decision-making process.

19.3.7 Incentive to use
The incentive to use the system should be its ability to facilitate clinical decision making for the individual physician. It helps the physician to make a complicated decision when dealing with common therapeutic problems and at the same time implements the knowledge and preferred behaviour built into the evidenced-based medical guidelines. This is possible due to the concentration on a few key issues.

19.3.8 Educational function
The idea is to remind the doctor of key therapeutic principles each time the CDSS is used. The preferred management of a certain medical issue is not only provided in the answer, but also built into the user-interface of the CDSS. The medical profile, the definition of its components and the wording of comments are intended to remind the user of the underlying evidence and principles put forward in guidelines. The repeated reminders of certain key elements and management sequences are built into the very use of the CDSS. The checkboxes with the request for key data are in their simplest form just a reminder of what is imperative to consider before making the decision.
One important source of evidence-based medical knowledge widely used today and easy to access from one's own computer is MEDLINE and other databases with huge amounts of medical information. Other examples are large sites dedicated to medical information, advertisement and collegial interaction, e.g. MedScape®. Guideline-based CDSSs, on the other hand, reside on the other end of the support spectrum providing support for key medical decisions.

19.3.9 Summary of basic features
The guideline-based CDSSs explicitly address problems associated with the use of guidelines in clinical practice by: (i) focusing on key medical decisions; (ii) presenting the collection of factors\textsuperscript{b} needed to make an evidence-based decision; (iii) keeping track of all relevant dependencies within the guideline; (iv) automatically processing the set of values following the rules stated in the guideline; (v) giving the recommendations for this particular medical profile.

The physician has to recognise and acknowledge the existence of a medical problem, and gather the values needed to submit the medical profile of the patient. The final analysis is made by the system and a statement that justifies the given recommendation is issued back to the physician. This statement together with information and knowledge not derived from the CDSS is finally compiled into a medical decision taken in mutual understanding between the physician and the patient.

The basic idea is to facilitate the use of knowledge by replacing the general description in the guideline by a specific description relevant for a certain individual or a certain medical profile. In other words, it should be easy for a physician to obtain the guideline recommendation for a given patient regarding the medical decision at hand.

Interaction between the user (physician) and the CDSS goes through the interface consisting of the medical profile of the patient. The medical profile is the raw material to which the knowledge derived from the underlying guidelines will be applied.

19.4 Formal representation
Medical decision-making is complex, and many steps in the decision-making are not obvious for a layman. The text, figures and tables in the guidelines must be described in a formal way, be reproducible, understandable and unambiguous. An important step in the development process includes a careful and thorough description of the factors involved in the decision, dependencies and how these facts interact to give the correct answer. A brief example of the formal representation of knowledge is given in the method section (paper I). A brief description of the technical architecture is given below.

\textsuperscript{b}A factor could be age (value 59) or systolic blood pressure (value 160) or diabetes (value yes/no) and so on.
19.5 Technical architecture
The technical architecture concerns the implementation of a dedicated kernel for presentation and execution of rules, internal and external communication, platforms, update, interfaces, installation, and distribution. The physician navigates to the prepared web page in order to use the CDSS.

The CDSSs are web-based and there are two main advantages with web versions. Firstly, there is no need for program installation on the client computer, avoiding considerable quantity of work. Breakdowns due to program incompatibilities when installing new programs are also avoided. Secondly, updating of current CDSSs is done in one place and additional CDSSs are in the same way installed on one server for all users, instead of program installation on each individual computer.

The EviBase Web system is currently being developed on a Windows NT (Win2000) platform for the server part, and Microsoft Internet Explorer (version 5.5+) for the client part. The application is delivered by standard web technologies. Application framework is implemented using Microsoft C++. For the whole system there are multiple programming languages involved; Microsoft C++ and JavaScript for server and client functionality, XML as an interface language, and HTML for client presentation. EviBase Web site is hosted by a commercial internet provider.

Ideally the platform should support all available hardware from personal computer platforms to handheld devices, computer pads and mobile phones.

The logic part is not limited in any way except for the parameters sent from/to the logic. Basic features of the EviBase systems are: (i) to be able to implement new CDSSs for various medical decisions whenever it is necessary and cost-effective to do so, (ii) when the logic module is in place it will run automatically on every device connected to the Internet, (iii) to maintain and update these CDSS.

The CDSS is a stand-alone application and can be used simultaneously with any patient record system. One “logic module” is a totally stand-alone component, and the system is not dependent on other modules on the client side. The architecture can use any security mechanism supported by the web browsers (i.e. server certificates using 128-bit encryption). However, no critical or personal identification is currently being transferred, only a medical profile submitted by the physician.

19.6 Usage in practice
It is important to separate the medical decision and the actual execution of that decision when it is made, e.g. the physician wants to know what antihypertensive drug class
patient A is recommended. He/she opens the EviBase window, supplements the patient-specific factors that govern this decision. He/she finds that the patient, according to the guidelines, should be given a thiazide diuretic and that it is highly cost-effective to do so. The EviBase is not needed anymore, the physician proceeds to execution of the decision (whatever that decision is), which will be done in the ordinary practice management system used for prescribing and documentation.

Why should a health care provider be interested in a CDSS? The cost-effectiveness is heavily dependent on key medical decisions, decisions made by physicians on a daily basis. Antihypertensive drug treatment costs from about 400 SEK to 2,500 SEK yearly depending on drug, statin treatment costs about 4,500 SEK yearly, and therapy is intended to be lifelong. Treating hypertension according to guidelines has the potential to save about 40% of antihypertensive drug costs in Sweden. We must pinpoint the most important decisions in each medical domain and try to support these decisions by the most updated and high-quality information available and then help the physician to implement this knowledge in clinical practice.

19.7 Limitations
We don’t yet know whether guideline based CDSS will be of any practical use to busy physicians. Secondly, only a very limited number of decisions can be supported in this way. Most medical decisions are far too complex to be handled in this way. Thirdly, and perhaps most important, the CDSS cannot be better or more trusted than the guideline which it is based upon. Also, a guideline cannot be better than the scientific evidence that it is founded on. A general-purpose programming language was used to develop the CDSS and this imposes some limitations: (i) it does not per se support implementation of logic-based rules, instead a dedicated kernel for representing and execution of rules has to be implemented; (ii) very complex problems have to be broken down into manageable pieces; (iii) the technical implementation requires a professional programmer.

20. Guideline-based antihypertensive drug treatment
Actual antihypertensive drug treatments given by physicians were compared in paper II to treatment recommended in hypertension guidelines. The strength of this study being the fact that the antihypertensive drug treatment proposed by the CDSS was influenced in a very elaborate way by available data in the patient record, in accordance with recommendations in guidelines. In this way the cost for antihypertensive drug treatment could be reduced by 40%, while keeping the amount of drugs and doses equal to actual treatment given by physicians. Another strength is that the principles used to accomplish this are well founded and mostly based on evidence from randomised controlled trials.
Bring hypertension guidelines into play

Paper II gives strong evidence for the opinion that the potential for cost saving with maintained treatment quality is great in hypertension, the weakness being the fact that it is a potential, not an obtained saving in a randomised controlled trial. Furthermore, the introduction and use of CDSSs by physicians can effectively be prevented by a heavy workload that hinders every effort to bring about management changes.

Changes in drug prices will of course have a huge impact on treatment cost. Perhaps the difference in cost will become less startling in the future. The opposite scenario is also possible, if new expensive drugs are introduced to the market. Since BP control was poor (21% controlled to <140/<90 mm Hg) and the average number of drugs given was about 1.5 it can at least be speculated that a CDSS that makes it easy to combine antihypertensive drugs can contribute to better BP control among patients that need several drugs. Furthermore, since the CDSS always proposes a thiazide-diuretic, if not already given or if no compelling indication exists for another drug class, it is likely that the proposed treatment will be cost-effective.

Future challenges lie in studies defining CDSS usage, user satisfaction, user behaviour changes and effects on blood pressure control and treatment cost. To prove benefits by following hypertension guidelines concerning antihypertensive drug treatment on hard endpoints would require a large randomised controlled trial, and it is unlikely that such a trial will be carried out, if only for funding reasons. Another question concerns physicians' willingness to comply with evidence-based medicine and guidelines. Physicians who actively want to diverge from guidelines will not use a CDSS based on such recommendations. How large this group is compared to those who want to follow guidelines but for various reasons are unable to do so, is to my knowledge unknown.

21. Cardiovascular risk estimation

21.1 Blood pressure and risk estimation

Several aspects of high blood pressure have been studied in papers III, IV and V, and our findings will be discussed in relation to the current management of hypertension. Much of the data used are from Northern Sweden, and are therefore of high relevance for our own locally adopted treatment and management policy of hypertension. Data from the NSW MONICA study and the Västerbotten Intervention Programme tell us that high blood pressure is very common, and those with high blood pressure carry high risks of future cardiovascular disease. We can only conclude that treatment of blood pressure is poor, with a minority obtaining target blood pressure, and also that those inadequately treated carry a six fold increased risk of stroke compared to those adequately treated.
As resources, both time and money, are limited, it is of paramount importance that resources are allocated optimally to maximise outcome. The cost-efficiency of antihypertensive drug treatment is heavily dependent on short-term absolute risk of CV disease, and what is needed is an easy to use, yet accurate, risk prediction tool intended for use by busy physicians in the clinical setting. The fact that there are many different interventions, targeted at many different risk factors and all with different efficacy and price tags, makes resource allocation even more complicated. The risk estimate is not only used by health professionals in decision making but also to motivate patients to take appropriate actions.

**21.2 Blood pressure is not enough**
The prevalence of hypertension in the community is high (89, 107, 169), the increase in risk begins already at a blood pressure level of 115/75 mm Hg (14), and the risk increase associated with high BP applies to all ages; the consequences in disease events occur in the normal and high normal range of the BP scale as well as in mild, moderate and severe hypertension. Despite all this, the benefit of antihypertensive drug treatment is much more closely correlated to the global cardiovascular risk of the individual than to the exact BP level (1, 2).

These circumstances make blood pressure inadequate as a single determinant of how to manage hypertension, e.g. for specifying the intensity of preventive interventions and drug treatment. In consequence, most hypertension guidelines now acknowledge global risk estimation as an important part of hypertension management [1,2,3].

**21.3 Risk burden**
In paper III the NSW MONICA sample from 1999 was categorised according to the risk stratification scheme proposed by the 1999 WHO/ISH Hypertension Guidelines, in order to obtain an idea of the amount of risk in the hypertensive population [1]. One of the main findings was that drug-treated hypertensives also had a high associated risk of CV disease, and among drug-treated hypertensives not attaining target blood pressure 87% had medium, high or very high risk according to the guidelines.

Moreover, it is well known that hypertensives have more severe risk factor profiles than non-hypertensives, also known as risk factor clustering (43, 170). From data in paper IV it is also indicated that the metabolic profile among hypertensives is more unfavourable and drug-treated hypertensives seems to be a selected group of high-risk individuals.

**21.4 Comparing guidelines with risk equations**
The risk stratification proposed in the 1999 WHO/ISH Hypertension Guidelines is easy to use but implementation of age is weak and the medium risk group includes a
variety of risk factors and risk levels. By comparing each risk group defined by the 1999 WHO/ISH Guidelines with risk equations, we wanted to evaluate the spread of risk within a risk group due to variations in number and level of risk factors.

21.5 Risk equations

21.5.1 Risk equations used
Risk equations are used to get a more accurate individual risk prediction than obtained with the crude categories of the guideline. Risk equations, as a means of evaluating the WHO/ISH risk categorisation scheme, have several properties that make them suitable for that purpose. The risk equations assess the combined effect on risk of all risk factors and can use their exact values in the calculation, e.g. it is crucial to obtain a reliable estimate of the impact of the age variable since age is a dominating factor when absolute risk is calculated.

Primarily our aim was to develop a NSW MONICA risk equation and use that equation on the 1999 NSW MONICA cohort. The main comparison was planned between the 1999 WHO/ISH Hypertension Guideline’s risk groups and risk equations derived from previous MONICA samples in Northern Sweden. In this way both the risk spread and the absolute risk could be assessed.

Unfortunately, there were too few events during the follow-up of the MONICA samples from 1986, 1990 and 1994, and it was impossible to attain significant coefficients for all desired risk factors. This forced us to use the Framingham risk equations as well, in order to ensure that risk spread was not a chance finding. However, using the Framingham risk equations also had advantages, one being the fact that WHO/ISH Hypertension Guidelines’ authors had used risk estimates from the Framingham cohort to calculate risk levels in the four risk groups of the risk stratification scheme. Another was the possibility to compare differences between equations, while keeping in mind that these functions are not interchangeable. Absolute risk levels calculated with the NSW MONICA risk function were lower than the risks produced by the Framingham risk equation. This difference in absolute risk levels is explained by several factors: (i) there is a more restrictive definition of events in the NSW MONICA risk equation; (ii) it is based on a more recent material than the Framingham equation and reflects a decreasing incidence of coronary heart disease during the 90s; (iii) it has previously been shown that the Framingham risk function overestimates the risk of coronary heart disease when applied to Swedish populations, especially in subjects with few risk factors (11).

21.5.2 Included risk factors
Physicians and others often point out the fact that certain risk factors are missing in guideline algorithms or risk equations. The main reason for not including all factors is
that it is uncertain whether all factors have independent risk contribution exceeding that of the major risk factors. But this does not imply that they are clinically unimportant; on the contrary, they are very important since they influence the major risk factors. The important thing is always to incorporate the major risk factors as the basis for your decision and of course to give other factors some consideration as well. However, estimation of cardiovascular risk is not a critical issue for advocating interventions against smoking, obesity and physical inactivity.

The use of predisposing risk factors in risk equations is prevented mainly because they are difficult to quantify in a reliable way (food intake, physical activity and psychosocial factors) and secondly their independent contribution to CV disease beyond that of the major risk factors has been difficult to establish (23, 57), even if associations have been found in a number of studies (171-173).

The 1999 WHO/ISH risk stratification scheme specifies which risk factors to use, and we wanted to apply a risk function that matched these as closely as possible. A drawback with risk functions is that factors not included in the function have no impact on the risk estimated by the function. Using risk factors other than those included in the guideline specification could yield highly different risk estimates on the individual level just because of difference in the selected set of factors. The risk factors used by the guideline were also considered as well established major risk factors and widely used by physicians.

21.5.3 Average vs. individual risk
Is it fair and meaningful to compare these equations with the algorithm proposed in the 1999 WHO/ISH Guidelines; after all, each WHO/ISH risk group has been found to correlate to increased risk (162, 174). Furthermore, the Framingham risk equations have been used to estimate absolute risk in each of the four risk groups by the WHO/ISH Guidelines' authors. However, the crucial point is that average risk for the whole group is not equivalent to the risk experienced by each individual in the group, i.e. half of the subjects may have low risk and half high risk, but the group as a whole will have medium risk. Problems arise when the crude risk categorisation is applied to individuals, particularly as the result is intended to be used as a basis for treatment decisions. As the spread of risk increases within the category, the risk of misjudgement of individual cases increases, and that must be observed and corrected by the physician.

21.6 Who and how?
21.6.1 Global risk estimation
It may be obvious that global risk (defined as absolute risk of an event (MI, stroke or CV death), i.e. number of events in a certain period of time divided by population
count) has to be considered before a decision about intervention level is made. But it is somewhat less obvious for whom this global risk estimate is relevant and how to carry out this global risk estimation. Both underestimation and overestimation of future risk will cause a deviation from optimal treatment (optimal is here defined as the best use of available resources).

21.6.2 High risk groups
In two groups of hypertensives interventions are mainly governed by other circumstances than absolute risk: (i) an extreme deviation of one risk factor, which can often be a sufficient reason for intervention, e.g. familial hypercholesterolemia, severe hypertension and smoking; (ii) those belonging to high risk groups by definition (those with diabetes, target organ damage or established cardiovascular disease). The consensus is unanimous in most guidelines about these categories; they should be treated down to a target level of <140/<90 mm Hg and in certain subgroups even lower. Every individual in the specified group is at such a high risk now or in the foreseeable future that drug treatment is warranted.

For the remaining hypertensives global risk estimation is necessary and gives valuable and indispensable information about treatment benefits. This confines the clinically useful estimation of absolute risk to the low and medium risk categories according to the 1999 WHO/ISH risk stratification scheme for predicting absolute cardiovascular risk.

21.6.3 Medium risk group
The medium risk group as defined by the 1999 WHO/ISH Guidelines is heterogeneous, large and heavily dependent on diagnostic efforts to find TOD. Furthermore, when risk for each individual in the medium risk group was estimated by risk equations, the risk spread was large. In fact, when the Framingham risk equation was used, about half of the individuals in the medium risk group had a lower risk than that specified by WHO/ISH Guidelines and one quarter had higher risk. This spread of risk was caused by variations in age and risk factors within the boundaries given by the guidelines for each risk group. The conclusion from our work in papers III and V is that the WHO/ISH risk stratification scheme is valuable and easy to use, but that it is not accurate enough for the heterogeneous medium risk group, see figure 2 next page.

Instead I propose for the medium risk group a complementary risk estimation performed by a suitable risk equation. Risk equations need computation, e.g. by a CDSS or by using already calculated risk charts, e.g. those included in the New Zealand hypertension guidelines (175). The risk section of this thesis discusses some pitfalls and flaws concerning the use of risk equations and that discussion will not be repeated here.
21.6.4 Low risk group
The low risk group, according to the 1999 WHO/ISH Hypertension Guidelines, seems to be a well-defined low risk group, both according to the guideline algorithm for risk categorisation and according to risk estimates by equations from the Framingham Heart Study or the NSW MONICA Study. It is important to realise that this group of mild hypertensives is devoid of other risk factors, which makes them unusual, and furthermore they are young (male <55, female <65 years).

Further analysis showed that there was no large group of low risk patients with mild hypertension that accounted for a majority of poorly treated hypertensives. This is despite the fact that the MONICA data did not include information about target organ damage. Intense diagnostic efforts to establish the presence of target organ damage would have reclassified a substantial part of the low and medium risk group into the high risk group, further increasing CV risk (176-178). Only about one fifth belonged to the low risk group, hence four out of five had medium or higher risk, and this pattern was even more pronounced among poorly treated hypertensives (only 13% had low risk), see paper III.

21.6.5 Borderline groups
One nice feature of the risk stratification scheme described in the 1999 WHO/ISH Hypertension Guidelines is that it does not create huge borderline groups. Those with high normal BP and mild hypertension are a large, heterogeneous group, and if BP alone is used to decide whether drug treatment should be initiated or not, it will be very difficult to make a correct clinical decision. The risk stratification produces a low risk group, which is well defined and seems to contain only low risk patients, also when estimated by risk equations.

Figure 2. It is important to determine absolute risk for individuals in the medium risk group, e.g. by use of risk equations. Those with several risk factors, diabetes, target organ damage, established CV disease and severe hypertension should always be treated. The low risk group is well defined, and in this group drug treatment is not urgent.
22. Tougher target blood pressure for younger people

In paper III the impact of a lower BP target level for those below the age of 60 years was simulated, and the result showed that this would (not surprisingly) predominantly affect those with low and medium risk, and if it is not a mistake by the guideline committee, it is not consistent with the overall stated view in the WHO/ISH Guidelines to adjust the intensity of preventive measures depending on current risk. Of course, it could be speculated that intense treatments early will yield even less target organ damage and CV disease in the long run, which probably is true, but the cost-efficiency will probably be low, especially if the outcome measure is the number of events averted.

23. Absolute risk

Although risk equations certainly have many flaws and there are several pitfalls before they can be used in a reliable way, is it difficult to argue against risk equations as the best tool today for predicting absolute risk. The management of the medium risk group will be intensively discussed in the coming years, and I doubt that risk equations will put a final end to that discussion. The reasons for this is that absolute risk also has its shortcomings apart from the difficulties discussed earlier in this thesis.

Absolute risk as a measure of treatment benefit constrains drug treatment for a limited group with high risk, and the money spent will give the most possible averted events. As resources increase/decrease or costs change, the cut-off limit for intervention could be reduced/increased, still giving maximum averted events. Could it be any better?

However, the importance of absolute risk diminishes at both ends of the age scale, because young people always have low short-term risk due to the slowly progressive nature of cardiovascular disease, and for the same reason elderly have high risk, irrespective of risk factor levels. High cut-off levels of absolute risk before drug treatment is initiated will yield a high cost-efficiency, but most events will happen before treatment is started (179) and the dominating factor for when drug treatment is given will become old age.

Another recommendation given by the Second Joint Task Force of European and other Societies on Coronary Prevention was to project the risk to the age of 60 years, for younger people, to neutralise the age variable (33). This is less explicitly expressed in the New Zealand guidelines, which transfer the responsibility to the physician by wordings like “whether the benefits of treating the elderly should be discounted according to age, or alternatively a premium accorded younger people to be treated at a lower risk level, is a complex issue and difficult to adjust for in a risk equation” (175).

The trouble with absolute risk is that it gives equal weight to a death from coronary heart disease at 55 as at 80 years. It could be asked whether life years gained would not
be a better measure of treatment benefit than number of events averted in a specified time (179).

Using absolute risk in preference to life year gained or relative risk postpones treatment to older age, e.g. a 35-year-old with a doubled relative risk has to wait until age 60 before absolute risk reaches 2% yearly or 75 years before he reaches an absolute risk per year of 3% (179). The measure chosen for treatment benefit influences the choice of individuals that seem most advantageous to treat. If the number of events averted in five years is the outcome measure, then absolute risk will predict the most efficient therapy. If life years gained per year of treatment are instead considered, then more resources will be allocated earlier in life to those with high relative risk (179).

The preferred way to reduce high long-term risk, if short-term risk is low, is modification of lifestyle habits and then later on, if the short-term risk eventually rises to a high level (if lifestyle changes fails) initiating drug treatment. The drawback is of course that those just under the cut-off limit for treatment will never be treated or that drug treatment will be introduced late in life when most individuals in that category have already accumulated most of their lifetime events (179).

24. Limitations
What then are the limitations of papers III and V? The common and most important shortcoming in these two articles is the lack of data on target organ damage. Information about target organ damage is important and has consequences for both studies. The consequences are however predictable and are not crucial for the main conclusions drawn from the results. However, it is indisputable that the risk in the low and medium risk groups is underestimated when data on TOD are lacking. While proteinuria is relatively uncommon among mild and moderate hypertensives (180) without diabetes or established CV disease, left ventricular hypertrophy is prevalent (181, 182). The prevalence of LVH, diagnosed by electrocardiography, in hypertensives cared for in primary health care in Sweden has been estimated at 22% (183) and in the ALPINE study of newly detected hypertensives, conducted in Northern Sweden in 2001, the prevalence was 17% [Lindholm, et al. J Hypertens. In press]. Investigation by ultrasound and echocardiography would transfer additional individuals from the low and medium risk group to the high risk group. However, this fact would only have strengthened our finding that people with high blood pressure often carry a high risk of cardiovascular disease.

The MONICA study is population-based, i.e. a sample that represents the whole population within the catchment area. The MONICA sample is stratified according to age and sex, and this gives an overrepresentation of older individuals. Furthermore, there was a lower participation rate particularly among the youngest. With adjustment
for this, the low risk group increased from 16.2% to 22.6% among those not treated and from 5.5% to 13.0% among drug-treated hypertensives. Individuals seen at health care centres are probably somewhere in between these figures, because unawareness, especially among young men, is high (99).

Blood pressure is measured on one occasion, and some of those with high blood pressure at the MONICA screening would have lower blood pressure in repeated measurements. Blood pressure was measured using the random zero equipment, which slightly underestimates blood pressure. In the group “aware of having high blood pressure”, 65% also had high blood pressure at this MONICA screening, and the consistency of high blood pressure between 1994 and 1999 was 61%, which indicates that about two thirds had hypertension.

25. Blood pressure control
The size and importance of the hypertensive disease has successively been discovered, and several large studies have established high BP as a common, dangerous and important condition both for number of deaths and for lost years of life worldwide (9, 10). Epidemiological studies have verified that hypertension is very common (7), and the same was found in the 1999 MONICA sample.

In the 1999 NSW MONICA sample only 20% of drug-treated hypertensives had obtained target blood pressure, although the dangers of inadequately treated BP have been known for a long time. Blood pressure control in the Västerbotten Intervention Programme was 29% among drug-treated hypertensives, reflecting that participants in the VIP were younger than in the 1999 MONICA sample (average age 47 vs. 54 years).

These results, although disappointing, with the vast majority not obtaining adequate BP control, are consistent with results from many other countries, see table 3 (page 22). It is unusual to attain BP values below 140/90 mm Hg, which emphasises that antihypertensive drug treatment is difficult. A majority were not aware that they had high blood pressure, which is surprising since many studies have reported rather high values for awareness and treatment (95, 96, 100). Of course, not all will have hypertension when strict diagnostic criteria are applied, but we estimate that about two thirds of those with high blood pressure and not drug-treated would in fact have hypertension.

Paper IV also illustrates risk factor clustering in hypertension; those with high blood pressure had a high prevalence of obesity, and greater lipid and glucose concentrations. All of these factors will increase the risk of cardiovascular disease.
26. Management of hypertension
One important reason for poor BP control is of course changed treatment recommendations, with successively lower target levels as new discoveries from RCT have emerged. Studies showing that elevated systolic blood pressure is as bad as elevated diastolic blood pressure, and the efficacy of treating isolated systolic hypertension, have imposed further treatment demands.

Most uncontrolled hypertensives have a systolic blood pressure between 140 and 159 mm Hg, and might be dismissed by physicians as not necessary to treat, if the cardiovascular risk is not observed and apprehended. It is not yet fully understood that the benefit of treatment is much greater in a patient with a very high risk and a systolic BP of 140 mm Hg than in a person with low risk but a systolic BP of 160 mm Hg, and therefore a majority of older patients between 140 and 159 mm Hg are not treated adequately for their hypertension or even recognised as being hypertensives.

It must also be emphasised that a majority of hypertensives will not be controlled down to <140/<90 by one drug alone. Management of high blood pressure is numerically a huge problem, but above all a complex and time-consuming problem. However, we are not empty-handed in dealing with our most prevalent disease. Effective treatment exists and it is up to the medical profession to give this treatment to those at risk of cardiovascular disease together with high blood pressure.

Knowledge about hypertension, its risks, and how to avoid them is rapidly expanding, but the implementation is seriously lagging behind. While knowledge expands, so too does the complexity of management, and it becomes more and more difficult to actually carry out treatment recommendations tailored for the individual. The complexity is due to the many factors involved in the treatment decision, and the difficulty is due to the need for several consultations and several drugs used together and prescribed over a long period of time. The attitudes towards and understanding of cardiovascular risk associated with mild or moderate hypertension are important for willingness to treat and for the apprehension of patient benefit from drug treatment.

Could a clinical decision support system targeted at certain key decisions in the management of hypertension be useful in obtaining better blood pressure control and more efficient and cost-effective drug treatment? This could be obtained by better compliance with guidelines and easy access to information about how to combine several antihypertensive drugs in those needing several drugs in order to attain an acceptable BP in relation to their cardiovascular risk. However, the implementation and evaluation of CDSS in clinical practice is still to be done. As time for disease management decreases and the burden of bureaucracy increases, a real effort will be needed to enhance the management of hypertension.
Bring hypertension guidelines into play
CONCLUSIONS

- The prevalence of hypertension in Northern Sweden is high and the majority with high blood pressure are also at medium or high risk of developing cardiovascular disease.
- A majority of drug-treated hypertensives are poorly controlled and the risk of stroke is six times higher among poorly treated than among those with well-controlled blood pressure.
- Estimation of cardiovascular risk is important for selecting those to treat with antihypertensive drugs.
- The 1999 WHO/ISH Hypertension Guidelines risk stratification scheme is easy to use but is not accurate enough for the medium risk group where risk estimation by risk equations is recommended.
- Evidence-based treatment of hypertension is needed, even though antihypertensive drug treatment is complex and difficult.
- A clinical decision support system for drug treatment of hypertension was developed, supporting evidence-based selection and combination of antihypertensive drugs.
- Drug treatment according to recent hypertension guidelines could reduce costs by 40% with maintained BP lowering and treatment quality.
Bring hypertension guidelines into play
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