Summary and conclusions

Moderately Elevated Blood Pressure

A Systematic Review

Revision of SBU Report Moderately Elevated Blood Pressure (2004), no 170/1

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Summary and Conclusions of the SBU Report:

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September 2008

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SBU's Conclusions

Prevalence of High Blood Pressure

- ❑ An estimated 1.8 million people in Sweden, or 27% of the adult population (aged 20 or older), have high blood pressure (hypertension). The condition is just as common among women as men.

- ❑ Of the 1.8 million Swedish adults with elevated blood pressure:
  - 60% have mild hypertension (140–159/90–99 mm Hg)
  - 30% have moderate hypertension (160–179/100–109 mm Hg)
  - 10% have severe hypertension (≥180/≥110 mm Hg)

- ❑ Studies in Sweden find that the number of patients who reach the treatment goal of blood pressure below 140/90 mm Hg rarely exceeds 20–30% of those who have been prescribed blood pressure lowering drugs.

Risk Factor for Cardiovascular Disease

- ❑ Elevated blood pressure is a risk factor for coronary heart disease, stroke and other cardiovascular disease, including heart failure (Evidence Grade 1). High blood pressure is also a risk factor for dementia (Evidence Grade 3).

- ❑ An increase of 20 mm Hg in systolic pressure or 10 mm Hg in diastolic pressure above 115/75 mm Hg doubles the risk of death from cardiovascular disease (Evidence Grade 1). The increase is independent of other risk factors for cardiovascular disease, and it is similar for women and men (Evidence Grade 1).

- ❑ Women have a lower *absolute* risk of cardiovascular disease than men (Evidence Grade 1). However, blood pressure lowering treatment reduces *relative* risk equally in women and men (Evidence Grade 1).

Guidelines in Different Countries

- ❑ The guidelines released in various countries over the past few years for the management of hypertension are largely in agreement. The guidelines are basically the same for women and men. All guidelines:
  - Stress the importance of reaching the treatment goal of blood pressure below 140/90 mm Hg – below 130/80 mm Hg for patients with diabetes and/or renal disease.
  - Emphasise the need to consider the patients total risk of cardiovascular disease rather than treating high blood pressure in isolation.
  - Recommend a low-dose thiazide diuretic as the first-line therapy or as one of several first-line therapies.

Lifestyle Changes as the Basis of Successful Treatment

- ❑ With or without concurrently lowering blood pressure, a number of lifestyle changes – including physical activity, weight loss, dietary modifications, stress management, smoking cessation and the avoidance of excessive alcohol consumption – can minimise the risk factors for cardiovascular disease (Evidence Grade 1).

- ❑ Lifestyle measures can reduce the need for drug therapy and should form the basis for treating people with high blood pressure (hypertensives) (Evidence Grade 1). Smoking cessation measures should also be a priority for hypertensives and can generate major treatment benefits (Evidence Grade 1).

Pharmacological Treatment

- ❑ Blood pressure lowering treatment reduces the risk of stroke, myocardial infarction and premature death in hypertensives of both sexes (Evidence Grade 1).

- ❑ The various groups of blood pressure lowering drugs – thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, angiotensin receptor blockers (ARBs) and beta blockers – ordinarily used in Sweden are equally effective (reduction of approximately 10/5 mm Hg) when administered separately (Evidence Grade 1).

- ❑ Since the efficacy of different types of drugs can vary for a particular individual, switching to or adding one or more medications may be required in order to lower blood pressure sufficiently.

- ❑ For people with *uncomplicated* hypertension, all the major drug groups – thiazide diuretics, ACE inhibitors, calcium antagonists and ARBs – are equally effective in minimising the risk of cardiovascular disease (Evidence Grade 1). Beta blockers reduce the risk of stroke to a lesser extent (Evidence Grade 1). That is partly due to poorer reduction in blood pressure (Evidence Grade 2).

- ❑ Following stroke, blood pressure lowering drugs reduce the risk of myocardial infarction (Evidence Grade 3) and stroke recurrence (Evidence Grade 1). Treatment is equally effective with or without concurrent hypertension.

- ❑ At least half of all patients with type 2 diabetes also have hypertension. The effect of hypertension treatment on the absolute risk of cardiovascular disease morbidity and mortality is greater with concurrent diabetes (Evidence Grade 1).

In people with type 2 diabetes, the impact on relative risk is also greater (Evidence Grade 1).

- ❑ Patients whose treatment is based on drugs (ACE inhibitors and ARBs) that directly affect the renin-angiotensin-aldosterone system are less likely to develop type 2 diabetes than those whose treatment is based on a thiazide diuretic combined with a beta blocker or on a calcium antagonist (Evidence Grade 2).

- ❑ In patients with high risk (multiple risk factors) of cardiovascular disease *and concurrent* type 2 diabetes mellitus, blockade of the renin–angiotensin–aldosterone system may reduce the risk beyond the impact of simply lowering blood pressure (ACE inhibitors – Evidence Grade 2, ARBs – Evidence Grade 3).

- ❑ Blood pressure lowering treatment counteracts clinically relevant deterioration of renal function (Evidence Grade 1). No difference with regard to the long-term effect on renal function has been shown among the various groups of blood pressure lowering drugs in patients who have mild to moderate hypertension without other concurrent kidney complications. This report did not review treatment of patients with diabetes and impaired renal function.

- ❑ Hypertension leads to thickening of the heart muscle. Blood pressure lowering treatment reduces left ventricular mass (Evidence Grade 1). Such a reduction is associated with a lower risk of cardiovascular disease (Evidence Grade 2).

Economic Aspects

- ❑ Sales of blood pressure lowering drugs for the indication of hypertension more than doubled from 70 defined daily doses (DDSs) per 1 000 Swedes in 1992 to 155 in 2002. Costs for drug treatment of hypertension totalled SEK 1 656 million in 2002.

- Since satisfactory treatment of everyone with hypertension would involve both a larger number of patients and more medications per person, total drug costs would rise (Evidence Grade 2).

- Choice of medication has a major impact on both drug costs and cost effectiveness. Prescribing the least expensive equivalent medication whenever possible would reduce drug costs and improve cost effectiveness compared with current prescription patterns (Evidence Grade 2).

- Treatment of uncomplicated hypertension with the least expensive equivalent drug entails cost savings for older women, as well as middle-aged and older men. Improving the treatment of patients with moderate to high risk is more *cost-effective* than treating more people with low risk (Evidence Grade 2).

Ethical aspects

- The ethical dilemma of treating an apparently healthy person with drugs for what is likely to be a long period of time should be weighed against the risks associated with withholding treatment that may prevent serious disease.

Fact Box 1 Study Quality and Relevance, Evidence Grade.

Study quality and relevance refers to the scientific quality of a particular study and its ability to reliably address a specific question.

Evidence Grade refers to the total scientific evidence for a conclusion, ie, how many high-quality studies support the conclusion.

Evidence Grade 1 – Strong Scientific Evidence
A conclusion assigned Evidence Grade 1 is supported by at least two studies with high quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Evidence Grade 2 – Moderately Strong Scientific Evidence
A conclusion assigned Evidence Grade 2 is supported by at least one study with high quality and relevance and two studies with medium quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Evidence Grade 3 – Limited Scientific Evidence
A conclusion assigned Evidence Grade 3 is supported by at least two studies with medium quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Insufficient Scientific Evidence
If no studies meet the quality and relevance criteria, the scientific evidence is rated as insufficient to draw any conclusions.

Contradictory Scientific Evidence
If different studies are characterised by equal quality and relevance but generate conflicting findings, the scientific evidence is rated as contradictory and no conclusions can be drawn.

SBU's summary

The Assignment

The Swedish Council of Technology Assessment in Health Care (SBU) published its first report on *Moderately Elevated Blood Pressure* in 1994. The new 2001–2004 review of the literature includes many new studies. The past ten years have generated fresh data that confirm the value of treating women and the elderly, as well as patients with elevated systolic pressure. The report *Moderately Elevated Blood Pressure* (2004, no 170) is a revision of the 1994 version. Each chapter has been updated and expanded upon, while some are brand new. Chapter 11 describes the project group's meta-analysis of the effect of blood pressure lowering treatment on left ventricular hypertrophy. The compilation of the results of hypertension treatment in various countries is new, as is the section on different blood pressure lowering drugs. Most chapters call attention to any differences that have been demonstrated between men and women. Eight new studies have been included in Chapter 10 of the 2007 update.

The task of the report was to study moderately elevated blood pressure, rather than benefits from the treatment of severe hypertension or the prevention of cardiovascular disease in general. The review did not include any literature on impaired renal function associated with diabetes, hypertension during pregnancy or heart failure in hypertensives.

The report is based on a systematic, step-by-step perusal of the literature. Following a structured review, studies were selected that

exhibited satisfactory scientific quality (see Table 1 for a breakdown of those that were included in the final review). The project group members who had participated in one of the studies were not involved in the review of that study.

Special attention should be paid to publication bias, ie, studies that produced unfavourable results may be underrepresented among those appearing in scientific journals. However, the problem diminishes the larger and more well-known the study – for major studies of hypertension treatment, it would appear to be small.

Table 1 *Randomised controlled trials of the effect of blood pressure lowering treatments included in the review of the literature.*

Type of study	Number	
Active drug therapy with control group		21
Comparison of different drug therapies		21
Multifactorial risk factor intervention		6
Treatment when complications arise		19
• Following stroke	6	
• Kidney disease	2	
• Diabetes mellitus	7	
• High cardiovascular risk	4	
Totalt treatment studies		**67**

How Prevalent is Hypertension in Sweden?

The prevalence of hypertension was estimated on the basis of single clinical examinations. For such examinations, hypertension is generally defined as systolic pressure of at least 140 mm Hg and diastolic pressure of at least 90 mm Hg. People receiving drug

treatment for hypertension have been included regardless of their blood pressure reading.

Based on that definition, an estimated 1.8 million people in Sweden, or 27% of the adult population (aged 20 or older), have high blood pressure. The condition is just as common among women as men. Prevalence increases with age – more than half of all women and men of retirement age have hypertension. Of the 1.8 million Swedish adults with elevated blood pressure, 60% have mild hypertension (140–159/90–99 mm Hg), 30% have moderate hypertension (160–179/100–109 mm Hg) and 10% have severe hypertension (≥180/≥110 mm Hg).

Hypertension as a Risk Factor for Cardiovascular Disease

High blood pressure has long been identified as a risk factor for coronary heart disease, stroke and other cardiovascular disease. Hypertension also increases the risk of dementia. A large percentage of cardiovascular cases are the result of high blood pressure. An increase of an estimated 20 mm Hg in systolic pressure or 10 mm Hg in diastolic pressure above 115/75 mm Hg doubles the risk of death from cardiovascular disease. The increase is independent of other risk factors for cardiovascular disease, and it is the same for men and women. High blood pressure correlates more strongly with the development of stroke than with ischemic heart disease (see Table 2).

Most hypertension guidelines now recommend global or total risk assessment, ie, consideration of the cumulative impact of all risk factors, organ damage and any cardiovascular disease that is already present. Paying attention to blood pressure readings alone allows for only imprecise risk assessments and is usually insufficient to determine the appropriate treatment for mild hypertension or to properly measure the risk of cardiovascular disease.

Table 2 *Risk reduction for various cardiovascular diseases by age group when systolic pressure is lowered by 20 mm Hg (Multiple Risk Factor Intervention Trial [MRFIT], 1990).*

Cause of death	Age group	Risk reduction (%)	95% confidence interval
Stroke	40–49	70	60–77
	50–59	67	62–71
	60–69	65	60–69
Ischemic heart disease	40–49	58	53–62
	50–59	56	56–58
	60–69	54	52–56
Other cardio-vascular disease	40–49	65	58–70
	50–59	58	54–61
	60–69	56	52–59

The risk of death was 6.3 per 1 000 patient-years, of which 3.5 was from cardiovascular disease.

The most important risk factors for cardiovascular disease are advanced age, being male, hypertension, high cholesterol (high LDLs and low HDLs in particular), smoking, diabetes, overweight, physical inactivity and excessive alcohol consumption. In addition, psychosocial components include social stratification (such as educational level, occupation and neighbourhood), ethnicity, social safety net, home environment, work environment, stress, etc. A series of family-related risk factors, both genetic factors and learned behaviours, are also involved. Among new but still partially unexplored risk factors are infection (such as a microorganism called *Chlamydia pneumoniae*), elevated homocysteine levels, elevated C-reactive protein (CRP) levels, and insulin resistance.

Organ damage caused by high blood pressure – including left ventricular hypertrophy, kidney damage and thickening of the carotid artery – is also a major risk factor for cardiovasclar disease.

The presence of one or more of these types of organ damage increases blood pressure-related risk. The biggest risk factor is established cardiovascular disease. People with high blood pressure often have several of the abovementioned risk factors as well. Only a small percentage have no other risk factors.

The risk factors often reinforce each other. Thus, even a factor with a rather considerable presence carries a fairly moderate risk in and of itself. The presence of two factors substantially increases the risk. With three factors, the risk is high even if each one of them is present to only a modest degree.

There are considerable gender differences in terms of absolute risk and thereby the prevalence of disease, particularly cardiovascular. Women develop disease before the age of 50 approximately one third as often as men. The gap then narrows steadily until the percentages are approximately equal at the age of 70. The differences between the sexes are small when it comes to the relative risk occasioned by hypertension. Blood pressure levels alone do not justify treating women and men differently.

Guidelines for Management and Treatment of Hypertension in Different Countries

The guidelines released in various countries over the past few years for the treatment of hypertensives are largely in agreement. Every guideline stresses the importance of monitoring the patient's systolic and diastolic pressure, as well as reaching the treatment goal. Independent of the medication used or the advantages of any particular drug group, the target is usually a reduction to below 140/90 mm Hg (130/80 mm Hg for patients with type 2 diabetes or renal disease). All guidelines emphasise the need to consider the patient's total risk of cardiovascular disease rather than treating high blood pressure in isolation. The guidelines are basically the same for women and men.

All guidelines, in both Europe and the United States, recommend a low-dose thiazide diuretic as the front-line treatment or as one of several front-line treatments. They are also unanimous in recommending that non-pharmacological methods (lifestyle changes) form the basis of all treatment.

Estimating the Risk of Cardiovascular Disease

The risk of cardiovascular disease in people with high blood pressure can be estimated on the basis of the risk assessment method published by the European Society of Hypertension/European Society of Cardiology (ESH/ESC) in 2003 (see Table 3).

The risk categories are defined as follows: low risk means less than a 15% risk, medium risk a 15–20% risk, and high/very high risk better than a 20% risk of developing myocardial infarction or stroke within ten years.

Approximately 20% of hypertensives in Sweden are in the low risk category. Non-pharmacological treatment is sufficient for most people in this category. The medium risk category, to which just over half of all patients belong, requires drug therapy to lower blood pressure. For the remaining 30% who belong to the high/very high risk category, such therapy is a matter of urgency.

According to the guidelines, patients in the medium and high risk categories should be treated with blood pressure lowering drugs. That translates into 1.4 million people in Sweden. However, the salutary effects of drug therapy are not as well documented for the more than 400 000 hypertensives aged 80 or older.

Risk assessment is not gender neutral – being older than 55 is a risk factor in men, while being older than 65 is a risk factor in women. That discrepancy reflects the considerably lower propensity of women to develop cardiovascular disease – age and risk profile otherwise being equal.

Table 3 *Risk assessment in accordance with 2003 European hypertension guidelines.*

	Blood pressure (mm Hg)				
	Normal	**High normal**	**Hypertension**		
			Mild (Level 1)	**Moderate (Level 2)**	**Severe (Level 3)**
Other risk factors and diseases	SBT 120–129 or DBT 80–84	SBT 130–139 or DBT 85–89	SBT 140–159 or DBT 90–99	SBT 160–179 or DBT 100–109	SBT ≥180 or DBT ≥110
No other risk factors	Low risk	Low risk	Low risk	Medium risk	High risk
1–2 risk factors	Low risk	Low risk	Medium risk	Medium risk	Very high risk
3 or more risk factors, organ damage or diabetes	Medium risk	High risk	High risk	High risk	Very high risk
Established cardiovascular disease	High risk	Very high risk	Very high risk	Very high risk	Very high risk

DBT = Diastolic pressure; SBT = Systolic pressure.

Risk: 10-year risk for fatal/nonfatal stroke or myocardial infarct: low <15%, medium 15–20%, high 20–30%, very high >30%.

Risk factors: Advanced age, smoking, cardiovascular disease in the family, abdominal obesity, elevated cholesterol levels, elevated CRP.

Organ damage: Left ventricular hypertrophy, proteinuria, elevated creatine, atherosclerotic plaque.

Established cardiovascular disease: Myocardial infarction, angina pectoris, coronary heart disease, heart failure, impaired renal function, stroke/transient ischemic attack (TIA), peripheral arterial disease.

Degree of Blood Pressure Control in Different Countries

The experience of recent years has clearly demonstrated that most hypertensives need a combination of different blood pressure lowering drugs to reach their treatment goal. The studies that have examined the degree to which recommended treatment goals are reached have yielded very discouraging results. The number of well-treated patients (blood pressure reduced to less than 140/90 mm Hg) in Swedish studies has been only 20–30% of those who received blood pressure lowering drugs. The problem is normally a persistence of high systolic pressure. Poor blood pressure control is associated with advanced age, excess body weight, and organ damage such as left ventricular hypertrophy.

Relevance of Body Position When Measuring Blood Pressure and Assessing Risk

While Sweden traditionally takes blood pressure readings while the patient is in a supine position, many other countries do so in a sitting position. Yet even in Scandinavia, observation studies of the correlation between blood pressure and the risk of cardiovascular disease and death, as well as treatment studies, nearly always take measurements when the patient is sitting. Thus, a problem arises when risk and treatment data from studies in which measurements are taken in one way are applied to a clinical situation in which they are taken in another way.

Several studies compared blood pressure readings when the patient is in a supine and sitting/standing position. A systematic comparison found that the readings stabilised within three minutes of a change in body position. For people aged 50 and older, systolic pressure averaged 3 mm Hg lower, and diastolic pressure 10 mm Hg higher, in a standing than in a supine position. The discrepancies between supine and sitting, as well as between sitting and standing, were approximately half that much.

Hypertensives and people who had suffered a myocardial infarction exhibited essentially the same discrepancies in different body positions as those with normal blood pressure.

Thus, compared with available risk assessments, a supine position will yield a systolic reading that somewhat overestimates the risk of cardiovascular disease and a diastolic reading that underestimates it.

Treating Patients with High Blood Pressure

The chances of successfully treating hypertensives with drugs and/or non-pharmacological lifestyle measures are good. Individualised and consistently implemented treatment should satisfactorily lower blood pressure in most patients. Despite the extensive literature on the efficacies and side-effects of various treatments, considerable methodological problems complicate a comparative assessment. The large studies compare strategies based on different drugs and adjunctive therapies. That approach makes it harder to assess the efficacies and side-effects of individual drugs.

Regardless of whether or not blood pressure is lowered, a number of different lifestyle measures – including physical activity, weight loss, dietary modifications and stress management – can minimise the risk of disease. Such measures can reduce the need for drug therapy and should form the basis of treating people with high blood pressure. Smoking cessation measures can bring major treatment benefits and should be a priority for hypertensives.

Excessive consumption of alcohol raises blood pressure, particularly diastolic. Cutting back on alcohol consumption in such people is associated with a dose-dependent reduction of blood pressure. The effect, which has been observed in both men and women, appears to increase with age. Epidemiological studies have found a correlation between modest alcohol consumption and a lower risk of cardiovascular disease. Thus, whether alcohol

has a beneficial or harmful effect would seem to be a question of dosage. There is no documentation that lends credence to the preventive use of alcohol by non-drinkers.

When monotherapy is prescribed, the various drug groups – thiazide diuretics, ACE inhibitors, calcium antagonists, ARBs and beta blockers – ordinarily used in Sweden to treat hypertensives appear to be equally effective in lowering blood pressure (by approximately 10/5 mm Hg) and in reaching the treatment target (see Table 4).

Since the efficacy of various types of drugs can vary for a particular individual, switching to or adding one or more medications may be required in order to lower blood pressure sufficiently. To lower blood pressure most effectively with as few side-effects as possible, combining two drugs is generally preferable to administering a high dose of one. Worth emphasising is that non-pharmacological measures can reinforce the blood pressure lowering effect and minimise the side-effects of drug therapy.

Side-effects from neither the older nor the newer blood pressure lowering drugs available today lead to significant problems when they are administered in low to moderate doses. Not all the symptoms experienced by hypertensives are caused by their blood pressure lowering treatment. Placebos can give rise to more symptoms (side-effects) that occasion dropouts than do active blood pressure lowering drugs.

Since the side-effect profiles of different drug groups vary, contraindications should be considered and care should be exercised in the choice of blood pressure lowering medication for certain types of patients (those with another concurrent disease or treatment). Vasodilating agents appear to cause more side-effects than other drugs. In most patients, the use of one or more drugs in low to moderate doses should allow for significant treatment benefits with few or no troublesome side-effects.

Table 4 *Percentage of patients who reached their target blood pressure or suffered side-effects that led to dropout in the Veterans Affairs Cooperative Study. The target was diastolic pressure of less than 90 mm Hg after titration and less than 95 mm Hg at the end of the study (1 year). The patients, all men, were more or less equally divided among Caucasians and African Americans.*

Treatment	No of patients	Percentage who reached target blood pressure	Percentage of dropouts due to side-effects in less than 1 year
Placebo	183	25	6
Hydrochlorothiazide	186	46	1
Beta blockers (atenolol)	173	51	2
ACE inhibitors (captopril)	181	42	5
Calcium channel blockers (diltiazem)	182	59	7
Alpha blockers (prazosin)	183	42	14

Measurements that reflect symptoms and psychosocial function suggest that lowering blood pressure improves quality of life in and of itself. Drug therapy has also proven to be more effective than placebo treatment in improving quality of life. The drug groups ordinarily used in Sweden (see above) do not appear to exhibit any significant differences in terms of impact on quality of life.

Patient compliance with the prescribed treatment is key to its efficacy. Studies indicate that up to half of drug intake does not conform to recommendations. However, the scientific evidence for determining the kinds of measures that promote compliance is insufficient.

Daily sales of blood pressure lowering drugs for the indication of hypertension rose considerably from 70 defined daily doses

(DDSs) per 1 000 Swedes in 1992 to 155 in 2002. While the percentage of patients who are prescribed ACE inhibitors, calcium antagonists and beta blockers has remained relatively constant in recent years, the percentage who receive thiazide diuretics has declined steadily and the percentage for ARBs is up sharply (Figure 1).

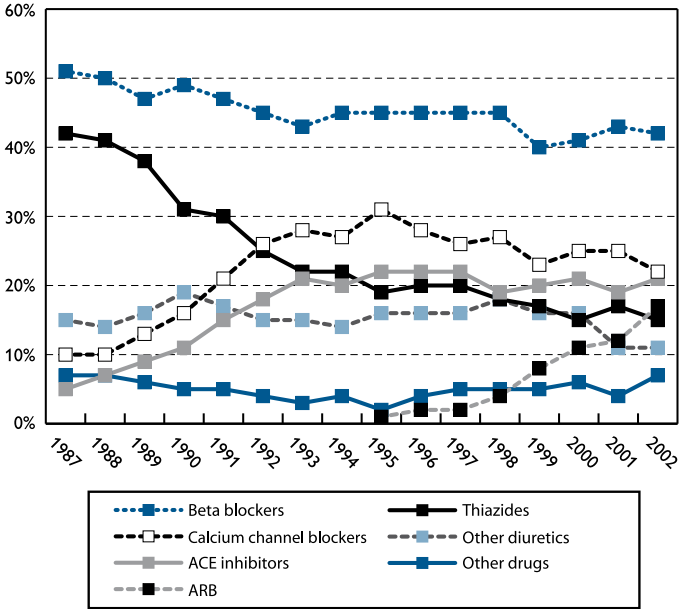

Figure 1 *Prescription patterns (percentage of patients) for drug treatment of hypertension, 1987–2002.*

Costs for drug treatment of hypertension totalled SEK 1 654 million in 2002. Calcium antagonists (SEK 541 million) and ARBs (SEK 398 million) accounted for the greatest costs, whereas ACE inhibitors and beta blockers accounted for approximately SEK 300 million each and diuretics for only SEK 100 million (Table 5).

Table 5 *The most common blood pressure lowering drugs and their sales in Sweden, 2002.*

Drug group	DDD/TID	SEK (million)	Percentage for hypertension
Diuretics	39.9	97	43
ACE inhibitors	31.8	290	65
Calcium antagonists	34.3	541	84
Angiotensin receptor blockers (ARBs)	18.1	398	84
Beta blockers	30.6	309	57
Miscellaneous, including alpha blockers	0.7	19	52
Total for hypertension treatment	**155.4**	**1 654**	
Total for these drugs, regardless of indication	247	2 424	

Sources: Sales figures from Apoteket AB (National Corporation of Swedish Pharmacies) and Diagnos–receptundersökningen (Diagnosis Prescription Study).
DDD/TID = Defined daily dose/1 000 inhibitants per day

Benefits of Lowering Blood Pressure

The benefits of treating patients with mild to moderate hypertension are well documented. Blood pressure lowering treatment reduces the risk of stroke, myocardial infarction and death. The experience of the past ten years has further confirmed the value of treating women and the elderly, as well as patients with elevated systolic pressure. In prescribing blood pressure lowering drugs, consideration must be paid to the patient's aggregate risk of cardiovascular disease.

Most older treatment studies set a goal (usually below 90 mm Hg) for diastolic pressure only, while the newer studies targeted systolic pressure as well (usually below 140 mm Hg). The higher the

initial blood pressure, the greater the effect of hypertension treatment on the *absolute* risk of cardiovascular disease.

The impact on *relative* risk is the same for women and men. However, a woman's lower absolute risk of cardiovascular disease should be considered before treatment is initiated. The benefits of treating hypertensives up to the age of 80 are well documented. Although treatment appears to remain effective beyond that age, the scientific evidence is not unequivocal. The effect on the absolute risk of morbidity and death from cardiovascular disease is greater with concurrent coronary heart disease and/or left ventricular hypertrophy.

When concurrent untreated high cholesterol levels, obesity or smoking are present, blood pressure lowering treatment alone is less efficacious in reducing the risk of cardiovascular disease, while simultaneous intervention to deal with multiple risk factors appears to have a favourable impact on morbidity.

At least half of all people with *type 2 diabetes mellitus* also have hypertension. The effect of antihypertensive treatment on the absolute risk of morbidity and mortality from cardiovascular disease is greater when there is concurrent type 2 diabetes mellitus. The reason is that diabetics have a greater absolute risk of developing cardiovascular disease. The impact on the relative risk of cardiovascular disease is also greater for diabetics. With concurrent type 1 or 2 diabetes mellitus, the perusal of the literature suggested that the treatment goal should be blood pressure below 130/80 mm Hg in order to reduce the risk of kidney damage. However, the importance of that lower target for reducing the risk of cardiovascular disease in diabetics has not been fully studied.

For people with *uncomplicated hypertension*, all the major drug groups – thiazide diuretics, ACE inhibitors, calcium antagonists and ARBs – are equally effective in minimising the risk of cardiovascular disease. Treatment with beta blockers is less effective, particularly in the elderly. In patients with high risk of cardiovascular disease *and concurrent* type 2 diabetes mellitus, blockade of the renin-angiotensin-aldosterone system with ACE inhibitors or

ARBs can reduce the risk beyond the impact of simply lowering blood pressure.

Untreated hypertension leads to *kidney disease*. No randomised trials have focused primarily on the impact of hypertension treatment on the risk of cardiovascular disease and death in *non-diabetics* with kidney damage. The blood pressure level that the patient reaches during treatment is of major significance in preventing the development of renal failure. Although evidence is lacking that lowering the blood pressure of such patients even more than otherwise called for would reduce the risk of myocardial infarction, stroke or death, the issue has not been fully studied.

In patients who have had a *stroke*, blood pressure lowering drugs reduce the risk of myocardial infarction or stroke recurrence. The treatment is equally effective in both hypertensives and people with normal blood pressure. Whether or not the various types of drugs differ with respect to reducing the risk of stroke recurrence has not been fully studied. No gender dependent discrepancies have been established.

There is a correlation between hypertension and the development of *dementia*. Only in recent years, however, have large randomised trials examined the effect of blood pressure lowering treatment on cognitive function and the development of dementia. A couple of studies have shown that such treatment does not impair cognitive function. In addition, the more recent studies indicate that treatment reduces the risk of dementia and allows for better retention of cognitive function while effectively lowering blood pressure. The favourable impact might stem from a decrease in the incidence of stroke among the actively treated group, thereby reducing the number of new dementia cases. Data are lacking about possible differences between the sexes.

One relatively common complication of hypertension is hardening of the peripheral arteries. That can show up as narrowing and insufficiency in the arteries of the legs (intermittent claudication) or as carotid artery stenosis in the neck. There is no scien-

tific evidence that blood pressure lowering treatment, even with beta blockers, is harmful in normal cases.

Patients with arterial insufficiency of the legs are at a substantially higher risk of myocardial infarction and stroke. That far overshadows the risk of circulatory disorders with the complications of gangrene and amputation. For that reason, hypertension treatment is particularly urgent for patients with peripheral arterial disease. The specific degree to which blood pressure lowering treatment can protect the cardiovascular systems of patients with symptomatic arterial insufficiency of the legs has not been studied to any significant extent.

Efficacy of Blood Pressure Lowering Drugs on Left Ventricular Hypertrophy

Left ventricular hypertrophy is a risk factor for cardiovascular disease. Blood pressure lowering treatment of hypertensives is associated with a reduction of left ventricular mass, which in turn minimises the risk of cardiovascular disease. Effectively lowering the blood pressure of hypertensives is the single most important measure for reducing left ventricular hypertrophy.

When blood pressure is lowered by comparable amounts, beta blockers appear to reduce left ventricular mass less than do other groups of antihypertensive drugs. No demonstrable differences have been established among the other drug groups. Comparisons based on *double-blind* trials alone have not uncovered any statistically significant differences among the efficacies of the various drug groups when it comes to reducing ventricular mass. Since the studies have been small, their statistical reliability is relatively low.

The Effect of Blood Pressure Lowering Drugs on Metabolic Risk Factors

Blood pressure lowering drugs in the calcium antagonist, ACE inhibitor, ARB and alpha blocker groups have no negative metabolic effects. Thiazide diuretics have a negative impact on both lipid and glucose metabolism, with particular changes in LDL cholesterol and triglycerides, as well as glucose and insulin variables. However, the quantitative changes are small for monotherapy with a low-dose thiazide diuretic. Beta blockers also have a negative impact on both lipid and glucose metabolism, with particular changes in LDL cholesterol, HDL cholesterol and triglycerides, as well as glucose and insulin variables. But the quantitative changes are small for monotherapy with a beta blocker.

The long-term metabolic effects of various combinations of blood pressure lowering drugs have not been fully studied. Combining a beta blocker and thiazide diuretic appears to reinforce the negative impact on triglycerides and glucose variables.

Hypertension treatment based on metabolically neutral drugs (ACE inhibitors and ARBs) that interact directly with the renin-angiotensin-aldosterone system have been shown to lead to less development of type 2 diabetes mellitus than treatment based on calcium antagonists or a combination of thiazide diuretics and beta blockers.

The prognostic significance of changes in lipid and glucose metabolism that arise in connection with drug treatment of hypertension is still unclear.

Effect of Elevated Blood Pressure on the Kidneys

Untreated mild to moderate hypertension can affect the kidneys, leading to proteinuria (protein in the urine) and impaired renal function. Hypertension and concurrent kidney impairment increases the risk of cardiovascular disease.

Effective blood pressure lowering treatment counteracts clinically relevant deterioration of renal function. No difference with regard to the long-term effect on renal function has been shown among the various groups of blood pressure lowering drugs in patients who have mild to moderate hypertension without other concurrent kidney complications.

Economic Assessment of Hypertension Treatment

Since satisfactory treatment of everyone with hypertension would involve both a larger number of patients and more medications per person, total drug costs would rise.

Choice of medication has a major impact on both drug costs and cost effectiveness. The use of the least expensive equivalent medication whenever possible would reduce drug costs and improve cost effectiveness compared with current prescription patterns.

An increase in the risk of cardiovascular disease reduces the cost per quality-adjusted life year (QALY) gained, ie, it is more cost-effective to treat high-risk patients. Given the absence of agreement about the value of a QALY gained, however, there is no generally accepted threshold for determining which treatments are cost-effective. Nor is there any consensus as to how much society should spend for a QALY gained.

Table 6 *Approximate daily costs for different blood pressure lowering drugs, May 2004.*

Drug	Daily cost (SEK)
Thiazide diuretics	0.50–1.50
Beta blockers	1.00–4.00
Angiotensin converting enzyme (ACE) inhibitors	0.75–7.00
Calcium channel blockers	1,25–7,50
Angiotensinreceptor blockers (ARBs)	6,00–10,00

Treatment of *uncomplicated* hypertension with the least expensive equivalent drug provides *cost savings* for older women and men, and for middle-aged men. Other treatment of high blood pressure is more *cost-effective* than many healthcare interventions. Further reducing the blood pressure of people with moderate to high risk is more cost-effective than lowering the treatment threshold and thereby caring for more low-risk patients.

More Knowledge and Research Needed

More knowledge about blood pressure lowering treatment is needed in a number of areas. Following are the five major areas from a population perspective.

1. Given our current ability to lower moderately elevated blood pressure to normal levels, the low percentage of well-treated patients is unsatisfactory. Thus, more knowledge is needed about how to improve patient compliance with blood pressure lowering treatment. Additional information is also required about suitable ways for the healthcare profession to adopt the desired changes.

2. There are currently several types of antihypertensive drugs, the combination of which can modestly lower blood pressure. However, new drugs are required that can more effectively lower systolic pressure.

3. Non-pharmacological lifestyle measures have a favourable impact on cardiovascular risk factors and should form the basis of all hypertension treatment. However, studies examining the effect of such treatment on cardiovascular disease are still few in number. More such studies are needed.

4. Given an aging population, it is also important to study how very old (over 80) hypertensives should be cared for. Of interest in that connection is to study dementia in very old hypertensives and to determine whether blood pressure lowering treatment can arrest its development.

5. A strong correlation has been established between blood pressure, diabetes and obesity. Certain blood pressure lowering drugs appear to constitute a risk factor for diabetes. Since the consequent effect on the risk of cardiovascular disease remains unclear, however, long-term studies are called for. Also important to study is the impact of moderate changes in glucose metabolism on the risk of both diabetes mellitus and cardiovascular disease.

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SBU Evaluates Health Care Technology

Below is a brief summary of the mission assigned to SBU by the Swedish Government:

- SBU shall assess healthcare methods by systematically and critically reviewing the underlying scientific evidence.
- SBU shall assess new methods as well as those that are already part of established clinical practice.
- SBU's assessments shall include medical, ethical, social and economic aspects, as well as a description of the potential impact of disseminating the assessed health technologies in clinical practice.
- SBU shall compile, present and disseminate its assessment results such that all parties concerned have the opportunity to take part of them.
- SBU shall conduct informational and educational efforts to promote the application of its assessments to the rational use of available resources in clinical practice, including dental care.
- SBU shall contribute to the development of international co-operation in the field of health technology assessment and serve as a national knowledge centre for the assessment of health technologies.

Moderately Elevated Blood Pressure

The SBU report is based on a systematic and critical review of the scientific literature. It is one of a series of scientific reports published by SBU (The Swedish Council on Technology Assessment in Health Care).

The Summary and Conclusions of the report, presented in this booklet, have been approved by the SBU Board of Directors and the Scientific Advisory Committee.

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