

Intensive Glucose-Lowering Therapy in Diabetes

A Systematic Review

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Summary and Conclusions of the SBU Report:
**Intensive Glucose-Lowering
Therapy in Diabetes**

A Systematic Review

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This report reviews the scientific evidence for intensive therapy aimed at lowering blood glucose levels to near normal in patients with type 1 and type 2 diabetes. In diabetes, risks for diabetic complications are associated with high average blood glucose levels as measured by HbA_{1c}. Hence, in treating diabetes it is natural to aim at lowering HbA_{1c} to normal or near normal levels. In type 1 diabetes, we refer to this as *intensive insulin therapy*. Since several different types of drugs are used to treat type 2 diabetes we refer to this as *intensive glucose-lowering therapy*. The report was commissioned by the Swedish National Board of Health and Welfare (NBHW) to provide a foundation for their national guidelines for diabetes care. Within the framework of the NBHW guidelines program, SBU is producing three additional reports addressing patient education in managing diabetes, self-monitoring of blood glucose in noninsulin-treated diabetes, and dietary treatment of diabetes.

Conclusions

- Intensive insulin therapy for type 1 diabetes is demanding for health services and the patient alike, but reduces the risk for cardiovascular disease and substantially reduces the risk for damage to the retina, kidneys, and nerves. The risk is increased for serious hypoglycemia, which places the greatest limitation on treatment. In many patients, successful intensive therapy should reduce diabetes complications in the long term. Treatment is cost effective.

- In newly diagnosed type 2 diabetes, intensive glucose-lowering therapy helps reduce the risk of cardiovascular disease and serious damage to the retina of the eye. Treatment is relatively simple, and the risks for side effects are small. Successful intensive therapy of newly diagnosed type 2 diabetes should reduce such complications in the long term. Treatment is cost effective.

- ❑ In patients who have had type 2 diabetes for 5 to 10 years, or longer, the benefits of intensive glucose-lowering therapy are not uniformly greater than the risks, and the cost effectiveness is not clear. The risk for kidney damage is somewhat reduced. Studies present conflicting findings regarding the risk for cardiovascular diseases. It is important to individualize the treatment goals for these patients and balance the risks of side effects (eg, serious hypoglycemia) against the risks of late diabetes complications, which increase with the rise in HbA_{1c}. New studies with longer follow-up are urgently needed in this patient group.

Results

Intensive insulin therapy in type 1 diabetes

Microvascular disease

- Intensive insulin therapy in type 1 diabetes reduces the risk for complications in the eyes, kidneys, and nerves (microvascular disease). The absolute effect is large, approximately 2 to 3 fewer cases per 10 patients during 7 years of treatment (Strong scientific evidence ⊕⊕⊕⊕).

Cardiovascular disease

- Intensive insulin therapy in type 1 diabetes reduces the risk for cardiovascular disease in the long term (Limited scientific evidence ⊕⊕○○).

Risks/side effects

- The risk for serious hypoglycemia increases with intensive insulin therapy for type 1 diabetes (Strong scientific evidence ⊕⊕⊕⊕). The risks increase substantially, approximately 3 times.

- Intensive insulin therapy in type 1 diabetes increases the risks for weight gain (Strong scientific evidence ⊕⊕⊕⊕).
- Intensive insulin therapy in type 1 diabetes does not appear to affect quality of life during a 6-year period (Limited scientific evidence ⊕⊕○○).

Health economics

- Intensive insulin therapy in type 1 diabetes involves low to moderate costs per quality-adjusted life-year (QALY) and is cost effective.



Table 1 Summary of findings for intensive insulin therapy in type 1 diabetes. The data are based primarily on the Diabetes Control and Complications Trial (DCCT). Average follow-up was 6 to 7 years.

Outcomes	Number of patients (no of studies & study design)	Mean risk in standard group (min-max)
New cases of serious non-proliferative retinal effects or worse	842 (3 RCTs)	40% (35–57%)
New cases of nephropathy	866 (3 RCTs)	11% (9–19%)
New cases of nerve effects	1 161 (1 RCT)	13% (10–17%)
Cardiovascular disease	1 441 (1 OBS)	14% after 17 years
* Number of serious hypoglycemia cases	1 441 (1 RCT)	18.7%
* Number of episodes of insulin coma or seizure	1 441 (1 RCT)	5.4%
* Number of patients with increased Body Mass Index (BMI) exceeding 5 kg/m ²	1 246 (1 RCT)	8% (3–15% in intensive group)

* Side effects of treatment.

** Stettler C, Allemann S, Juni P, Cull CA, Holman RR, Egger M, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. *Am Heart J* 2006;152:27-38.

Relative risk (95% CI)	Absolute effect	Quality of evidence	Comments
0.43 (0.34–0.55)	22.6% fewer	Strong ⊕⊕⊕⊕	Secondary prevention studies
0.47 (0.29–0.77)	5.7% fewer	Strong ⊕⊕⊕⊕	Secondary prevention studies
0.36 (0.24–0.55)	8.7% fewer	Strong ⊕⊕⊕⊕	DCCT. Primary + secondary prevention study arms
0.43 (0.30–0.62)	7.0% fewer	Limited ⊕⊕○○	Results from EDIC. Supported by meta-analysis (Stettler 2006**)
3.3	42 more per 100 patient years	Strong ⊕⊕⊕⊕	DCCT 2 study arms
3.0	11 more per 100 patient years	Strong ⊕⊕⊕⊕	DCCT 2 study arms
3.73 (2.81–4.97)	22% more	Strong ⊕⊕⊕⊕	DCCT 2 study arms

CI = Confidence interval; EDIC = Epidemiology of diabetes interventions and complications; RCT = Randomised controlled trial

Table 2 Summary of evidence for intensive insulin therapy in type 1 diabetes. The table specifies the basis for grading evidence in the report. A zero indicates: no reason to criticize this point. A minus sign with question mark indicates: some deficiencies, but not great enough to lower the strength of the evidence. Minus 1 or 2 indicate:

Outcomes	Number of participants (number of studies)	Study type	Risk of bias
Microvascular disease (damage to the eyes, kidneys, and nerves)	Approximately 1 500 (3)	RCT ⊕⊕⊕⊕	-? Unblinded
Cardiovascular disease	1 441 (1)	OBS ⊕⊕○○	0
Serious hypoglycemia	1 441 (1)	RCT ⊕⊕⊕⊕	-? Unblinded
Substantial weight gain BMI >5 kg/m ²	1 246 (1)	RCT ⊕⊕⊕⊕	-? Unblinded

BMI = Body mass index; RR = Relative risk

deficiencies lower the strength of the evidence. A plus sign indicates: the evidence strength can be raised. However, it is not possible to achieve an overall evidence grade above ⊕⊕⊕⊕ (strong scientific evidence), or total evidence grade below ⊕○○○ (insufficient scientific evidence).

Incon- sistency	Indirect- ness	Impreci- sion	Publica- tion bias	Effect size	Quality
0	0	0	0	+1 RR <0,5	Strong ⊕⊕⊕⊕
0	0	-1 <200 cases	0	+1 RR <0,5	Limited ⊕⊕○○
0	0	0	0	+1 RR >2	Strong ⊕⊕⊕⊕
0	0	0	0	+1 RR >2	Strong ⊕⊕⊕⊕

Results

Intensive glucose-lowering therapy in type 2 diabetes

Newly diagnosed type 2 diabetes

- Intensive glucose-lowering therapy in newly diagnosed type 2 diabetes reduces the risk for cardiovascular disease in the long term (Limited scientific evidence ⊕⊕○○).
- Intensive glucose-lowering therapy in newly diagnosed type 2 diabetes reduces the risk for clinically important complications in the eye (Strong scientific evidence ⊕⊕⊕⊕). The absolute effect is small, approximately 3 fewer cases per 1 000 patient years.

Type 2 diabetes of longer duration

- The effects of intensive glucose-lowering therapy on cardiovascular disease in people with type 2 diabetes and longer disease duration are conflicting (Insufficient scientific evidence ⊕○○○).
- Intensive glucose-lowering therapy in people with type 2 diabetes and longer disease duration reduces the risk for clinically important kidney complications (Strong scientific evidence ⊕⊕⊕⊕). The absolute effect is small, approximately three fewer cases per 1 000 patient years.

Risks/side effects

- Intensive glucose-lowering therapy in type 2 diabetes leads to a higher risk of serious hypoglycemia (Strong scientific evidence ⊕⊕⊕⊕). This risk, however, is substantially less than the risk associated with intensive therapy in type 1 diabetes and depends on the type of drug or drug combinations used.

- Intensive glucose-lowering therapy in type 2 diabetes increases the risk for weight gain (Strong scientific evidence ⊕⊕⊕⊕). The size of this risk varies depending on the type of drug or drug combinations used.

Health economics

- In newly diagnosed type 2 diabetes, intensive therapy aimed at reducing blood glucose is associated with low to moderate costs per quality-adjusted life-year (QALY) and is cost effective. The cost per QALY for intensive therapy is, however, related to age at onset and increases with the patient's age.
- Studies are lacking on the cost effectiveness of treating patients that have had type 2 diabetes for a prolonged time, and the lack of solid medical data makes economic studies difficult.

Table 3 Summary of findings on intensive glucose-lowering therapy in newly diagnosed type 2 diabetes. The results are from UKPDS 33 (United Kingdom Prospective Diabetes Study) and its observational follow-up study. Follow-up in UKPDS was 10 years, followed by another 7 years.

Outcomes	Number of patients (no of studies & study design)	Absolute risk in standard group/ 1000 patient years
Mortality	3 867 (1 OBS)	30.3
Cardiovascular mortality	Not reported	
Myocardial infarction (fatal and non-fatal)	3 867 (1 OBS)	19.6
Stroke	3 867 (1 OBS)	6.9
Retinopathy (photocoagulation)	3 867 (1 RCT)	11.0
Nephropathy (albumin in urine >200 µg/day)	Not reported	
Episodes of serious hypoglycemia	3 867 (1 RCT)	7
Weight gain	3 867 (1 RCT)	–

CI = Confidence Interval; OBS = Observational study;
RCT = Randomised controlled trial

Relative risk (95% CI)	Absolute effect/ 1000 patient years	Quality of evidence	Comments
0.87 (0.79–0.96)	3.5 fewer	Limited ⊕⊕○○	Follow-up study
0.85 (0.74–0.97)	2.8 fewer	Limited ⊕⊕○○	Follow-up study
0.91 (0.73–1.13)	0.6 fewer	Insuffi- cient ⊕○○○	Follow-up study
0.74 (0.59–0.92)	3.1 fewer	Strong ⊕⊕⊕⊕	UKPDS 33
2.0	7 more	Strong ⊕⊕⊕⊕	Uncommon side effects in UKPDS 33
	3 kg in the intensive group	Strong ⊕⊕⊕⊕	UKPDS 33

Table 4 Summary of evidence for intensive glucose-lowering therapy in newly diagnosed type 2 diabetes. The table specifies the basis for grading evidence in the report. A zero indicates: no reason to criticize this point. A minus sign with question mark indicates: some deficiencies, but not great enough to lower the strength of the

Outcomes	Number of participants (number of studies)	Study type	Risk of bias	Incon- sistency
Mortality	3 867 (1)	OBS ⊕⊕○○	–? Unblinded	1 study
Myocardial infarction	3 867 (1)	OBS ⊕⊕○○	0	1 study
Stroke	3 867 (1)	OBS ⊕⊕○○	0	1 study
Retinopathy (photo-coagulation)	3 867 (1)	RCT ⊕⊕⊕⊕	–? Unblinded	1 study
Nephropathy (albumin in urine >200 µg/minute)	Not reported			
Serious hypoglycemia	3 867 (1)	RCT ⊕⊕⊕⊕	–? Unblinded	1 study
Weight gain	3 867 (1)	RCT ⊕⊕⊕⊕	–? Unblinded	1 study

OBS = Observational study; RCT = Randomised controlled trial

evidence. Minus 1 or 2 indicate: deficiencies lower the strength of the evidence. A plus sign indicates: the evidence strength can be raised. However, it is not possible to achieve an overall evidence grade above ⊕⊕⊕⊕ (strong scientific evidence), or total evidence grade below ⊕○○○ (insufficient scientific evidence).

Indirectness	Imprecision	Publication bias	Effect size	Quality
0	0	0	0	Limited ⊕⊕○○
0	0	0	0	Limited ⊕⊕○○
0	-1	0	0	Insufficient ⊕○○○
0	0	0	0	Strong ⊕⊕⊕⊕
				Not reported
0	0	0	0	Strong ⊕⊕⊕⊕
0	0	0	0	Strong ⊕⊕⊕⊕

Table 5 Summary of findings on intensive glucose-lowering therapy in type 2 diabetes of prolonged duration (8–11 years at study outset). The results are from the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT). Follow-up periods in these studies ranged from 3.5 to 5.6 years.

Outcomes	Number of patients (no of studies & study design)	Absolute mean risk	Relative risk (95% CI)
Mortality	23 182 (3 RCTs)	7.2%	1.08 (0.88–1.32)
Cardiovascular mortality	23 182 (3 RCTs)	3.6%	1.13 (0.79–1.62)
Myocardial infarction (non-fatal)	23 182 (3 RCTs)	4.0%	0.86 (0.75–0.98)
Stroke	23 182 (3 RCTs)	2.7%	1.00 (0.86–1.17)
Retinopathy (photocoagulation)	12 681 (2 RCTs)	7.4%	0.96 (0.85–1.09)
Nephropathy (albumin in urine >200 µg/day)	12 599 (2 RCTs)	5.0%	0.77 (0.65–0.91)
Episodes of serious hypoglycemia	23 182 (3 RCTs)	3.2%	2.9 (2.4–3.5)
Weight gain	23 182 (3 RCTs)		

CI = Confidence Interval; RCT = Randomised controlled trial

Absolute effect of intensive therapy for approximately 5 years	Quality of evidence	Comments
Effects not confirmed	Conflicting results	Large, well-executed RCTs
Effects not confirmed	Conflicting results	Large, well-executed RCTs
6 fewer per 1 000 patients	Moderate ⊕⊕⊕○	
No effects	Limited ⊕⊕○○	Small effect not ruled out
No effects	Moderate ⊕⊕⊕○	
13 fewer per 1 000 patients	Strong ⊕⊕⊕⊕	
2 more per 100 patients per year	Strong ⊕⊕⊕⊕	
1 to 4 kg on average in the studies	Strong ⊕⊕⊕⊕	Depends on intervention

Table 6 Summary of evidence for intensive glucose-lowering therapy in type 2 diabetes of prolonged duration. The table specifies the basis for grading evidence in the report. A zero indicates: no reason to criticize this point. A minus sign with question mark indicates: some deficiencies, but not great enough to lower the

Outcomes	Number of participants (number of studies)	Study type	Risk of bias	Inconsistency
Total mortality	23 182 (3)	RCT ⊕⊕⊕⊕	−? Unblinded	Con- flicting
Myocardial infarction (non-fatal)	23 182 (3)	RCT ⊕⊕⊕⊕	−? Unblinded	−?
Stroke	23 182 (3)	RCT ⊕⊕⊕⊕	−? Unblinded	0
Retinopathy (photocoagulation)	12 681 (2)	RCT ⊕⊕⊕⊕	−? Unblinded	0
Nephropathy (albumin in urine >200 µg/minute)	12 599 (2)	RCT ⊕⊕⊕⊕	−? Unblinded	0
Episodes of serious hypoglycemia	23 182 (3)	RCT ⊕⊕⊕⊕	−? Unblinded	0
Significant weight gain compared to control group	23 182 (3)	RCT ⊕⊕⊕⊕	−? Unblinded	−? Less in ADVANCE

* In this case, multiple question marks have been interpreted as −1.

ADVANCE = Action in diabetes and vascular disease: Preterax and dia-micron modified controlled evaluation; RCT = Randomised controlled trial.

strength of the evidence. Minus 1 or 2 indicate: deficiencies lower the strength of the evidence. A plus sign indicates: the evidence strength can be raised. However, it is not possible to achieve an overall evidence grade above ⊕⊕⊕⊕ (strong scientific evidence), or total evidence grade below ⊕○○○ (insufficient scientific evidence).

Indirectness	Imprecision	Publication bias	Effect size	Quality
0	0	0	0	Conflicting
-?	-?	0	0	Moderate ⊕⊕⊕○
0	-2	0	0	Limited ⊕⊕○○
0	-1	0	0	Moderate ⊕⊕⊕○
0	0	0	0	Strong ⊕⊕⊕⊕
0	0	0	+1	Strong ⊕⊕⊕⊕ Risk depends on intervention
0	0	0	0	Strong ⊕⊕⊕⊕ Depends on intervention

SBU's Summary

Background and aim

In someone without diabetes, blood glucose is regulated through intricate interactions in the body. This regulation is so refined that the glucose levels in blood are relatively constant whether you drink a soft drink or starve. The most important factor in this interaction is insulin, a glucose-lowering hormone from the pancreas, but several other hormones and factors are also involved. In diabetes, this interaction does not function.

Fact Box 1 Type 1 diabetes.

Type 1 diabetes comprises 10% to 15% of all diabetes.

In type 1 diabetes, the body's own insulin production has partially or almost completely stopped. The body's immune system destroys the insulin-producing cells in the pancreas, which, in the long term leads to total insulin deficiency and life-long insulin therapy.

Treatment of type 1 diabetes primarily involves administering insulin in multiple doses or via an insulin pump. Insulin therapy in type 1 diabetes requires frequent self-monitoring to manage the blood glucose levels and avoid hypoglycemia. Furthermore, regularity is necessary regarding meal times and other lifestyle factors. Regular exercise is recommended.

The general goal in treating diabetes is to maintain a high quality of life while preventing acute and long-term complications.

Fact Box 2 Type 2 diabetes.

Type 2 diabetes accounts for 80% to 90% of all diabetes.

Type 2 diabetes is a disease that usually debuts in people older than 40 years and is strongly associated with overweight/obesity.

Heredity, overweight, and insufficient physical activity jointly contribute to the development of the disease.

Type 2 diabetes reduces sensitivity to insulin (insulin resistance), eg, in muscles and fat cells, which leads to an increased need for insulin. With time, the insulin produced by the body is insufficient to meet the body's need, resulting in diabetes.

Basically, treatment aims at reducing insulin resistance. Achieving this requires lifestyle interventions, eg, increased physical activity and changes in diet. If these lifestyle changes are insufficient to maintain needed blood glucose levels, pharmaceuticals (tablets and/or insulin) are administered.

Since type 2 diabetes is a progressive disease, most people will require insulin injections after approximately 10 years of treatment.

The basic treatment goal in treating diabetes is to maintain a high quality of life and prevent acute and long-term complications.

In diabetes, there is an association between average blood glucose levels measured as HbA_{1c} and the risk for complications from the disease. This risk is high, with elevated HbA_{1c} (mainly in HbA_{1c} above 9%, see Fact Box 3). Hence, in treating diabetes it is natural to work toward reducing HbA_{1c} to levels close to 5%, ie, the upper limit of the normal value.

In type 1 diabetes we refer to this as intensive insulin therapy. In type 2 diabetes, several different types of drugs are used, and therefore we refer to intensive glucose-lowering therapy. From a practical standpoint, achieving this high goal is shown to be difficult, except in patients early in the course of their disease. In patients with relatively newly diagnosed diabetes, the body's regulation mechanisms still function to some extent and may retain some insulin production capacity. Unfortunately, insulin production decreases with the length of time the patient has diabetes, and multiple drugs and/or higher insulin doses are required to achieve low blood glucose levels. Since blood glucose levels are held down largely by drugs and injected insulin, the body does not have the possibility to regulate itself. Hence, the risk for episodes of very low blood glucose levels and so-called "shifting" blood glucose increases the longer the patient has diabetes. Shifting blood glucose means that the values during the same day swing from very low levels (Fact Box 4) to very high levels, which is a problem primarily in type 1 diabetes.

Fact Box 3 What is HbA_{1c}?

HbA_{1c} refers to molecules in hemoglobin, the red blood pigment to which glucose binds.

Depending on the blood glucose level, different amounts of HbA_{1c} are formed during the entire 120-day life of red blood cells, reflecting the average blood glucose level.

HbA_{1c} shows, with greatest precision, glucose control during the preceding 4 to 6 weeks.

HbA_{1c} is the most important measure of long-term average glucose control and is usually measured during each clinical checkup for diabetes.

HbA_{1c} is expressed as the percent of HbA_{1c} in relation to the total hemoglobin volume in the blood, and the upper limit of the normal range is 5.0%.

A change in HbA_{1c} of 1 percentage point corresponds to approximately 1.6 mmol/L change in mean blood glucose during the day.

Fact Box 4 Definitions of hypoglycemia.

Symptomatic hypoglycemia is expressed in symptoms such as sweating, heart palpitations, tremors, hunger, or signs of glucose deficiency in the central nervous system, eg, difficulty concentrating, tiredness, moodiness, and irritability.

Serious hypoglycemia is defined in most clinical studies as hypoglycemia (lower than normal level of blood glucose) at a level of severity that requires help from others (eg, relatives, healthcare staff). In the most serious manifestation of diabetes, patients lose consciousness. As a rule, this requires the injection of glucose. Rare cases of prolonged, deep hypoglycemia involving unconsciousness could lead to permanent brain damage. In extremely severe cases the condition is potentially life threatening.

Type 1 and type 2 diabetes are two different diseases having completely different causes and courses (see Fact Box 1, Fact Box 2). Approximately 330 000 people in Sweden have diabetes. They all have elevated blood glucose levels and will develop diabetes complications over time. The most common complications in type 1 diabetes result from damage to the small vessels (capillaries) in the retina, kidneys, and nerves. Potential manifestations include impaired vision, impaired kidney function, and impaired nerve function – all categorized as microvascular complications. In their most severe form these can lead to blindness, severe kidney failure, and foot ulcers/amputation. In type 2 diabetes, cardiovascular diseases (eg, myocardial infarction, stroke, and impaired circulation in the legs) are more common and represent a substantially greater problem.

Treatment, mainly in type 2 diabetes, targets several risk factors including elevated blood glucose, hypertension, blood lipid disorders, overweight, and smoking. Strong scientific evidence shows that improved treatment of hypertension and blood lipid disorders helps reduce the risk of microvascular complications and cardiovascular disease in type 2 diabetes.

In general, it is more difficult to normalize elevated blood glucose values than to optimize blood pressure and blood lipids. Treatment of high blood glucose levels also requires changes in lifestyle and pharmacotherapy. Pharmacotherapy aimed at reducing blood glucose is, however, more complicated and, for example, carries greater risks for serious side effects (eg, serious hypoglycemia) than does antihypertensive treatment. Primarily it is important to try to reduce blood glucose to low or near normal levels, as in intensive glucose-lowering therapy. The effects of improving glucose control have not been as thoroughly studied as have the effects of treating blood pressure and blood lipids. Hence, there is reason to study the scientific evidence regarding intensive glucose-lowering therapy in diabetes.

Limitations

This report focuses on intensive glucose-lowering therapy in type 1 diabetes and type 2 diabetes in adult patients.

Questions

- Are the risks for microvascular complications and cardiovascular disease reduced when intensive pharmacotherapy clearly lowers blood glucose in type 1 and type 2 diabetes?
- Is there an increased risk for side effects, eg, serious hypoglycemia and substantial weight gain?
- How is quality of life affected?
- Are treatments cost effective?

Methods

SBU uses thorough and systematic methodology to search bibliographic databases for relevant literature on the issue being studied. Included studies are assessed individually for quality, and specially designed methodology is used to summarize key information in table format. Findings are graded to reflect the strength of the evidence, and the assessment aims to cover medical, economic, social, and ethical perspectives.

Fact Box 5 Study quality and strength of the evidence.

Study quality refers to the scientific quality of an individual study and its ability to provide a valid answer to a specific question.

Strength of the evidence refers to a judgment of the total strength of all scientific evidence and its ability to provide a valid answer to a specific question. SBU uses GRADE, an international grading system for the body of evidence. Study design is a key element in the overall judgment of each outcome measure. Other factors that can weaken or strengthen the power of the evidence are: risk of bias, inconsistency of results, indirectness of evidence, data precision, risk of publication bias, and other aspects, eg, effect size and the dose-response relationship.

Grading the strength of the evidence – four levels:

Strong scientific evidence (⊕⊕⊕⊕) is equivalent to high quality of the body of evidence according to GRADE.

Moderately strong scientific evidence (⊕⊕⊕○) is equivalent to moderate quality of the body of evidence according to GRADE.

Limited scientific evidence (⊕⊕○○) is equivalent to low quality of the body of evidence according to GRADE.

Insufficient scientific evidence (⊕○○○) is equivalent to very low quality of the body of evidence according to GRADE.

The stronger the evidence, the less likely it is that the results presented will be affected by new research findings within the foreseeable future.

Conclusions

SBU's conclusions represent our overall judgment of benefits, risks, and cost effectiveness.

Type 1 diabetes

Four randomized trials (n=1 657 patients) were included: the Diabetes Control and Complications Trial (DCCT), the Stockholm Diabetes Intervention Study (SDIS), Verillo, and the Microalbuminuria Collaborative Study Group (MCSG). The two largest studies, DCCT (1 441 participants) and SDIS (102 participants), were judged to be high-quality studies, and the other two were of moderate quality. Average follow-up in the studies was slightly less than 7 years.

The Diabetes Control and Complications Trial (DCCT) is a large study and alone accounts for most of the scientific evidence. In some respects the study comprises two studies since, at the outset, patients were divided into two study arms – those who had had diabetes for a maximum of 5 years and were without complications, and those who had had diabetes for more than 5 years and/or had mild complications. The results in both study arms were, however, similar. Risks for developing substantial damage involving the eyes, nerves, and kidneys were much lower in the intensive groups than in the control groups. It should be noted that intensive insulin therapy carried a much higher risk for serious hypoglycemia, insulin coma, and weight gain compared to standard treatment in the control groups. The results of DCCT (published in 1993) were very clear and were supported by the concurrent so-called Stockholm Study, SDIS (Table 1). At the conclusion of these two studies, all participants were offered the option of continuing their follow-up in observational studies, and the great majority accepted. All participants were then offered intensive insulin therapy, which in conjunction with publication of DCCT became standard practice in type 1 diabetes. These observational studies revealed even greater benefits in the previous intensive therapy groups compared to the control groups.

In summary, the patient benefits of intensive insulin therapy in terms of reduced prevalence of diabetes complications outweigh the increased risks for side effects from treatment (mainly serious hypoglycemia and substantial weight gain). It should also be noted that not every patient can handle the rigor of intensive insulin therapy, which places major demands on the patient in terms of frequent self-monitoring of blood glucose and regular, healthy lifestyle habits.

Type 2 diabetes

Four randomised trials were included, ranging from approximately 1 800 to slightly over 11 000 patients that were followed up to 10 years (Table 7).

Table 7 Important characteristics of the included studies.

Measure	UKPDS (33 and 34) 1998	ACCORD 2008	ADVANCE 2008	VADT 2008
N	4 209	10 251	11 141	1 791
Follow-up (years)	10 plus another 7*	3.5	5	5.6
Age at inclusion (years)	53	62	66	60
Duration (years)	Newly diagnosed	10	8	11
BMI (kg/m ²)	28	32	28	31
HbA _{1c} at study start (%)	7.1	8.3	7.5	9.4
Cardiovascular disease (%)	–	35	32	40
Microvascular complications (%)	36	–	27	62

* Observational follow-up where the difference in HbA_{1c} between the groups had disappeared within 1 year after the start.



In interpreting the results we have considered that UKPDS differs substantially from the other studies with regard to several components. The most important of these are probably: the inclusion of only those patients with newly diagnosed diabetes, the lack of target HbA_{1c}, the limited treatment of other risk factors, the use of only older glucose-lowering drugs (the study was started in 1977), and the prolonged follow-up period. UKPDS initially reported a lowering of HbA_{1c} levels, but during the course of the study HbA_{1c} in both groups increased to levels that were higher than those at the outset of the study, before intensive glucose-lowering therapy was started. UKPDS differs so much from the other studies that it is not included in our meta-analysis, which includes data only from ACCORD, ADVANCE, and VADT. Data from UKPDS has, however, been reported visually in the meta-analysis for the purpose of completeness.

Effects of intensive glucose-lowering therapy on microvascular complications

Both UKPDS and ADVANCE showed a reduced risk for microvascular complications, retinopathy in UKPDS, and nephropathy in ADVANCE. The effects, however, were relatively small and corresponded to approximately 3 cases per 100 patients during the 10 years of the study. No statistically significant difference was found between the groups in VADT, but the study was also of insufficient statistical power. The microvascular data from ACCORD have yet to be presented.

Effects of intensive glucose-lowering therapy on cardiovascular disease

UKPDS reported a reduction in the number of myocardial infarctions corresponding to 7 cases per 1 000 patient years only in a subgroup of patients with obesity who were treated with metformin. Otherwise, no statistically significant effects of intensive therapy on cardiovascular disease were observed. However,

the observational follow-up study approximately 7 years after the conclusion of the study showed a reduction in total mortality and a lower number of myocardial infarctions in the intensive groups (in both metformin and the SU/insulin therapy groups) compared to the control group.

In ADVANCE and VADT, no significant effects of intensive glucose-lowering therapy on cardiovascular disease were observed. ACCORD was stopped approximately 1.5 years prematurely due to increased total mortality corresponding to approximately 11 cases per 1 000 patients during the 3.5 years that the study was in progress. Our meta-analyses including these three studies revealed no significant effects on either total mortality or mortality from cardiovascular diseases. However, the number of myocardial infarctions decreased significantly. The types of myocardial infarctions are reported differently in the studies.

Side effects of intensive glucose-lowering therapy

In UKPDS, the intensive group gained approximately 3 kg more than the control group during the 10 years of the study. In the three later studies, the results differ: in ADVANCE, no substantial weight gain was observed, but in ACCORD and VADT a clearly greater average weight gain was observed in the intensive groups compared to the control groups (3 versus 4 kg respectively). The risk for serious hypoglycemia was also elevated in the intensive groups in these two studies, but not to the same extent as with type 1 diabetes.

Health economics

The studies suggest that intensive therapy aimed at lowering blood glucose involves low to moderate costs per quality-adjusted life-year and is thereby cost effective in newly diagnosed type 2 diabetes.

The cost per quality-adjusted life-year for intensive therapy is related to age of onset and rises as patient age increases.

Cost-effectiveness studies are lacking on the treatment of patients with type 2 diabetes who have had the disease for a longer period. Without solid medical data, economic studies are difficult to conduct.

Ethical and social aspects

Patients should be given maximum opportunity to participate in decisions concerning their treatment. Where the scientific evidence is somewhat clear – intensive insulin therapy for type 1 diabetes – healthcare staff should establish the conditions needed for the patient to make an informed decision. If these conditions are met, the patient’s decision should be respected.

When the scientific evidence is less clear, and more difficult to implement – intensive glucose-lowering therapy for type 2 diabetes – the conditions for informed decisions should also be established. Hence, it is important for healthcare personal to consider their level of influence on the decision. They should be aware that the greater the degree of influence they exercise, the greater their responsibility for the consequences of the decision to treat or not to treat.

Consequence analysis

Type 1 diabetes

Intensive insulin therapy in type 1 diabetes helps reduce the risk of complications in the eyes, kidneys, and nerves and reduces the risk of cardiovascular disease. The longer the patient has an unsatisfactory average blood glucose level, the greater the risk for developing serious diabetes complications in the long term.

As a rule, it is also easier to maintain good average blood glucose levels early in the disease course, even in type 1 diabetes. This suggests that intensive insulin therapy should be started as quickly as possible after diagnosis. Since the risk for diabetes complications decreases as HbA_{1c} declines, it is important to aim for the lowest possible HbA_{1c} while concurrently considering the risks for serious hypoglycemia. A reasonable target value, according to the studies reviewed, is HbA_{1c} of approximately 6.0% (Mono-S). This goal may need to be adjusted, particularly considering the risk for serious hypoglycemia. The best possible HbA_{1c} value varies depending on several factors and needs to be adapted to the individual patient. A large percentage of patients will be unable to achieve this target value for various reasons. In clinical practice the values appear to be higher, and the diabetes registry shows that HbA_{1c} exceeds 7% in approximately one half of the people with diabetes that debuts before 30 years of age.

Intensive insulin therapy is demanding on the patient, and for most patients it means that they must adjust their life to optimize factors such as diet, exercise, sleep, stress, and medication. To enable intensive insulin therapy, substantial support is needed from health services in the form of medications, educational input, devices for self-monitoring of blood glucose, etc. Intensive insulin therapy requires regular follow-up visits at appropriate intervals and the possibility to quickly contact care staff, eg, to adjust insulin dosage and discuss different types of problems that might arise.

For intensive insulin therapy, resources are needed to enable adequate care of patients that can benefit. This can lead to increased costs for society in the short term.



Type 2 diabetes

Intensive glucose-lowering therapy for newly diagnosed type 2 diabetes reduces the risk for retinal changes. After prolonged follow-up periods, a reduced risk for cardiovascular-related events is also observed. Intensive glucose-lowering therapy for newly diagnosed type 2 diabetes is relatively uncomplicated, associated with few side effects, and is cost effective. It is difficult to find support for clear target values for HbA_{1c} in UKPDS. International guidelines suggest target values around <5.5% to 6.0% (adjusted for Mono-S). Intensive glucose-lowering therapy requires patient education and regular visits at adequate intervals.

Even in type 2 diabetes of longer duration, intensive glucose-lowering therapy is associated with some reduced risk for nephropathy. Very high HbA_{1c} is harmful and should be avoided. The effects on cardiovascular disease in the studies are conflicting. A reduced risk for non-fatal myocardial infarction is reported in the intensive groups, but the risk of death was higher in a large study (ACCORD). This makes it more difficult to judge the relationship between benefit and risk. Hence, cost-effectiveness is uncertain. Intensive glucose-lowering therapy aimed at achieving low HbA_{1c} after many years of type 2 diabetes is complicated. As a rule, treatment requires several different drugs in combination. Nevertheless, it can be difficult to achieve the low target values established for HbA_{1c}. The risks for side effects, primarily severe hypoglycemia, increase with the number of years one has had diabetes. These factors could lead to recommendations to individualize treatment goals to a greater extent in patients with type 2 diabetes of long duration and/or cardiovascular disease, and accept target values less stringent than previously recommended.

The situation may require attention to this patient group in case that provider reimbursement is linked to the HbA_{1c} achieved, as reported in the quality registry. Knowledge concerning long-term effects could change if the patients that participated in the large ACCORD, ADVANCE, and VADT studies continue to be followed up for a longer period after the conclusion of the randomised trials.

Knowledge gaps

Important research questions

Type 1 diabetes

- How does intensive insulin therapy influence the risk for cardiovascular disease and damage to the retina, kidneys, and nerves in patients that have had type 1 diabetes for a long period, and in patients that already have such injuries?
- What levels of HbA_{1c} are optimal in different patient groups, considering the balance between benefit and risk?
- How should the patient's ability and motivation to carry out intensive insulin therapy be supported and developed?

Type 2 diabetes

- How does intensive glucose-lowering therapy, where HbA_{1c} is kept low for a prolonged period (10 years or longer) affect the risks for diabetes complications and cardiovascular disease?
- How has intensive glucose-lowering therapy affected the occurrence and degree of long-term complications in the ADVANCE, ACCORD, and VADT studies?

- How should the patient's ability and motivation to carry out intensive glucose-lowering therapy be supported and developed?
- Are different drug combinations associated with differences in the occurrence of cardiovascular diseases, microvascular complications, and side effects?
- What level of HbA_{1c} is optimal in different patient groups, considering the balance between benefits and risks?

Target groups

The report is intended to serve as a basis for national guidelines on diabetes care issued by the Swedish National Board of Health and Welfare and targets healthcare professionals responsible to care for people with diabetes. It also target politicians and administrators in decision-making positions in health care. This report may also provide valuable information to patients and their families.

Reports published by SBU

SBU reports in English (1997-2009)

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Interventions to Prevent Obesity (2005), no 173E

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Sickness Absence – Causes, Consequences, and Physicians' Sickness Certification Practice Scandinavian Journal of Public Health, Suppl 63 (2004), 167/suppl

Radiotherapy for Cancer (2003), Volume 2, no 162/2

Treating and Preventing Obesity (2003), no 160E

Treating Alcohol and Drug Abuse (2003), no 156E

Evidence Based Nursing: Caring for Persons with Schizophrenia (1999/2001), no 4E

Chemotherapy for Cancer (2001), Volume 2, no 155/2

CABG/PTCA or Medical Therapy in Anginal Pain (1998), no 141E

Bone Density Measurement, Journal of Internal Medicine, Volume 241 Suppl 739 (1997), 127/suppl

SBU Summaries in English (2004–2009)

Patient Education in Managing Diabetes (2009), no 510-47

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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.

Intensive Glucose-Lowering Therapy in Diabetes

SBU's report on Intensive Glucose-Lowering Therapy in Diabetes builds on a systematic, critical review of the scientific literature in the field.

The report is one in a series of reports published by SBU (Swedish Council on Technology Assessment in Health Care).

This document presents the summary and conclusions of the full report, which has been approved by SBU's Board of Directors and Scientific Advisory Council.