Acknowledgements

The work presented in this dissertation was carried out during my appointment as a research fellow at the Department of Cardiology at Bispebjerg University Hospital, Copenhagen, Denmark, from 2002-2005. I am indebted to the participating patients in the DANSUK study, - for their patience, perseverance and faith in me undertaking their treatment. This work would have been difficult to accomplish without the supervision from chief physician, Jørgen Fischer Hansen DMSc, chief investigator, Mette Madsen DSc, Thomas M. Melchior MD, PhD, Eva Hommel DMSc, and professor Christian Torp-Pedersen DMSc.

I wish to thank all the personal in the unit of cardiac rehabilitation at Bispebjerg University Hospital for their outstanding help. I also wish to thank my colleagues Ann-Dorthe Olsen Zwisler MD, PhD for allowing the DANSUK study to become a reality as part of the DANREHAB trial and Marianne Frederiksen, MD for her support and encouragement when needed. I thank the two research nurses affiliated to the project, Jeannette Larsen and Malene Ejlertsen, for their great involvement and enthusiasm in the process of developing and promoting the DANSUK study.

I thank the following supporters of the DANSUK study: The Copenhagen Hospital Corporation Research Council, the Danish Pharmacy Foundation of 1991, The Research Foundation of Bispebjerg Hospital, Eva and Henry Frænkels Memorial Foundation, The Scandinavian Jewish Foundation, Desireé and Niels Ydes Foundation, the Danish Heart Foundation, the Danish Animal Protection Foundation, Builder Laurits Peter Christensen and Wife Sigrid Kirsten Christensens Foundation, Bristol-Myers Squibb, Merck Sharp & Dohme and AstraZeneca A/S.

Finally I want to thank my beloved family: Kenn, Peter and Julie Sofie for their understanding and helpfulness in periods with incomprehensible behaviour as well as mentally and physically absent-mindedness.

I dedicate this PhD dissertation to my father Valdemar Soja.

"Agere considerate pluris est quam cogitare prudenter"

Preface

It is sad that in their lifetime, patients with type 2 diabetes suffer from quality of life reducing microvascular complications as retinopathy that may lead to blindness, nephropathy with the risk of renal failure and dialysis, and neuropathy with intangible pain and amputations. However, ultimately, the majority of the patients with type 2 diabetes will die of premature macrovascular disease prior to a disabling cerebrovascular catastrophe or congestive heart failure following a silent myocardial infarction. Because of the malignant nature of type 2 diabetes and a long symptom-less period prior to the diagnosis, the patients often experience belated admissions and greater cardiac morbidity and mortality. And even if there have been major advances and successes in the understanding and treatment of cardiovascular disease during the last decades, patients with type 2 diabetes with multiple cardiovascular disease risk have not yet obtained the full benefits of these endeavours. Both micro- and macrovascular complications to type 2 diabetes are potentially preventable given prompt diagnosis and effective patient and professional education as well as comprehensive care.

This PhD study was initiated at the suggestion and guidance of chief physician Jørgen Fischer Hansen MDSc, when I worked as a resident at the department of Cardiology at Bispebjerg University Hospital. Elaborating the DANSUK protocol, fundraising, developing the educational diabetes programme while undertaking the intensified patient care in the unit of cardiac rehabilitation was a great educational and personal challenge which at times seemed overwhelming.

This dissertation will describe type 2 diabetes from a cardiovascular perspective. Studies in preventing the development of type 2 diabetes in patients with impaired glucose tolerance, prevalence of impaired glucose metabolism among patients with ischemic heart disease and the body of evidence in secondary preventive treatment of type 2 diabetes are scrutinized. Methods and results of the DANSUK study are described in details and the implications of type 2 diabetes and prediabetes in the settings of comprehensive cardiac rehabilitation are discussed.

This dissertation is based on 2 articles and 1 book chapter:

1. Soja AMB, Zwisler ADO, Melchior T, Hommel E, Torp-Pedersen C, Madsen M. Prevalence and characteristics of impaired glucose metabolism in patients referred to comprehensive cardiac rehabilitation – the DANSUK study. Eur J Cardiovasc Pre Rehabil 2006,13:784-790

2. Soja AMB, Ejlertsen M. Cardiac Rehabilitation and type 2 diabetes. In Cardiac Rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital. Eds.: Zwisler ADO, Schou L, Soerensen LV. Copenhagen, H:S Bispebjerg Hospital, National Institute of Public Health; 2003*.

3. Soja AMB, Zwisler ADO, Melchior T, Frederiksen M, Torp-Pedersen C, Hommel E, Madsen M. Use of intensified comprehensive cardiac rehabilitation to improve risk factor control in patients with type 2 diabetes or impaired glucose tolerance – the randomized DANSUK study. Accepted Am Heart J, January 2007.

*The original book was published in Danish in November 2003. The above listed book chapter have been translated into English as part of the PhD dissertation and is available at the homepage www.CardiacRehabilitation.dk

Supervisors:
Jørgen Fischer Hansen, DMSc, chief physician, Bispebjerg University Hospital, Copenhagen
Mette Madsen DSc, research director, National Institute of Public Health, Copenhagen
Thomas M. Melchior, PhD, Roskilde County Hospital, Roskilde
Eva Hommel, DMSc, Steno Diabetes Centre, Gentofte

List of abbreviations and acronyms:

ADA	American Diabetes Association
ABPI	Ankle-brachial pressure index
ACEI	Angiotensin-converting enzyme inhibitor
ARA	Angiotensin receptor-II antagonist
ASA	Acetylsalicylic acid
BMI	Body mass index
CVD	Cardiovascular disease
CHF	Congestive heart failure
CR	Cardiac rehabilitation
DANSUK	Det DANske stadium af hjertepatienter med SUKkersyge
FPG	Fasting plasma glucose
GIK	Glucose-insulin-potassium-infusion
HbA1c	Glycosylated haemoglobin A1c
HDL	High density lipoprotein
HOMA-IR	Insulin resistance based on the homeostasis model
HR	Patients at high-risk for ischemic heart disease
IHD	Ischemic heart disease
IFG	Impaired fasting glucose
IGM	Impaired glucose metabolism synonymous with glucose intolerance
IGT	Impaired glucose tolerance
KT2DM	Known T2DM at baseline
LDL	Low density lipoprotein
Mets	1 Mets denotes resting metabolic rate at 3.5 ml O^2/kg/min
MI	Myocardial infarction
NGT	Normal glucose tolerance
ST2DM	Screen-detected T2DM
OGTT	Oral glucose tolerance test
PAD	Peripheral artery disease
Prediabetes	Designates IGT and IFG
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UC	Usual care
UKPDS	UK Prospective Diabetes Study
VLDL	Very low-density lipoprotein
WHO	World Health Organization

Part I: Type 2 diabetes mellitus – a cardiovascular perspective

1. Introduction and objectives 8
1.1. Source reference 9

2. Background 10
2.1. Prevalence of IGM in patients with IHD 10
2.2. Secondary prevention of T2DM 11
2.3. Mono- and multifactorial treatment of T2DM in reducing CVD 13
2.4. Behavioural modifications 14
2.5. Treatment of hyperglycaemia 16
2.6. Treatment of arterial hypertension 19
2.7. Treatment of dyslipidemia 22
2.8. Integrated care in settings of CR 24

Part II: The DANSUK study

3. Background and design (the book chapter, appendix 1) 26
3.1. Background 26
3.2. Design and endpoints 26
3.3. Classifying IGM 27
3.4. Comprehensive cardiac rehabilitation 28
3.5. The diabetes module – the DANSUK study 29

4. Methods 30
4.1. Data collection 30
4.2. Definitions 32
4.3. Intensive treatment modalities in the unit of CR 34
4.4. Statistical methods 38

Part III: Prevalence of IGM in the DANSUK study

5. Results – DANSUK 1 (article 1, appendix 3) 40
5.1. Baseline characteristics of the study population 40
5.2. Prevalence of IGM in the DANSUK study 41
5.3. Age and sex specific prevalence of IGM 42
5.4. IGM and cardiac disease group assignment 42
5.5. The WHO definition compared to the ADA criteria 42
5.6. FPG as a screening tool 43
5.7. Cardiovascular risk profile 45
5.8. Predictors of T2DM and IGT 45
5.9. Discussion 46
5.10.Conclusions (DANSUK 1) 47

Part IV: Intensive multifactorial intervention in patients with glucose intolerance

6. Results – DANSUK 2 (article 2, appendix 4) 50
6.1. Baseline characteristics of the two study groups 50
6.2. Main results 51
6.3. Discussion 52
6.3.1. Intensive treatment of hyperglycaemia (primary endpoint) 52
6.3.2. Intensive treatment of blood pressure and lipids (secondary endpoints) 54
6.3.3. Intensive treatment of behavioural modifications (secondary endpoints) 55
6.4. Obtaining treatment goals 56

6.4.1. Pharmacological treatment 58
6.4.2. Adherence to polypharmacy 59

6.5. Conclusions (DANSUK 2) 60

7. Final comments 61
7.1. Study limitations and representativity of the DANSUK study 62

Part V: Implications from the DANSUK study

8. Future prospects of CR in patients with IGM 64
8.1. Barriers for implementation and success 65
8.2. Concluding remarks 66

Summary 67
Resumé 68
References 70

Appendix 1: Chapt. 11. Type 2 diabetes. Anne Merete Boas Soja, Malene Ejlertsen. In Cardiac rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital. Eds.: Zwisler ADO, Schou L, Sorensen LV. Copenhagen, H:S Bispebjerg Hospital, National Institute of Public Health; 2003.

Appendix 2: Scheme of self-monitoring blood measurements

Appendix 3: Article 1. Prevalence and characteristics of impaired glucose metabolism in patients referred to comprehensive cardiac rehabilitation - the DANSUK study

Appendix 4: Article 2. Use of intensified comprehensive cardiac rehabilitation to improve risk factor control in patients with type 2 diabetes or impaired glucose tolerance – the randomized DANSUK study

Part I: Type 2 diabetes mellitus – a cardiovascular perspective

1. Introduction and objectives

Type 2 diabetes (T2DM) is a complex clinical problem that has reached epidemic proportions. The World Health Organisation (WHO) has proclaimed that in the year of 2025 at least 300 million people (5.4% of the worlds population) will suffer from T2DM and as today the disease accounts for 4 million deaths per year that is close to 9% of global deaths [1-3]. Globalization and the increasing prevalence of obesity and sedentary lifestyle are key contributors to the raising prevalence of T2DM and prediabetes throughout the world [4-8]. The overall prevalence of cardiovascular disease (CVD) is as high as 55% among patients with newly diagnosed T2DM causing up to 80% of deaths among these patients [9-12]. The cardiovascular mortality rate is doubled in men who have T2DM compared to their normal metabolic counterparts and more than quadrupled in women in whom T2DM tends to eliminate the usual female advantage in risk of death from CVD [13-16]. Type 2 diabetes is also a recognized risk factor for poor outcome after myocardial infarction (MI) and after either percutaneous or surgical coronary revascularization [17-20], making secondary prevention in these patients highly demanding. Since mortality after MI are decreasing, the potential need for cardiac rehabilitation (CR) in the population of MI survivors, is growing [21]. Moreover, as duration of hospital stays for MI have decreased over time, reducing the opportunity for in-hospital based risk factor intervention, outpatient hospital-based CR has become an important instrument in obtaining and continuing lifestyle improvements [22].

Cardiac rehabilitation has been defined by the WHO as *'the sum of activity required to influence favourably the underlying cause of the disease, as well as to ensure the patients the best possible physical, mental and social conditions so that they may, by their own efforts, preserve, or resume when lost, as normal a place as possible in the life of the community'* [23]. In 1994 the American Heart Association declared that CR should not be limited to an exercise training programme but should also include an individualized comprehensive, multifactorial intervention encompassing modalities as baseline patient assessment, patient education, dietary counselling, smoking cessations, psychosocial and vocational support, risk factor control including appropriate use of cardioprotective drugs and clinical follow-up visits [24].

The prevalence of T2DM in patients with ischemic heart disease (IHD) attending CR has been estimated to 20-30% [25-28]. Although studies have reported beneficial impact of CR on outcome in these patients, most data are generated from small trials before the era of reperfusion and revascularization and includes mostly middle-aged men [29,30]. Recently a meta-analysis has indicated that a broader target group could benefit from comprehensive CR [31]. T2DM causes lesser participation in CR programmes and independently predicts re-hospitalizations [32,33] indicating that patients with T2DM and CVD are more ill and disabled than their metabolic normal counterparts. Patients with T2DM seem to highly benefit from treatment reducing morbidity of CVD, but they have often been withheld from evidence-based treatment [34-37]. Patients with T2DM also do not appear to obtain the same benefit from standard CR programmes as patients without T2DM [35]. A survey in 2002 among randomly

selected patients with T2DM revealed that 70% of the patients did not believe they were at serious risk for CVD [38]. This ignorance among the patients and inadequacy among the care providers underline the great educational needs and future challenges in the prevention and treatment of CVD in patients with T2DM.

The objectives of this dissertation are:

1. To estimate the prevalence and characteristics of known and unrecognized type 2 diabetes, impaired glucose tolerance, and impaired fasting glucose in accordance with modern diagnostic criteria in a group of patients referred to hospital-based outpatient comprehensive cardiac rehabilitation – The DANSUK study.
2. To examine, in the DANSUK population, the concordance rate between impaired fasting glucose and impaired glucose tolerance and thereby evaluate a systematic use of an oral glucose tolerance test.
3. To describe, in the DANSUK population, independent predictors of different stages of impaired glucose metabolism and clarify differences in cardiovascular risk profile between these groups.
4. To develop and implement a chronic disease management programme including optimal diabetes and cardiac risk factor control in patients with type 2 diabetes or impaired glucose tolerance.
5. To evaluate the effect of intensified comprehensive cardiac rehabilitation in patients with type 2 diabetes or impaired glucose tolerance compared to usual care.

1.1. Source reference

In the following chapter secondary diabetes prevention trials, observational trials as well as mono- and multifactorial controlled risk reducing trials in patients with T2DM with and without CVD will be presented. Individuals with T2DM or impaired glucose tolerance (IGT) were either the focus of the mentioned studies or subgroups of larger trials. It is beyond the frames of this dissertation to give a thorough description of all the non-pharmacological core components of CR. The review will mainly cover the latest evidence of pharmacological intervention towards patients with T2DM and CVD addressing hyperglycaemia, systemic hypertension, and lipid control on which the physician performed intensified treatment in the DANSUK study was based. The searches were all done in Medline/PubMed in the autumn of 2005 focusing on randomized controlled trials, systematic reviews and meta-analyses, published in English after the period of 1990, involving only adults with T2DM or IGT. Keywords were 'type 2 diabetes', 'diabetes' and 'randomized controlled trials', 'cardiac rehabilitation' combined with:

Secondary diabetes prevention studies: 'impaired glucose tolerance', 'diabetes prevention', 'lifestyle intervention', 'behavioral modification'.
Glucose lowering trials: 'hyperglycaemia', 'glucose control', 'haemoglobin A1c', and names for different individuals drugs

Blood pressure lowering trials: 'systemic hypertension', 'arterial hypertension', 'hypertension', and names for different individual drugs.
Lipid lowering trials: 'dyslipidaemia', 'lipid control', 'hypercholesterolemia', 'statin' and names for different individual drugs

2. Background

2.1. Prevalence of IGM in patients with IHD

Impaired glucose metabolism (IGM) is common in patients with IHD, but a major obstacle in treating and preventing T2DM and the associated CVD is that it often remains undiagnosed. The importance of early diagnostic procedures of T2DM is seen in many studies [39-42], where the prevalence and severity of CVD are closely related to the duration of T2DM.

It has been known for years that non-diabetic patients with an acute myocardial infarction (MI) often present with glucosuria and hyperglycaemia [43,44]. The stress-induced increased glucose turnover and insulin resistance of hyperglycaemia have previously been interpreted as a plea for tolerating moderately elevated blood glucose levels during MI although hyperglycaemia in these patients was associated with a worse prognosis compared to normoglycaemia. Table 2.1 shows some of the recent studies establishing the prevalence of IGM in groups of patients mainly with IHD. Through the last decades the prevalence of T2DM, IGT and IFG in patients with MI have increased probably due to the global increase in obesity and improved diagnostic procedures [57]. The prevalence of known T2DM in patients with MI lies between 15%-24% [34,58,59] and the prevalence of previously unrecognized T2DM seems to be in the same range or even much higher as shown in a prospective study of Glucose tolerance in patients with Acute Myocardial Infarction (GAMI) which included only patients with no previous diagnosis of T2DM and a FPG-level above 11.1 mmol/l [47]. In the same study, IGT was diagnosed in 40% of the patients before discharge and it was suggested that FPG taken on admittance day 4 and an oral glucose tolerance test (OGTT) before discharge could be used as early markers for IGM [47]. The European Heart Survey revealed that more than 60% of the patients admitted with MI had IGM, thus IGM is more common among ischemic patients than normal glucose tolerance (NGT) [27]. A prevalence of IGM as high as 85% has also been reported in individuals referred to elective coronary angiography [54,52] and the advancement of coronary artery disease seems to correlate with the degree of glucose deterioration [52]. The prevalence of the specified classes of glucometabolic abnormalities in patients eligible for CR has never been investigated.

Like the increase of IGM in patients with CVD, the prevalence of IGM has also increased in the Danish background population. Coincide with an increase in BMI over a 22-year period, a marked increase in the prevalence of T2DM and IGT among 60-year-old individuals has been observed [60]. In the DANSUK study there is no matched group of non-cardiac diseased individuals. As part of a population-based primary prevention study on CVD and T2DM, the Inter99 study will therefore be referred to as an external reference population to the DANSUK study, representing the general population in Denmark (overall N=13.016). The Inter99 study determined the age- and sex-specific prevalence of IFG, IGT,

Table 2.1. Recent studies investigating the prevalence of glucose intolerance in patients with high-risk of ischemic heart disease (IHD) and in patients with established cardiovascular disease (CVD)

	Publication year	Patient category	Number of patients	Age (mean)	Male (%)	BMI (mean)	KT2DM (%)	ST2DM (%)	IGT (%)	Isolated IFG (%)	NGT (%)
Surveys											
MMWR[45]*	2003	CVD	720	62	41	NA**	25	NA	NA	NA	NA
European heart survey[27]	2004										
Acute group		CVD	2107	67	70	27	31	15	22	3	29
Elective group		CVD	2854	68	71	28	30	10	22	3	35
EUROASPIRE I & II[28]	2004	CVD	5556	63	75	29	20	9	NA	NA	NA
Ischemic heart disease											
Farrer et al.[46]	1995	elective CABG	353	59	69	26	6	4	19	NA	72
The GAMI study[47]	2002	MI	181	64	68	27	NA	25	40	NA	35
Conaway et al.[48]	2005	MI	1199				27	11	NA	29	33
High-risk of IHD											
Fujiwara et al.[49]	1995	elective CAG	127	59	100	23	NA	35	32	NA	33
Seibaek et al.[50]	1997	elective CAG	99	59	100	26	NA	16	21	NA	63
Natali et al.[51]	2000	elective CAG	2253	60	73	27	10	2	NA	NA	88
Kowalska el al.[52]	2001	elective CAG	363	53	100	28	NA	16	36	NA	48
The LURIC study[53]	2003	elective CAG	3266	64	70	28	17	15	NA	NA	68
Wascher et al.[54]	2004	elective CAG	160	65	66	28	23	32	30	NA	15
Cardiac rehabilitation											
Milani et al.[26]	1996	Mainly IHD	291	64	73	29	24	NA	NA	NA	76
Suresh et al.[35]	2001	IHD	1804	58	77	NA***	12	NA	NA	NA	88
Banzer et al.[55]	2003	Mainly IHD	952	62	54	34	26	NA	NA	NA	74
The ELMI study[25]	2003	Mainly IHD	305	64	83	28	20	NA	NA	NA	80
Hindman et al.[56]	2005	Mainly IHD	1505	63	73	32	19	NA	NA	NA	81

CVD, cardiovascular disease; MI, myocardial infarction; IHD, ischemic heart disease; CAG, coronary angiography; BMI, body mass index; KT2DM, known type 2 diabetes; ST2DM, screen detected type 2 diabetes; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; NGT, normal glucose tolerance; NA, data not available; MMWR, Morbidity and Mortality Weekly Report

* information based on telephone interview

** 75% of the patients were overweight (BMI>25 kg/m^2 and BMI<30 kg/m^2) and 30% were obese (BMI>29.9 kg/m^2)

*** 38% of the patients were overweight having a BMI >29.9 kg/m^2

screen-detected type 2 diabetes (ST2DM) and known type 2 diabetes (KT2DM) in a Danish population aged 30-60 years (N=6.784) [61]. The prevalence of IGM increased with age and the crude prevalence of IFG was 8.1% (age group of 60 years; women: 5.1% and men: 16.3%). The crude prevalence of IGT was 11.7% (age group of 60 years; women: 17.3%; men: 17.8%). The total prevalence of T2DM in the age group of 60 years was 12.2% for women and 15.5% for men (ST2DM for women: 6.3% and men: 9.7%) [61]. Likewise parallels will be drawn between the DANSUK study and the population-based pan-European Diabetes Epidemiology Collaborative analysis Of Diagnostic criteria in European studies (DECODE) (N=47.396), that included individuals aged 60-79 years and with no previously knowledge of T2DM [62].

2.2. Secondary prevention of T2DM

Impaired glucose tolerance implies an increased risk for T2DM and CVD, which is often present prior to the diagnosis of T2DM [63-65]. The annual progression rate of IGT to T2DM ranges from 4-8% in different populations [66,67]. The progression of IGT to T2DM may be prevented or postponed by behavioural modifications as weight loss and regular exercise [68-70]. Physical exercise improves blood

lipid profile, reduces blood glucose, and is associated with substantial reductions in CVD risk and mortality [71-74]. Thus physical exercise is one of the core elements in rehabilitation of patients with IHD with or without T2DM. Several randomized controlled trials have shown the beneficial effects of lifestyle intervention programmes in high-risk populations [68-70,75-77]. Table 2.2 shows some of the first larger well-controlled diabetes prevention trials with a transparent randomization and well-defined study groups. The applied lifestyle intervention programmes in these studies are comparable to the ones recommended in CR settings by the American Heart Association [24] and the European Society of Cardiology [78].

Although initial successful, many of the non-pharmacological diabetes preventive treatment intervention programs have difficulties in producing long-term changes in behaviour, weight, or physiological parameters. Even if the progression rate was lower than in the control groups, the intensively treated groups continued to develop T2DM at rates greater than their metabolic normal counterparts throughout the trials. To obtain a real prevention of developing T2DM on a long-term basis, additional pharmacotherapy with metformin, arcobase, and most likely the thiazolidinediones may be essential [75-77]. A cost-benefit analysis of the Diabetes Prevention Program [69] found that, despite the greater efficacy of lifestyle intervention, the cost per case of T2DM prevented was higher than that of metformin [79]. But it is important to notice that metformin was almost ineffective in individuals above the age of 60 years and in patients with a BMI less than 30 kg/m^2 [69].

Table 2.2. Randomized controlled diabetes prevention trials in patients with IGT

	Pub. year	Type of IGM	Study period	Number of patients	Mean age	Mean BMI	Intervention form	RRR% in development of T2DM*
Da Qing Study[68]	1997	IGT	6	577	45	26	Diet Exercise Diet+exercise Control	31% 46% 42%
The Finnish Diabetes Prevention Study[70]	2001	IGT	3.2	522	55	31	Intensified programme Conventionel guidelines + exercise	58%
Diabetes Prevention Programme[69]	2002	IGT	2.8	3234	51	34	Intensified programme Metformin Placebo	58% 31%
TRIPOD[75]	2002	GDM	2.5	235	35	30	Troglitazon Placebo	56%
STOP-NIDDM[76]	2002	IGT	3.3	1449	54	31	Arcobase Placebo	25%
XENDOS[77]	2004	21% IGT 79% NGT	4	3304	43	37	Zenecal+ lifestyle councelling Placebo + lifestyle councelling	37%

IGM; impaired glucose metabolism; IGT, impaired glucose tolerance; GDM, gestational diabetes mellitus; RRR, relative risk reduction

* all $p<0.05$

Other cardiovascular medications have been mentioned as being able to delay or prevent diabetes properly by improving insulin sensitivity or by mechanisms that are not yet known [80-83]. Several trials have compared the possible diabetes preventive effect of angiotensin-converting enzyme inhibitors (ACEI) with drugs known to worsen glucose tolerance. It may also be noted that the diagnosis of T2DM

in many of these trials was based on either self-reported T2DM or on fasting plasma glucose (FPG) values equal to or above 7.0 mmol/L [81,82].

In 1997 the American Diabetes Association (ADA) followed by the WHO introduced the concept of IFG, defined as FPG values between 6,1-6,9 mmol/l (measured on two occasions), in order to limit the need for the more time consuming OGTT [84,85]. The definition of IGT is based on an OGTT. Since 1997 evidence emerged that individuals diagnosed on behalf of an OGTT had a different cardiovascular and diabetic risk profile than individuals diagnosed on FPG-values alone. In an attempt to obtain a higher concordance between IFG and IGT, the ADA recently recommended a further lowering of the glucose values defining IFG to concentrations between 5,6-6,9 mmol/L [86]. It is worthy of note that the DECODE study [87] and other studies [88,89] showed that IGT was a stronger predictor of mortality than elevated FPG. The association between IFG and CVD seems less clear [89]. That IGT is a stronger predictor of CVD mortality than IFG could be explained by the higher progression rate to T2DM [90]. The difference between IGT and IFG with regard to CVD risk may be of great clinical importance. Using the ADA criteria to screen for T2DM will misclassify some of the patients with isolated IGT and will not discriminate those with isolated IFG from those with both IGT and IFG, who are at higher risk for CVD. Early T2DM may also manifest itself as postprandial hyperglycaemia while FPG measurements and HbA1c levels may be normal.

Arguments for the recent lowering of the FPG level for IFG could be explained by data from observational studies suggesting that hyperglycaemia is an independent risk factor for CVD with no obviously apparent threshold [91-94]. The possible relationship between the degree of hyperglycaemia and CVD is based on large observational studies and two meta-analyses [39,95,96]. It is estimated that 1% rise in HbA1c values above 5% increases the risk for CVD by about 20% [39]. In another observational study of 4662 men without T2DM, individuals with HbA1c of 5.0% to 5.5% had a 2.5-fold increased risk of dying from CVD, compared to individuals having HbA1c levels below 5.0% [97].

In **conclusion**, it is important to emphasize from the mentioned randomized controlled trials, that the aim was diabetes prevention. There is still no solid evidence from prospective randomized controlled trials that prevention of T2DM in patients with IGT reduces morbidity or mortality of CVD. Before implementation of preventive strategies towards patients with isolated IFG e.g. in the settings of CR, a better understanding of the prognostic significance of isolated IFG is needed, as it is not yet obvious, that the benefit of preventive measures tested in patients with IGT will apply to patients with isolated IFG.

2.3. Mono- and multifactorial treatment of T2DM in reducing risk of CVD

When treating T2DM it is crucial to limit the number of cardiovascular risk factors because the mortality rate from CVD doubles in patients with T2DM with one additional risk factor and more than triples with three additional risk factors [10,98]. The observation that patients with T2DM without CVD had as high a risk of future CVD events as patients with CVD without T2DM has changed the whole concept of prevention in patients with T2DM [99]. The disease is now acknowledged as a CVD risk equivalent. Once

T2DM has been diagnosed, the approach to CVD is that of secondary prevention [100] even though this alignment of T2DM with CVD has been both consolidated [101] and disputed [102].

For many years treatment of T2DM has been empirical based on extrapolations of intervention forms for type 1 diabetes (T1DM) and for patients with NGT. In the last decades several single drug intervention trials against risk factors such as hypertension and dyslipidemia have emerged often with a more pronounced benefit in the patients with T2DM revealed by sub group analyses. Seven randomized multifactorial intervention trials towards patients with T2DM are identified [103-111]. In most of these trials, the patients had newly diagnosed T2DM and no established diagnose of CVD at inclusion. The STENO 2 study deserves some special attention [103]. The study randomized 160 patients with T2DM and microalbuminuria to intensified multifactorial intervention (N=80) or usual care at their general practitioner (N=80). Mean age was 55 years and women constituted nearly 25%. Almost 25% of the patients included had known IHD. The primary endpoint was nephropathy. Secondary endpoints were the incidence or progression of diabetic retinopathy and neuropathy. Macrovascular events and deaths were tertiary endpoints. At baseline the mean HbA1c was 8.5% and mean blood pressure was 148/86 mmHg and 20% of the patients were treated with ACEI and 13% with ASA. The main result of the STENO 2 study was a reduction in risk of cardiovascular and microvascular events by 50% after a mean study period of 7.8 years. Up to 66% of the patients in the conventional group had received treatment at an outpatient diabetic clinic during study period [105].

2.4. Behavioural modifications

Many of the risk factors for T2DM and CVD are modifiable through lifestyle changes that therefore are the basis in comprehensive CR programmes. Data from the UK Prospective Diabetes Study (the UKPDS) based on relatively young individuals with newly diagnosed T2DM found, that once T2DM has developed, hypertension, increased LDL-cholesterol, decreased HDL-cholesterol, and hyperglycaemia were greater risk factors for CVD than the precipitating factors for T2DM i.e. upper body obesity, decreased physical activity and hyperinsulinemia [112]. The first line of intervention aiming to reduce the cardiovascular risk is dietary therapy [113-115] along with smoking cessation and physical exercise [116]. Table 2.3 emphasizes that the body of evidence for reducing both mortality and morbidity is well documented for the non-pharmacological treatment modalities and that they posses the same level of recommendation as the pharmacological treatment [117].

Nutritional counselling lowers blood glucose [118,107], improves lipid profile [119,120] and blood pressure control [121], but because of the progressive nature of the T2DM, hyperglycaemia will arise and strict nutritional counselling alone has never been able to reduce LDL cholesterol by more than 0.65 mmol/l [120]. The possible effect on both the systolic and diastolic blood pressure is closely related to weight loss and sodium restricted diet but has never been investigated as a randomized controlled trial in patients with T2DM.

Smoking cessation is of great importance in patients with T2DM and CVD as the rate of atherosclerotic progression in current smokers with T2DM is almost twice that seen in current smokers

without T2DM [122]. In patients with and without T2DM, a strong association exists between smoking and the risk of CVD [123]. Recent studies also including patients with T2DM, have reveiled that the longer duration of smoking and heavy smokers are at a higher risk of CVD [124,125]. Intensive counselling during admission with one-month follow-up seems more effective [126] than courses with no long-term follow-up [127].

Regular exercise improves insulin sensitivity and also improves plasma lipid levels, blood pressure, and body weight [128-130] but individuals with T2DM generally exhibit poor cardiovascular response, and may have to expend more effort for a given amount of work than their metabolic normal counterparts [131]. Among patients with known CVD, regular exercise has been shown to reduce the rates of CVD and all-cause mortality [132]. Physical exercise programmes for patients with T2DM are well described in CR settings in the US [133] and exercise is readily accessible and cost-effective in reducing CVD risks and should be encouraged in all patients.

Table 2.3. Documented effect of some non-pharmacological and pharmacological treatment modalities encompassed in comprehensive CR [117]

	Mortality	**Disease progression**
Non-pharmacological treatment		
Exercise	xxx	xxx
Smoking cessession	xxx	xxx
Dietary guidance	xxx	xxx
Pharmacological treatment		
Aspirin	xxx	xxx
Statin	xxx	xxx
Beta-blockers	xxx	xxx
ACEI/ARA	xxx	xxx

xxx, substantial benefits; xx, moderate benefits; x, slight benefit; ACEI, angiotensin-converting enzyme inhibitor; ARA, angiotensin receptor-II antagonist

An estimated 60% to 90% of all T2DM is related to obesity [134]. A weight gain of 5 kg in men increases the risk of CVD by almost 30% and the estimated changes in lipids and blood pressure related to this weight gain increases the risk by approximately another 20% [135]. Thus obesity is the true vicious playmate in T2DM. Surprisingly patients with T2DM only loose half the weight compared to their metabolic normal counterparts when receiving the same weight management programme [136]. Weight loss also improves glycaemic control [137] and may even cause a remission of diabetes [138]. The UKPDS demonstrated that a mean weight loss of 10 kg was sufficient to obtain normal FPG-values throughout the first year of the study. The more glycaemic deteriorated the patients were, the more they had to loose in weight to normalize FPG-levels [139]. Unfortunately intensive glycaemic control to achieve normal HbA1c values may cause weight gain [104]. Many patients with T2DM do not adhere to the recommended guidelines for diet and exercise [140]. Managing chronic diseases as T2DM and CVD can be a substantial source of stress, and patients with T2DM are more likely to be depressed than are those in the general population [26,141,142]. This can lead to poor adherence to lifestyle modifications as well as to pharmacotherapy [143].

2.5. Treatment of hyperglycaemia

Hyperglycaemia as a cause of vascular disease has been investigated clinically by examining the benefits of tight glucose control. The randomized controlled trials examining this issue are divided into studies focusing on the immediate effect of glucose-insulin-potassium (GIK)-infusion in patients with MI with a relatively short follow-up period (months) and in studies focusing on the long-term effect (years) of intensive glycaemic control. The possible beneficial effect of GIK-infusion to protect the ischaemic myocardium has been known since the 1960s [144] supported by the glucose hypothesis primarily asserted by Opie [145]. Many small studies [146-154] were systematically reviewed [155] involving 1932 patients mainly from the pre-thrombolytic period and concluded that especially high-dose GIK scheme in the first few hours of MI with a treatment duration from 6 hours to 14 days, may play an important role in in-hospital mortality which was reduced by 28% (95% CI: 14-83, p=0.004), with an estimate of 49 lives saved per 1000 patients treated. One of the first randomized controlled trials of GIK-infusion of MI in the era of reperfusion was the Diabetes mellitus Insulin Glucose infusion in Acute Myocardial Infarction study (DIGAMI) [156] (table 2.4.). This study included 620 patients with T2DM or hyperglycaemia (FPG $\geq$ 11.1 mmol/l) on admission and assigned them to either conventional therapy or adjunctive therapy with GIK-infusion followed by a multidose insulin regimen for at least 3 months. Patients treated with GIK-infusion had a significantly lower 1-year mortality (18.6% versus 26.1%, p=0.03) and three years relative mortality was reduced 25%. The studies to follow showed conflicting results of the effect of GIK-infusion that may be due to different dosage of insulin, infusion rate and considerable population diversity [157-161]. A recent meta-analysis [162] addressing the effect of GIK-infusion regimes pooled almost 5000 patients from 16 trials conducted from 1965 to 2003 [146-154,156-159,163-165]. The analysis indicated an 18% relative risk reduction in mortality (p=0.03). But the analysis should be interpretated with caution mixing high- and low-dose GIK-regimes and ischemic patients with or without congestive heart failure, the latter being especially vulnerable to volume load [164,165]. Thus the current evidence for the use of GIK-infusion in MI is still not conclusive [166] but an ongoing trial, combining reperfusion therapy and high-dose GIK-infusion, will maybe answer some of the questions [167].

Several studies have shown that chronic glycaemic control (as reflected by HbA1c) may be more effective in avoiding microvascular complications compared to macrovascular complications. The reduction of microvascular complications by improved glycaemic control was clearly demonstrated in the UKPDS where fasting glucose levels of less than 7.1 mmol/l resulted in a 25% relative reduction in the risk of microvascular disease over 10 years (p=0.01) [168]. Similar results were obtained in the smaller Kumamoto study in a relatively lean less Western like population [169,170]. A pronounced benefit of strict glycaemic control in patients with T1DM was found in the Diabetes Control and Complication Trial study (DCCT) that showed a reduction in the incidence of retinopathy, microalbuminuria and neuropathy by 76%, 39% and 60%, respectively [171]. The importance of glycemic control in preventing macrovascular complications is less consolidated especially in patients with T2DM. A systematic review from 1999 concluded that there was a weak association between hyperglycaemia and mortality [172]. Half of the 27 studies included, showed a positive association between hyperglycaemia and CVD, but

randomized as well as not randomized trials were included, and the variable degree of adjustment of other confounders not to mention the diversity in the used measurements of HbA1c and FPG, may allow the homogeneity of the analysis to be disputed. A meta-analysis investigating blood glucose threshold for increased mortality in patients with MI concluded, that hyperglycaemia is associated with an increased risk of in-hospital mortality in patients with and without T2DM. A non-fasting blood glucose threshold for increased mortality of acute MI for patients without T2DM was reported as 6.1 mmol/l and the threshold for patients with KT2DM was 10 mmol/l [173]. An observational study of hyperglycaemia in 336 patients with acute MI revealed that mortality was higher in patients with KT2DM (40%) compared to patients with NGT defined as a non-fasting admission plasma glucose less than 5.6 mmol/l (16%, $p<0.05$) and that mortality rose progressively to 44% for blood glucose above 11.0 mmol/l [174]. Intensive glycaemic control in patients with T1DM resulted in a decreased progression of the intima-media thickness that is a marker for increased risk for cardiovascular events [175]. Follow-up data from the same study have recently shown that the risk of cardiovascular events was significantly reduced by 42% in the intensively treated group compared to usual care [176].

Table 2.4. Glucose-lowering randomized controlled trials in patients with T2DM

	Pub. year	Duration (years)	Number of patients	Age*	Male (%)	BMI*	T2DM duration*	History of CVD (%)	Intervention form	HbA1c* baseline	FPG* baseline	ΔHbA1c* %	ΔFPG* mmol/l	RRR% in CV events
VASCDM[179]	1997	2.3	153	61	100	31	8	38	Insulin/glipizide *v* insulin	9.8	11.8	-2.1	-5.57	NS
KUMAMOTO[169]	1995	8.0	110	49	49	20	8	0	Multiple insulin *v* conventional insulin injections	9.1	8.9	-2.2	-2.22	NO
UKPDS[168]	1998	10.0	3867	53	61	28	0	0	Diet/SU/insulin (intensive care) *vs* Diet/SU/insulin (usual care)	7.1	8.0	-0.9†	-1.33	NS††/** (p=0.052)
DIGAMI I[156] (20% T1DM)	1995	1.0	620	68	63	27	0	60	Insulin-glucose infusion + insulin sc. *vs* usual care	8.1	14.2	-0.3	NA	29 (p=0.027)
DIGAMI II[161]	2005	2.1	1253	68	67	28	8	50	1) GIK-infusion + insulin long-term 2) GIK-infusion + standard glucose control 3) Local practice glycaemic control	7.3	12.7	-0.5	-0.9	NS

NS, not statistical significant; NO, few events to obtain any difference; NA, not avaible, SU, sulphonylurea; GIK, glucose-insulin-potassium; Pub. year, year of publication; CV, cardiovascular. * Mean values; † after one year; †† RRR = 12% (p=0.03) for 'any diabetes-related endpoint' encompassing fatal and non-fatal MI, heart failure and angina ** RRR = 39% (p=0.01) for MI in 753 overweight patients treated with metformin [177].

Looking at the existing randomized controlled trials conducted after 1980 addressing whether improved glycaemic control reduces CVD in patients with T2DM, the Kumamoto Study including 110 patients did not find that good glycaemic control retards the progression of macrovascular disease but obtained significant risk reductions for nephropathy, retinopathy and peripheral neuropathy [169]. The difference in HbA1c between the study groups was substantial (table 2.4) but the event rate of macrovascular complications was low and did not reach statistical significance [169,170]. The larger UKPDS tested whether intensive glycaemic control with either sulphonylurea or insulin influenced the risk of micro- or macrovascular complications compared with conventional treatment [168]. More than 4000 patients with newly diagnosed T2DM and no CVD at baseline were treated for 10 years. The incidence of MI was reduced 16% but this reduction was only marginally significant (p=0.052). The overweight patients in the

same study treated with metformin obtained a significantly reduced risk of MI (relative risk reduction: 39%, p=0.01) [177].

Epidemiological analyses of the UKPDS study estimates that a 14% decrease in risk of fatal or nonfatal MI is associated with a 1% lower mean HbA1c value [91]. This is almost similar to the findings in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), where a 10% increase in risk of mortality from IHD in T2DM patients was seen in association with a 1% increase in HbA1c [178]. The Veteran Affairs Cooperative Study on glycaemic control and complications in NIDDM (VACSDM) included relatively obese patients with dysregulated insulin-dependent T2DM [179]. Despite an excellent separation in HbA1c between the study groups that was maintained throughout the study period of nearly 3 years, there was a trend toward a worsening of cardiovascular outcome in the intensively treated patients (p=0.1). A possible explanation for this outcome was that a transient aggravation of other outcomes e.g. retinopathia had been observed in the intensive treatment of hyperglycaemia in patients with T1DM [180]. A new and larger trial addressing the same objective; the Veteran Affairs Diabetes Trial (VADT) began inclusion of the same kind of patients in 2000 [181]. The Diabetes mellitus Insulin Glucose infusion in Acute Myocardial Infarction II study (DIGAMI II) recruited 1253 patients suspected for acute MI. The patients were randomized into 3 treatment groups (table 2.4). A difference in cardiovascular mortality or morbidity between the 3 study groups was not observed. A possible explanations was a significant difference in baseline characteristics between the 3 groups due to different inclusion rates among the many centres and not following protocol procedures as prescribed, al-lowing a slackly procedure in the most intensively treated group (group 1) and cross-over treatment in the 'conventional' treated group 3, where as many as 41% received extra insulin injections and 14% GIK-infusion [161]. There are many limiting factors in the trials intervening against hyperglycaemia listed in table 2.4. Methods of assessment of blood glucose are heterogeneous and HbA1c assays vary and therefore make the comparability difficult [182].

In **conclusion**, the body of evidence of strict chronic glycaemic control is mostly based upon relatively young individuals (mean age: 58 years) with a relatively short duration of T2DM (range: 0-8 years). The overall impact of glycaemic control on risk reduction and prevention of major cardiovascular events in patients with T2DM still remains controversial although metformin seems to be beneficial in obese patients. The cut-off value for the diagnosis of T2DM has been determined in the past by microvascular rather than macrovascular complications [183]. This diversity and the lack of unambiguous randomized controlled trials may explain why different advisory bodies recommend different HbA1c goal levels ranging from below 6.5% [78,184,185] to below 7.0% [186] to within the range of 7-8% [117]. Randomized controlled trials investigating risk-to-benefit ratios in older patients with a limited life expectancy and a long lasting T2DM are still lacking. Until now no randomized controlled trial have obtained and sustained a mean HbA1c level below 7% in the intensively treated arm throughout the study period.

2.6. Treatment of arterial hypertension

The WHO has identified arterial hypertension as the single most important preventable cause of premature death [187]. The prevalence of arterial hypertension in patients with T2DM depends upon age, obesity, diabetes duration, and the definition used. Using the criterion above or equal to 140/90 mmHg, up to 80% of the patients with T2DM have hypertension [188,189]. Using the recent recommendations of a treatment target below 130/80 mmHg, the prevalence of hypertension in T2DM patients is likely to be even higher [190-192]. About twice as many patients with T2DM are hypertensive compared to normoglycaemic patients [193]. In patients without overt T2DM, hypertension is often associated with insulin resistance, dyslipidemia, and increased risk of CVD [194]. In patients with T2DM or IGT, hypertension is found to be a particularly strong risk factor for CVD and death [195] and the increased risk are higher at every level of systolic pressures assessed and more pronounced if the patients also have nephropathy [10,196]. Table 2.5 summarises randomized controlled trials addressing the impact of different antihypertensive therapies on major cardiovascular outcome in patients with T2DM. Only the UKPDS [197], the Appropriate Blood pressure Control in Diabetes study (ABCD) [198] and the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) [199] were designed to specifically examine patients with T2DM. The result of major cardiovascular events in the diabetic population in the remaining studies listed in table 2.5 are based on subgroup analyses of larger trials examining the effect of lowering the blood pressure compared to placebo [200,201], between different active agents [202-206] or in a strict versus less strict strategy using the same first-line active agent in both treatment groups [207,197].

Intensive treatment of arterial hypertension seems to be especially beneficial in patients with T2DM. In fact, in several of the larger trials, the sub group analyses of the diabetic population were the only cardiovascular outcome to reach statistical significance [201,202,207]. Despite the certainty of therapeutic benefit, some of the studies shown in table 2.5 have also caused controversies especially in the use of potentially harmful drugs [198,199]. The interpretation of the results of the ABCD study [198] and the FACET study [199] has caused some dispute. These two studies both had cardiovascular events as secondary outcome. They both compared the efficacy of a dihydropyridine calcium-channel blocker with an angiotensin-converting enzyme inhibitor (ACEI) and suggested that ACEIs were preferable compared to calcium-channel blockers and that the latter could possess a harmful effect in the treatment of hypertension in patients with T2DM. In contrast to the ABCD and the FACET studies, the Systolic Hypertension in Europe Trial (Syst-Eur) showed that treatment with a long-acting calcium channel blocker was both effective and beneficial in reducing cardiovascular morbidity and mortality [201]; a conclusion that was later reproduced in several other studies [209-212]. The UKPDS was both a study of the effect of tight blood pressure control on microvascular and macrovascular complications as well as a comparison of a beta-blocker versus an ACEI [197,209]. A target blood pressure below 150/85 mmHg resulted in a 24% risk reduction in diabetes-related endpoints ($p<0.005$), including a 34% risk reduction ($p<0.02$) in combined macrovascular disease (MI, sudden death, stroke, and peripheral arterial disease (PAD)). The risk of heart failure decreased 56% ($p<0.005$) while the 21% reduction in MI did not reach statistical difference [197]. The study was also the first to show, in patients with T2DM, a beneficial effect of blood

pressure lowering therapy on microvascular complications that decreased 37% in the intensively treated group. There was no difference within the tight intervention group between patients treated with the beta-blocker and patients treated with an ACEI [209]. Observational data from the same study estimated that each 10 mmHg decrease in systolic blood pressure was associated with reduction in risk of 12% for any complication related to diabetes (11% for myocardial infarction; 95% CI: 7-14%, p<0.0001) with the lowest risk being in those with systolic blood pressure less than 120 mmHg [210].

Table 2.5. Blood pressure-lowering randomized controlled trials in hypertensive patients with T2DM

	Pub. year	Duration (years)	No. of patients	Age§	Male (%)	BMI§	T2DM (yrs) duration§	History of CVD (%)	Intervention form	sBP/dBP§ baseline	sBP/dBP§ follow-up	RRR% in major CV events	% improvement sBP	% improvement dBP
UKPDS-HDS[197]	1998	8.4	1148	56	54	30	2.6	0	Captopril/Atenolol (C/A) *vs* other drugs (O)	160/94	C/A:144/82 O:154/87	34 in favour of C/A** (p=0.019)	10	13
HOT[207*]	1998	3.7	1501	62	53	28	NA	6	Felodipine (intensive) *vs* Felodipine 1:≤90 mmHg; 2:≤85 mmHg; 3:≤80 mmHg	170/105	1:144/85 2:141/83 3:140/81	29 (1 *vs* 2) 18 (2 *vs* 3) 47 (1 *vs* 3) (all p<0.05)	15 17 18	19 21 23
SHEP[200*]	1996	4.5	583	72	43	NA	NA	5	Chlorthalidone/Atenolol/Reserpine (I) *vs* placebo (C)	170/77	I:143/68 C:155/72	34 in favour of I (p<0.05)	16	12
Syst-Eur[201*]	1999	2.0	492	70	26	NA	NA	30	Nitrendipine/Enalapril/Hydrochlor-thiazide (I) *vs* Placebo (C)	175/85	I:153/76 C:162/81	69 in favour of I (p<0.05)	13	11
CAPPP[202*]	2001	6.1	572	55	62	31	8.7	10	Captopril (C) *vs* Diuretics/ Beta-blockers (D/B)	163/97	C:156/89 D/B:154/88	33 in favour of C*** (p=0.03)	4	8
FACET[199]	1998	2.8	380	63	60	NA	10.6	NA	Fosinopril (F) *vs* Amlodipin (A) *vs* Fosinopril/Amlodipin	171/95	F:157/88 A:153/86	51 in favour of F (p=0.03)	8	7
ABCD[198]	1998	5.0	470	58	68	32	8.7	27	Enalapril (E) *vs* Nisoldipine (N)	156/98	E:135/78 N:135/78	9 (in favour of E)	14	20
STOP-2[203*]	2000	2.0	719	76	40	28	NA	15	ACEI (A) *vs* Felodipine/Isradipine (FI) *vs* Diuretics/beta-blockers (C)	195/96	A:160/80 CA:161/78 C:161/80	49 (A *vs* CA)† (p=0.025)	18	17
INSIGHT[204*]	2003	3.0	1302	60	48	NA	NA	7	Nefidipine (N) *vs* Co-Amilozide (C)	175/98	N:145/82 C:144/82	24 (in favour of N)†† (p=0.03)	17	16
LIFE[205*]	2002	4.7	1195	67	47	30	NA	24	Losartan (L) *vs* Atenolol (A)	177/96	L:146/79 A:148/79	24 in favour of L (p=0.03)	18	18
ALLHAT[206*]	2005	4.9	13101	67	51	31	NA	36	Chlorthalidone (C) *vs* Amlodipine (A) *vs* Lisinopril (L)	147/83	C:135/74 A:136/74 L:138/75	NS†††	8	11
ASCOT-BPLA[208*]	2005	5.5	5145	63	77	29	NA	0	Amlodipine based regimen (AM) *vs* Atenolol based regimen (AT)	164/95	AM:138/77 AT:138/79	13 (in favour of AM) (p=0.03)	16	22

§ Mean values * Sub group analyses of larger trials

** Combined macrovascular end point including: myocardial infarction, sudden death, stroke and peripheral vascular disease in favour of strict control. No difference in in mortality and/or microvascular disease between Captopril and Atenolol found in sub study.

*** RRR in all myocardial infarction of 66% in favour of Captopril

† all myocardial infarction

†† secondary outcomes (combined cardiovascular death, MI, CHF and stroke (primary outcome), all-cause mortality and death from vascular and non-vascular causes)

††† increased incidence of congestive heart failure (relative risk, 1.39 [95% CI, 1.22-1.59], p=0.001) for those assigned to amlodipine compared with chlorthalidone except from the RRR that represent total cardiovascular events, all data based on the total population

RRR, relative risk reduction; NA, not available; sBP, systolic blood pressure; dBP, diastolic blood pressure; Ca-A, Calcium-channel antagonist; NS, no statistical difference

Pub. year, year of publication

The importance of lowering the diastolic blood pressure in patients with T2DM was shown in the Hypertension Optimal Treatment study (HOT) where a diastolic blood pressure below 80 mmHg halved the incidence of major cardiovascular events compared to patients with a target diastolic blood pressure

of 90 mmHg (table 2.5) [207]. Thus clinical trials [196,206] and observational studies [210] emphasize the need for tight blood pressure control in patients with T2DM and hypertension. The question of how far and in what way the blood pressure should be lowered in patients with T2DM is highly relevant and several reviews and meta-analyses have addressed this issue [211,212]. Different advisory boards have chosen to recommend a relatively strict blood pressure control below 130/85 mmHg [213,214] and other boards recommend a treatment target below 130/80 mmHg and below 120/70 mmHg in patients with albuminuria [215,216]. These recommendations are based partly on epidemiological studies and meta-analyses [210-212] since none of the randomized controlled trials listed in table 2.5 reached the recommended treatment target or were close in doing so [197,201,203]. The latest statement is, that lowering of the blood pressure seems to be the essential part for CVD prevention rather than the drug classes used to achieve it [212] but the evidence is not unified. In the Heart Outcomes Prevention Evaluation study (HOPE) an ACEI or placebo were administrated to high-risk patients with a history of IHD, stroke, PAD or T2DM, and at least one additionally cardiovascular risk factor [217]. A total of 3577 patients with T2DM were included, of whom 1135 had no clinical signs of CVD. Nearly one-third of the patients had microalbuminuria and 56% had a history of hypertension. Baseline blood pressure was 142/80 mmHg and despite a mean reduction in blood pressure of only 3/2 mmHg in the intervention group, treatment with an ACEI for 4 years significantly reduced deaths from cardiovascular disease and stroke. The decreased risks of MI and stroke were similar to those seen in the UKPDS, where the mean difference in blood pressure was 10/5 mmHg between the two groups (table 2.5) [197].

The ACEIs may possess beneficial effects on the cardiovascular system that is beyond the blood pressure lowering effect. The size of this effect may be dependent of concomitant diseases. The choice of antihypertensive agent should therefore be individualized and guided by the presence of concomitant clinical disease and the need to protect any specific target organ system. In overt nephropathy, it is recommendable to start or supply the antihypertensive therapy with an angiotensin receptor-II antagonist (ARA), which in several studies have shown to be very beneficial in slowing the progression to end stage renal disease in hypertensive patients with T2DM [218-220]. To reduce left-ventricular hypertrophy, ACEI or calcium-channel antagonists seems superior to both diuretics and beta-blockers [221,222] and in the presence of congestive heart failure, calcium-channel blockers are relatively contraintradicted [206,212]. But hypertensive patients with T2DM often need multiple drugs to reach treatment goal. After 8 years in the UKPDS, nearly 30% of the patients in the intensively treated group needed 3 or more antihypertensive drugs to reach and maintain a mean blood pressure of 144/82 mmHg [197]. In the same study, almost 40% needed at least 2 drugs to maintain target and still the obtained mean blood pressure was relatively far from current recommendations (table 2.5). Looking at the metabolic effect of the antihypertensive agents in preventing the development of T2DM in high-risk patients, treatment strategies are further challenged. Beta-blockers and thiazide diuretics are considered metabolically inappropriate, calcium-channel blockers as neutral and ACEI and ARA maybe even metabolically beneficial [223,224].

In **conclusion**, there is substantial data supporting the great impact on cardiovascular events by lowering the blood pressure in hypertensive patients with T2DM. The risk reduction may depend upon the starting point, but a relative risk reduction of major cardiovascular events up to 50% should be expected if the blood pressure is lowered 10-20% (table 2.5). There is no data from randomized controlled trials that treatment of the blood pressure below 130/80 mmHg, will result in a further reduction in major cardiovascular events.

2.7. Treatment of dyslipidemia

The most common lipid abnormality in patients with T2DM is elevated triglycerides and low HDL-cholesterol [225]. Although statin therapy mainly reduces LDL-cholesterol, it decreases cardiovascular risk in patients with T2DM. Which lipoprotein is the most atherogenic and should be the primary target of lipid management in diabetic dyslipidemia is debatable but LDL-cholesterol is a strong predictor of cardiovascular events in patients with or without T2DM [226]. Fibrates are known to increase HDL-cholesterol levels and lower plasma triglycerides and thus seems to be the logical choice in the treatment of diabetic dyslipidaemia [227-229]. Statins also reduce the triglyceride level in patients with T2DM [230] and have shown beneficial effects in doing so in several randomized controlled trials [231-241]. Table 2.6 summarises trials addressing the impact of major cardiovascular outcome in patients with T2DM treated with a statin compared to placebo. Many of the trials are based upon sub group analyses of larger trials but T2DM patients show similar or greater cardiovascular benefit from statin-based therapy compared with overall study populations [231-234,236,238,239,241]. After a coronary event, patients with T2DM have a two- to threefold higher risk of a second coronary event [99,242]. It is estimated that patients with T2DM and established IHD have a 50% incidence of recurrent MI over 7 years [243]. Even though clinical trials often include carefully selected patients, primary prevention trials as the Heart Protection Study (HPS) [233] and the Collaborative AtoRvastatin Diabetes Study (CARDS) [235] further showed that it may be equally important to initiate statin-based treatment in T2DM patients at a lower cardiovascular risk threshold than is recommended by several advisory boards [244,245].

Unlike some of the studies concerning treatment of hypertension in patients with T2DM [197,207], the statin trials in table 2.6 do not entirely answer the question of what lipid level should be targeted although statin therapy was equally effective in patients with high and low plasma LDL-cholesterol levels in the HPS [233]. However after 2 years of treatment in the PRavastatin or atOrVastatin Evaluation and Infection – Thrombolysis in myocardial infarction 22 investigators study (PROVE-IT), a composite cardiovascular endpoint was reduced by 16% ($p<0.005$) in acute coronary patients receiving atorvastatin in doses of 80 mg/day (mean attained LDL-cholesterol level: 1.60 mmol/l) compared to the patients receiving 40 mg pravastatin per day (mean attained LDL-cholesterol level: 2.46 mmol/l) [246]. Patients with T2DM in the study constituted 25% and they received the same cardiovascular benefit from aggressive lowering of the LDL-cholesterol. Based upon the randomized controlled trials and epi-demiological studies, it has been estimated that in the over all population, every 0.78 mmol/l change in the LDL-cholesterol concentration will reduce the relative risk for CVD by about 30% [99].

A meta-analysis of lipid-lowering trials based on 10 trials (79 494 patients with and without T2DM) showed that statin treatment of the overall population reduced major cardiovascular events by 27% ($p<0.05$) [247]. A separate analysis of the trials with available access to outcome data [230,233,235,237], showed a reduction in major cardiovascular events of 19% in patients with T2DM

Table 2.6. Lipid-lowering randomized controlled trials using statins in patients with T2DM

	Pub. year	Study duration	No. of patients	Age§	Male (%)	Study type	T2DM (yrs) duration§	History of CVD (%)	Intervention form *vs* placebo	End LDL Intervention§	End LDL Placebo§	%RRR in major CV events	% improvement
AFCAPS/TexCAPS[231*]	1998	5.2	155	58	85	P	NA	0	Lovastatin 20-40 mg/day	2.97	4.03	NS**	24
ALLHAT-LLT[232*]	2002	4.8	3638	66	51	P	NA	14	Pravastatin† 20 mg/day	2.72	3.34	NS	19
HPS[233*] (10% T1DM)	2003	5.4	2912 2426	62	70	P S	9.3	0 45	Simvastatin 40 mg/day	2.30	3.31	33% (p=0.0003) 27% (p=0.0007)	28
ASCOT-LLA[234*]	2005	3.3	2532	64	76	P	NA	0	Atorvastatin 10 mg/day	2.15	3.02	NS††	35
CARDS[235]	2004	3.9	2838	62	68	P	7.9	0	Atorvastatin 10 mg/day	2.11	3.12	37% (p=0.001)	30
4S[236*]	1997	5.4	202	60	72	S	NA	100	Simvastatin 40 mg/day	3.03	4.81	55% (p=0.002)	36
CARE[237]	1998	5.0	586	61	80	S	NA	25	Pravastatin 40 mg/day	2.53	3.59	25% (p=0.05)	28
LIPID[238*] (2.6% T1DM)	2003	6.1	782	64	81	S	NA	100	Pravastatin 40 mg/day	2.92	3.88	21%*** (p<0.008)	21
LIPS[239*]	2005	3.5	202	63	80	S	NA	100	Fluvastatin 80 mg/day	2.46	3.80	51%††† (p=0.0088)	24
Post-CABG[240]	1999	4.3	120	63	85	S	NA	100	Lovastatin¥ 20-40 mg/d	2.40	3.52	NS	39
PROSPER[241*]	2002	3.2	397 228	75	48	P S	NA	0	Pravastatin 40 mg/day	2.77	3.78	NS	23

§ Mean value

* Sub group analyses of larger trials

** lovastatin reduced the incidence of first acute major coronary events by 37% (95%; CI: 0.50-0.79, p<0.001) in all patients

*** denotes RRR for any cardiovascular event. The RRR of major cardiovascular events of 19% did not reach statistical significance (p=0.11)

† statin treatment allowed in control arm

†† using an expanded cardiovascular endpoint as major cardiovascular events + procedures a RRR of 23% (p=0.0036) was obtained

††† reduction of major adverse cardiac events

¥ aggressive cholesterol-lowering (± cholesterymin) versus moderate lowering and low-dose warfarin versus placebo.

RRR, relative risk reduction; NA, data not available; NS, not statistical significant; P, primary prevention study; S, secondary prevention study

($p<0.05$) [247]. Another meta-analysis exclusively focusing on the lipid-lowering effect on diabetes included 6 primary prevention trials and 8 secondary prevention trials and showed a relative risk reduction in cardiovascular events of 22% and 24%, respectively [248]. This analysis also allowed the inclusion of 2 fibrate-based studies [227,249]. Based on observational studies [227,250], and upon the fact that patients with T2DM who receive primary prevention often are at an advanced stage of atherosclerosis, the National Cholesterol Education Program (NCEP) has recently suggested an even lower treatment goal of LDL-cholesterol to below 1.81 mmol/l in some high-risk patients with CVD exemplified by the patients with T2DM and high-risk of recurrent episodes of IHD [251]. Both the NCEP and the ADA agree upon the recommendations that patients with T2DM and CVD should initiate statin

treatment regardless of baseline LDL-cholesterol levels. In patients with T2DM and no overt CVD having a LDL cholesterol level below 3.0 mmol/l, statin treatment should be based on the clinical situation [251].

In **conclusion**, lowering the LDL-cholesterol to a level between 2.30-3.00 mmol/l, as part of primary or secondary prevention in patients with T2DM, induces a relative risk reduction in major cardiovascular events of 20-35% (table 2.6).

2.8. Integrated care in the settings of CR

Little is known of the effect of CR in patients with T2DM in both exercise-based CR and comprehensive CR. No prospective randomized controlled trials exclusively examining the effect of CR in patients with T2DM have ever been performed and in the meta-analyses shown in table 2.7, no separate outcome analyses are available for the patients with T2DM [30-32,252,253]. The patients taking insulin had also often been excluded from the clinical trials finally included in the meta-analyses.

Table 2.7. Effect of CR on mortality based on meta-analyses of clinical controlled trials

	Publication year	Number of trials included	Number of patients	Patient category	RRR% in mortality	
					All-cause	Cardiac
Oldridge et al[30]	1988	19	4347	post-MI	24*	NS
O'Connor et al[32]	1989	22	4554	post-MI	20*	22*
Joliffe et al[252]	2000	32	8440	post-MI + IHD	27*	31*
Brown et al[253]	2003	46	8677	post-MI + IHD		
Exercise-based			2984		24*	27*
Comprehensive CR			5693		NS	20*
Taylor et al[31]	2004	48	8940	post-MI + IHD	20*	26*

MI, myocardial infarction; IHD, ischemic heart disease (also revascularizations and stable angina); RRR, relative risk reduction

* $p<0.05$

The results from the meta-analyses clearly show that CR reduces cardiovascular and all-cause mortality in the overall population compared to non-attendants. The earlier analyses mainly included exercise-based trials [30,32], while the recently performed also allowed comprehensive CR programmes to be included [31,252,253]. The meta-analyses have also shown that the attendants in CR programmes obtain a significantly reduction in lipids [21,252,253], systolic blood pressure and in smoking [31] compared to usual care.

Only a few not randomized studies have looked upon the effect of exercise-based and comprehensive CR programmes in patients with T2DM as a sub group [26,35,55,56,254]. Looking at the changes in classical cardiovascular risk factors as lipid profile, blood pressure, exercise capacity and depression, these studies do not agree. In one study, 59 patients with T2DM were enrolled in a 2-months comprehensive CR programme after an acute coronary event [254]. The improvement in exercise capacity was significantly less in patients with T2DM compared to their metabolic normal counterparts. The patients with T2DM showed lower levels of peak workload, duration of exercise test, maximal heart rate and anaerobic threshold compared to the patients with NGT having similar left ventricular ejection fraction and class of MI. No information was given about the effect on other risk factors in this study but an important observation was, that the response to the exercise seemed to be influenced by their

glycaemic control more than their BMI [254]. In another study offering comprehensive CR to 1505 patients, the patients with T2DM (19%) benefited the same in improving traditional cardiovascular risk factors as the patients with NGT [56]. Both groups obtained the same percentage improvement in lipids, and exercise capacity but fewer patients with T2DM achieved the predefined treatment goals, probably because of more deteriorated baseline values.

In **conclusion** from this review, there is an abundance of evidence-based documentation that intensive treatment of single factors as arterial hypertension, dyslipidaemia and smoking in patients with T2DM reduces cardiovascular morbidity and mortality. Although limited data addressing the effect of CR in patients with T2DM or IGT, CR has shown itself to be highly effective in reducing mortality in the overall population. The DANSUK study was therefore designed to address this issue by assessing the effectiveness of participation in a comprehensive CR programme on clinical outcome in patients with T2DM or IGT compared to usual care. It was hypothesized that treatment goals would be reached to a higher degree in these patients, if focus was brought upon glucometabolic abnormalities and if the metabolic care became an integrated part of the comprehensive CR. Beside behavioural modification, the DANSUK study should also focus on the use of combined evidence-based medical therapies with the potentiality of a synergistic benefit in these patients.

Part II: The DANSUK study

3. Background and design (the book chapter, appendix 1)

3.1. Background

Although much of the literature is before the year of 2000, international research has documented that cardiac rehabilitation (CR) improves quality of life and survival rates among patients with cardiovascular diseases [30-32,255]. Bispebjerg University Hospital has a catchment area of nearly 140.000 individuals making it one of the largest hospitals in Denmark. As part of being selected as a model hospital for health promotion, the department of cardiology at Bispebjerg University Hospital developed a comprehensive, integrated CR programme in 1997. The CR programme was based on the guidelines of the Danish Heart Foundation and the Danish Society of Cardiology [256]. To test the programme, the randomized controlled DANish cardiac REHABilitation (DANREHAB) trial was carried out with inclusion of 770 patients over 3 years in the period of 2000 to 2003 [257]. The aims of the DANREHAB trial were to investigate whether a comprehensive, integrated CR programme at a hospital-based outpatient clinic had an immediate and long-term effect on morbidity and mortality compared to usual care in patients discharged from a department of cardiology. The primary endpoint after 12 months were the combined endpoint of overall mortality, non-fatal re-infarctions, readmissions due to ischemic heart disease (IHD), congestive heart failure (CHF) or other cardiovascular diseases (CVD). Secondary endpoints after 12 months were overall mortality, acute ischemic syndrome, deterioration of CHF and total readmission rate. Tertiary endpoints after 12 months were quality of life, lifestyle changes, changes in risk factor control and uses of social services. Register based investigation of all cause mortality, causes of deaths, number and causes of readmissions will be performed after 5 and 8 years [257].

During the first two years of inclusion in the DANREHAB trial, 20% of the 569 patients enrolled were registered as having diabetes at baseline. Due to publication of sensational studies during study period an increased focus on T2DM and its precursors arose [103,104,106,204,205,217,233]. The DANSUK sub study was therefore designed to examine the patients included within the last year of the DANREHAB trial for unrecognized type 2 diabetes (T2DM), impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (DANSUK 1) [258]. Another aim of the sub study was to develop and integrate a diabetes module into the settings of comprehensive CR and to optimize the intensive risk factor control in patients with T2DM or IGT comparing the outcome with usual care (DANSUK 2) [259].

3.2. Design and endpoints

The DANREHAB study was designed as a two-armed centrally randomized clinical trial comparing hospital-based CR to usual care (UC). Patients from the department of cardiology at Bispebjerg University Hospital with IHD, CHF or high-risk (HR) of ischemic heart disease with at least 3 classical cardiovascular risk factors were consecutively screened for eligibility. There was no age limit for participation but only patients living at home were eligible. Other exclusion criteria were severe non-cardiovascular disease, NYHA stage IV, unstable patients awaiting revascularisation, severe abuse of alcohol and sedatives, dementia, and linguistic problems. Consenters were randomized 1:1 to CR or UC using a centralized

randomization procedure with stratification according to cardiac diagnosis group, age, gender and history of T2DM. In the last year of the DANREHAB study, 201 patients were included and randomized and became also a part of the DANSUK study (figure 3.1.).

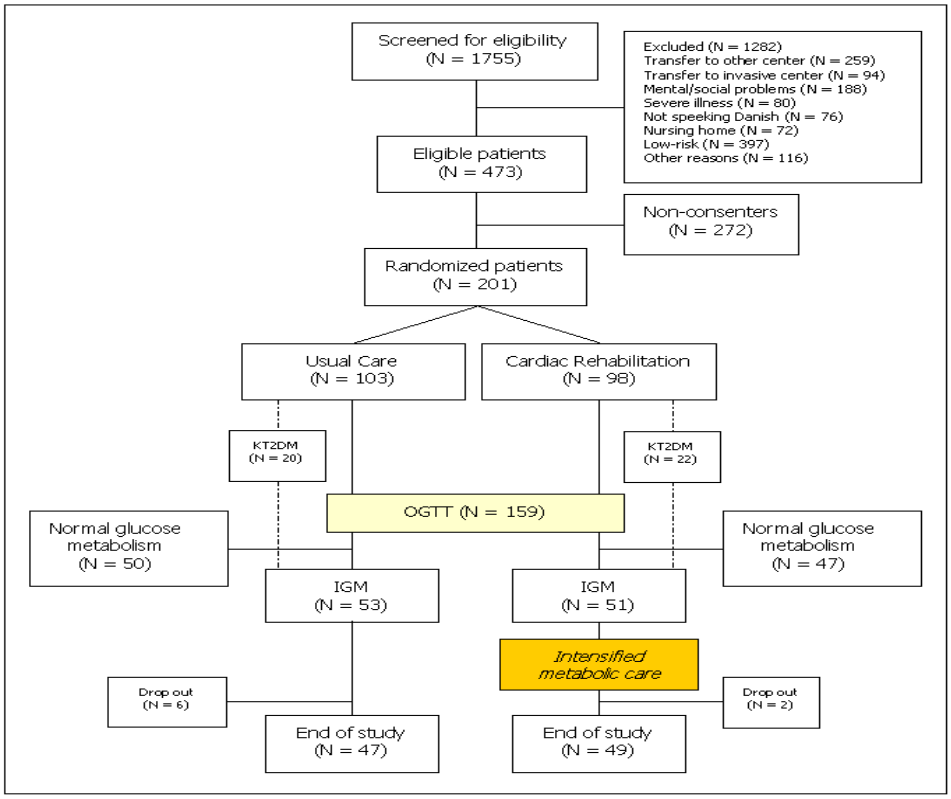

Figure 3.1. Trial profile – the DANSUK study. KT2DM, known type 2 diabetes at baseline; OGTT, oral glucose tolerance test; IGM, impaired glucose metabolism denotes type 2 diabetes and impaired glucose tolerance

Besides the determination of the prevalence of IGM among patients eligible for CR, the primary objective of the DANSUK study was to evaluate if an intensified integrated approach of treatment would result in a better glycaemic control measured by differences in HbA1c compared to usual cardiac and diabetic re-gimes. Differences in blood pressure, lipid control, exercise capacity and other life style modifications were secondary objectives.

3.3. Classifying IGM

Classification of impaired glucose metabolism (IGM) was based on known type 2 diabetes (KT2DM) at baseline or by the performance of a standardised 75-gram oral glucose tolerance test (OGTT) after 3 months of follow-up in the remaining population invited independently of the randomization. Blood glucose was measured fasting, and after 120 minutes. Based on the outcome of the OGTT and two fasting glucose values the patients were divided into 4 groups according to the WHO definitions of glucometabolic disturbances [85] (figure 3.2.). The patients were informed of the restrictions they had to undertake prior to the test [258]. The patients diagnosed with isolated IFG did not undergo the inten-sified metabolic care but participated in the comprehensive CR programme like the patients with NGT.

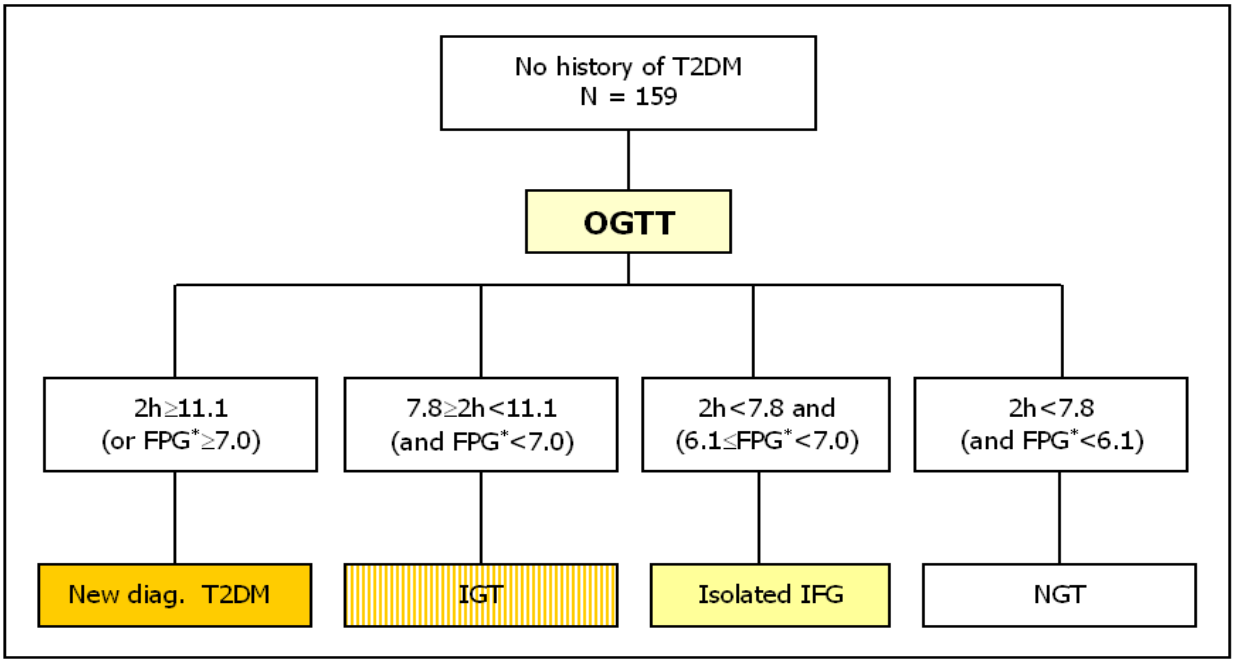

Figure 3.2. - Flow chart of metabolic group assignment in the DANSUK study according to the outcome of fasting plasma glucose (FPG) values and an oral glucose tolerance test (OGTT) using the WHO definition (85).
* Measured on two occasions

3.4. Comprehensive cardiac rehabilitation

The 12 months of CR was constructed according to international guidelines and was individually tailored [256,257]. The first six weeks of the CR programme contained elements of patients education, supervised exercise training, dietary counselling and supervised cooking lessons on location, smoking cessation, psycho-social support including a 24-hour telephone line, pharmacological therapy and risk factor management supported by a minimum of consultations by a physician after 3, 6 and 12 months (figure 3.3). A team of doctors and nurses trained in internal medicine and cardiology treated the patients in the CR group. Other members of the team were dieticians, physical therapists, social workers, and psychiatrists. Patients randomized to CR were grouped and accompanied each other throughout the 6 weeks of lectures and physical training. The six weeks of supervised exercise training consisted of 90 minutes of training twice a week aiming at an intensity of 60% to 85% of maximal heart rate based on an initial symptom limited bicycle test. The training plan was highly individualized and the patients were monitored clinically in terms of cardiopulmonary response to the exercise and by the use of pulse watches. The physical exercise was conducted as a mixture of endurance and strengthening training using various upper and lower body modalities easily implemented as activities that the patients could perform at home. Rating on Borg's scale was used since it have been found to relate closely to other objective measures of exercise intensity such as oxygen uptake and heart rate [260]. Adherence to the advised increased level of physical activity was registered by validated self-administrated questionnaires, interviews and maximal bicycle exercise capacity tests after 3 and 12 months [261-267]. Adherence to other behavioral modification was also registered by questionnaires and interviews [257].

3.5. The diabetes module – The DANSUK study

T2DM is a chronic disease that requires ongoing care tailored to the needs of the patient. In the process of integrating the diabetes module in the overall comprehensive CR programme, the same life style intervention models as the health belief model were used [268]. In the DANSUK study, patient education formed the framework on which intensive medication, nutrition, and other lifestyle modifications were built. Besides ensuring that all the patients eligible to CR underwent a proper screening for IGM, the aims of the diabetes module were to combine systematic risk factor management of diabetic and cardiovascular complications in the overall rehabilitation by means of increasing patient adherence to physician-defined therapeutic goals and treatment strategies and to optimize active participation by patients through motivation and increased knowledge.

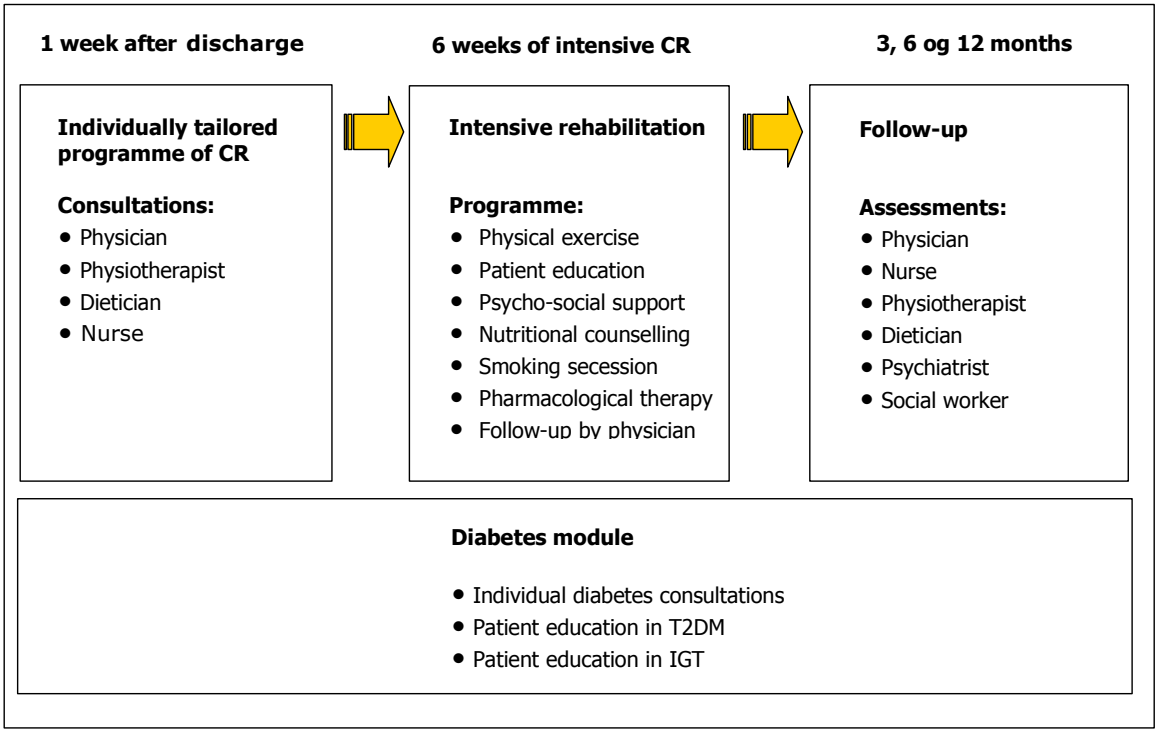

Figure 3.3. Patient flow throughout the study period showing the different components of the comprehensive CR programme and the supplementary diabetes module that became an integrated part

Patients with T2DM were gathered in groups and the diabetes module was implemented as a complete integrated part of the CR programme. The diabetes module was highly individualized to consider the appropriate intervention needs for different age groups, cardiac disease, duration of T2DM, self-care facilities, and severity of complications. Besides individual counselling in blood sugar measurements, the use of oral hypoglycaemic agents and adjustments of insulin doses, the diabetes module consisted of 3 interactive teaching sessions of 2½ hours each with focus on self-care principles involving symptoms of peripheral arterial disease (PAD), diabetic neuropathy, nephropathy and retinopathy. Regular surveillance by ophthalmologists and chiropodist was ensured for the patients. The programme was build up to emphasize the critical link between T2DM and IHD because of the crucial need for the patients truly to

understand the implications of T2DM on their cardiovascular health. Patients with newly diagnosed IGT were invited to a two-hour session with recommendations of further prophylactic initiatives to prevent the development of T2DM. No special exercise prescription and programming were developed for patients with T2DM although caution in patients with severe retinopathy or autonomic neuropathy was undertaken. The patients were informed of the immediate and long-term effects of exercise on improved glycaemia and the risk of exercise-induced hypoglycaemia. The diabetes module was organized to cover the whole range of care provision required to achieve the intensified goals of treatment. Patients with T2DM were encouraged to use a glucometer and on a regular basis each patient's monitoring technique and interpretation of data was evaluated [267].

4. Methods

4.1. Data collection

The data collection was comprehensive as part of the great DANREHAB trial [257]. Data collected as part of the DANSUK study is given in table 4.1. Examinations were done over two consecutively days and the patients received oral and written information prior to the tests. The time for all the assessment visits were computerized, so when an assessment visit was near by, the patients data appeared on screen in the database. Data on diabetic neuropathy (autonomic nervous function, peripheral nervous function), fundus photographs and measurement obtained by echocardiography and spirometry will not be described in details, as it is not within the frames of this dissertation.

Anthropometric measurements

Weight was measured to the nearest 0.1 kg and with the patient wearing indoor clothing without shoes. Height was measured to the nearest 0.5 cm with the patient wearing no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of heights in meters [269]. With the patients standing in a resting position, waist circumference was measured midway between the iliac crest and the costal margin. Hip circumference was measured at its maximum. Waist and hip circumference were measured to the nearest 0.5 cm and used in calculation of the waist-hip-ratio.

Blood pressure

Several blood pressure measurement were done using a standard sphygmomanometer and with the patient in both supine and sitting position after 10 minutes of resting. The mean of the last two measurements on each arm was used. Ambulatory blood pressure measurement was done at baseline and after 12 months with measurements taken every 15 minutes in the daytime and every half hour in the nights.

Ankle-brachial pressure index

The ankle-brachial pressure index (ABPI) was measured in all patients at baseline using the Doppler method. For ABPI assessment, the systolic pressure on both arms was measured by auscultation. The

Table 4.1. Data collection in the DANSUK study

	0 Baseline	3 months	6* months	12 months
Fasting plasma glucose	x	x	x	x
HbA1c	x	x	x	x
Fasting-C-peptide	x			
Fasting plasma insulin	x			x
Oral Glucose Tolerance Test		x		(x)
Lipidprofile	x	x	x	x
Standard blood tests	x	x	x	x
Frozen plasma [1]	x	x		x
Resting 12-lead ECG	x	x	x	x
E/I-ratio/Valsalva-ratio [2]	x			
Orthostatic hypotension test	x			
Ambulatory blood pressure	x			x
Morning spot urine	x	x		x
Echocardiography [3]	x			
Lung function test	x			x
Exercise stress test	x	x		x
Ankle/brachial pressure index	x			
Peripheral neuropathy [4]	x			
Medication (registration)	x			x
Questionnaires [5]	x	x	x	x

* Data collected only in patients assigned to cardiac rehabilitation

(x): Repeated in patients primarily diagnosed with IGT

[1] For future analyses of inflammatory markers and cardiac hormones

[2] Heart rate response to deep breating (Ex- and Inspiration) and the valsalva manoevre

[3] Transthoracal with measurements of various systolic and diastolic parametres

[4] Semmes-Weinstein's monofilament/10 g

[5] Validated questionnaires concerning patient satisfaction, depression, quality of life and behavioural modifications

blood pressure above the ankle was assessed on both lower extremities by applying a standard tonometer cuff to the leg above the ankles. The cuff was inflated above the expected systolic pressure and the pressure was slowly reduced. During the decline of pressure in the cuff the pulsating flow was restored and the volume of the leg increased and at that precise moment the systolic pressure was measured and registered. The pressure was registered primarily using the posterior tibial artery or if pulsation was absent, the dorsalis pedis artery. The pressure was measured twice for each extremity and the highest obtainable pressure was used in the calculation of the ABPI. Peripheral artery disease was defined as an ABPI of 0.9 or less [270].

Blood samples

Blood samples were taken in the morning after an overnight fast. Plasma glucose was determined by the hexokinase/G6P-DH method [271]. Few of the glucose concentrations were measured on capillary whole blood and converted to venous plasma glucose by means of a conversion factor (fasting plasma glucose = 0.102 + 1.066 x capillary whole blood glucose) established by the European Epidemiology Group [272]. HbA1c and plasma insulin were measured with commercial kits. Normal range: HbA1c 4.1-6.4% and plasma insulin 5-69 pmol/l) [273]. Serum cholesterol and HDL cholesterol were analysed by chromatogra-

phy and triglycerides by colorimetry [274]. VLDL and LDL cholesterol was calculated using the Friedwald's Equation in patients with a serum triglyceride concentration lower than 4 mmol/l [275]. The OGTT was given as 75 g of glucose dissolved in 200 ml of water and was performed on capillary blood. Blood samples for later analyses were immediately put on ice and spun within 60 minutes of sampling. Samples were hereafter stored frozen at –80°C.

Electrocardiography (ECG) and exercise stress testing

A 12-lead resting ECG was taken as a minimum of three times for later analysis of myocardial ischemia. Exercise stress testing was performed with a bicycle ergometer beginning at 25 Watt and increasing workload with 25 Watt at every second minute. In the patients whose latest admission was due to congestive heart failure, the workload increased with 10 Watt every minute.

Urine samples

At baseline and after 3 and 12 months of follow up patients delivered a first morning spot urine sample which has been demonstrated to correlate with the 24-hour urinary excretion rate [276,277]. Urine-albumin was determined turbidimetrically, and urine-creatinine was determined by creatinine Jaffé method.

Interviews and questionnaires

In terms of evaluation of non-pharmacological therapy, care management program, adherence to behavioural modification etc., the patients were interviewed and received self-completion questionnaires during the study period (table 4.1). Only the interviews and questionnaires evaluating the level of physical activity and smoking cessation are within the frames of this dissertation.

Ethics

The examinations of both study groups were obtained at the same place in the unit of CR, at the department of cardiology and at the department of biochemistry at Bispebjerg University Hospital. The patients randomized to usual care were told that they would be contacted after 3 and 12 months to follow-up assessments. Test results collected at the assessments visits were accessible in records, and on request the patients randomized to usual care could receive copies to bring about to their physician. All patients gave a written consent before taking part in the study. The study was approved by the Scientific Ethical Committee of Copenhagen (j.no.(KF) 11 – 121/01).

4.2. Definitions

Glucometabolic abnormalities

Impaired glucose metabolism (IGM) was defined using internationally accepted criteria: the WHO from 1999 [85] and the criteria from the ADA from 2003 [84] (table 4.2.). Patients with previously established diagnosis of T2DM, being on a diet or currently taking any form of hypoglycaemic drugs or insulin were categorized as KT2DM. In the DANSUK study it was decided to let all the patients with no history of

T2DM undergo a standardised OGTT [85]. Diagnosing IGT was part of the study objective as classification based on FPG alone has been shown to leave 31% of all patients with T2DM undiagnosed [272].

Cardiac disease groups

Definitions of myocardial infarction and congestive heart failure used internationally accepted criteria [278,279]. The patients were divided into one of three stratification groups: *The IHD group* defined patients who had known IHD prior to admission or who were admitted because of an acute MI. The patients stratified into *the CHF group* were patients whose latest admission was due to congestive heart failure. The group of *high-risk for IHD (the HR group)* were patients with at least 3 classical cardiovascular risk factors [257].

Table 4.2. The diagnostic criteria for impaired glucose metabolism used in the DANSUK study according to the WHO and the ADA definitions [84,85]

Glucose Tolerance	Fasting plasma glucose *		2 hours capillary glucose
Normal glucose tolerance (WHO)	≤ 6.0 mmol/L	AND	< 7.8 mmol/L
Normal glucose tolerance (ADA)	≤5. 5 mmol/L		
Impaired fasting glucose (WHO)	6.1-6.9 mmol/L	AND	< 7.8 mmol/L
Impaired fasting glucose (ADA)	5.6-6.9 mmol/L		
Impaired glucose tolerance	< 7.0 mmol/L	AND	7.8 - 11.0 mmol/L
Diabetes mellitus	≥ 7.0 mmol/L	AND/OR	≥ 11.1 mmol/L

* Tests taken on two occasions

Family history of diabetes

A positive family history of diabetes implied either a parent or sibling to have diabetes.

Arterial Hypertension

Patients were classified as having systemic hypertension if they received medical therapy for hypertension or if they had two resting blood pressure measurements during hospital admission above 140/90 mmHg.

Dyslipidaemia

The patients were diagnosed with dyslipidaemia if they were treated with lipid lowering drugs or if a lipid profile taken at admission showed values of total cholesterol above 5.0 mmol/l, HDL cholesterol less than 1.0 mmol/l, or triglycerides above 1.5 mmol/l [257].

Albuminuria

The Urine-albumin-creatinine ratio (mg/mmol) was calculated; normal range < 2.5 mg/mmol. If the morning spot urine samples had an albumin-creatinine index between 2.5 – 25 mg/mmol at baseline and at the 3 months assessment visit, the patients were diagnosed with microalbuminuria and if the value exceeded 25 mg/mmol the qualitative diagnosis of macroalbuminuria was definitive [276,277]**.**

Smoking

Smoking habits were graded as never, ex- or current smoker. At baseline and after 12 months current smokers and ex-smokers had their concentration of carbon monoxide in expired air measured. The carbon monoxide concentration was measured regularly among patients who had quitted to allow the patient to see that this parameter declines as a result of quitting. The patients who wanted to quit smoking were offered free accession to nicotine replacement therapy as well as motivated spouses could receive replacement therapy for one week free of charge [264].

Physical activity

Participants were given a self-completion questionnaire on health related behaviour including physical exercise at baseline and after 3 and 6 months. The level of physical activity was divided into 4 groups: 1) Almost physical passive responded to active less than 2 hours a week. 2) Moderate physical active for 2-4 hours a week 3) Moderate physical activity for more than 4 hours a week 4) High physical activity for more than 4 hours a week. For later analyses, group 1 and 2 were defined as sedentary life style and group 3 and 4 as physically active life style.

Overweight and obesity

The BMI was used to categorize patients as overweight if they had a BMI from 25.0 kg/m^2 to 29.9 kg/m^2 whereas BMI equal to or greater than 30 kg/m^2 was defined as obesity [269]. For central obesity waist circumference was used as well as the waist-hip-ratio. Different cut-off values have been suggested as part of describing the optimal applicable definition of the metabolic syndrome in epidemiological studies [280]. In the DANSUK study, waist circumference was considered increased if equal to or greater than 94 cm in men and equal to or greater than 80 cm in women.

Hyperinsulinemia and insulin resistance

Insulin resistance (HOMA-IR) as defined by the WHO requires a euglycaemic, hyperinsulinaemic clamp performance but as modified according to the European Group for the study of Insulin Resistance (EGIR) fasting plasma insulin was used in the DANSUK study [281] even though the use in patients with T2DM is questionable. Hyperinsulinemia was defined as the upper quartile of fasting plasma values and insulin resistance by the homeostasis model assessment (HOMA) determined in Danish population-based studies i.e. cut-off value of hyperinsulinaemia: 51 pmol/l and of HOMA-IR: 1.76 [282,283]. Insulin resistance (HOMA-IR) was calculated by: fasting plasma insulin (μU/ml) x FPG (mmol/l) divided by 22.5 [277,278].

4.3. Intensive treatment modalities in the unit of CR

The intensive intervention strategy involved a stepwise introduction of behavioural modification and pharmacotherapy aiming to reach the evidence-based treatment goals outlined in table 4.3. The treatment goals should be realistic and feasible within the study period of 12 months. At every individual assessment visit in the CR group, measurements were scrutinized thoroughly to see if the goals were

obtained and if not which initiative could be installed to accomplished this before the next assessment visit. This arrangement was thought only to be feasible if the patients participated and used their self-care learned principles at their highest. All measurements and treatment goals were written in a personal manual kept by the patients controlled and adjusted at every visit.

Table 4.3. Intensive treatment goals for patients with type 2 diabetes or impaired glucose tolerance in the DANSUK study

	Treatment goal
HbA1C (%)	< 6.5
Fasting plasma glucose (mmol/l)	4.0-7.0
Post prandial blood glucose (mmol/l)	4.0-8.0
Systolic blood pressure (mmHg)	< 130 [<120]
Diastolic blood pressure (mmHg)	< 80 [<70]
Total cholesterol (mmol/l)	< 4.5
HDL cholesterol (mmol/l)	> 1.1
LDL cholesterol (mmol/l)	< 2.5
Triglycerides (mmol/l)	< 1.7
Physical exercise	> 30 min per day
Body Mass Index (m^2)	< 25*
Functional and psycho social capacity	Optimal
Smoking**	Complete secession
ACEI/ARA irrespective of blood pressure	Yes
ASA irrespective of manifest IHD or PAD	Yes
Statin irrespective of cholesterol levels	Yes

[if macro- or microalbuminuria] * goal setting individualized aimed at loosing 10-15% of total body weight. Abbreviations: ACEI: Angiotensin-converting enzyme inhibitor, ARA: Angiotensin receptor-II antagonist, IHD: Ischemic heart disease, PAD: Peripherial arterial disease. ** Smoking patients and their spouses were invited to participate in smoking cessation course

Pharmacological care

Glucose-lowering treatment and glucose control

To achieve the predefined goal of an HbA1c-value below 6.5%, a stepwise approach was used concerning oral hypoglycaemic agents and insulin. As part of the comprehensive treatment algorithm to maintain optimal glycaemic control in the patients, many different hypoglycaemic agents were prescribed. There was a limited use of thiazolidinediones because of the lack of evidence when used in patients with coexisting cardiac diseases. Gliclazid or glimepiride were often chosen as sulfonylureas, because of their neutral effect on myocardial K^+-channels. Obese patients without a severe degree of congestive heart failure were treated with metformin in doses of 1 to 2 g per day. Lean patients were started on glimepride in doses of 1-4 mg per day. Second step for obese and lean patients was glimepride and metformin respectively. If HbA1c was above 6.5% despite of maximum treatment with oral hypoglycaemic agents, dietetic restrictions, and physical exercise, patients were given insulin usually NPH insulin at nighttime. The type and dose of insulin was adjusted by fasting plasma glucose values and by self-monitored blood glucose (appendix 2). Arcobase was used in some of the patients in the beginning of the study but often discontinued due to gastrointestinal side effects. In the DANSUK study great efforts were made in diminishing three aspects of the hyperglycaemic spectrum. The patients were carefully trained in

using self-monitored blood glucose and were educated in understanding the importance of trying to normalize FPG and postprandial hyperglycaemia as well as minimising glycaemic variabililty (appendix 1 and 2). Postprandial glucose is known to be an independent risk factor for CVD. But the importance of postprandial glucose in the overall glycaemic control increases as HbA1c percentages improves. In patients with an HbA1c between 7.3% and 8.3%, postprandial hyperglycemia has been shown to account for 50% of the elevated HbA1c [286]. Normalising the postprandial glucose values was therefore as important a goal as normalising FPG. To assure as normal glycaemic level as possible throughout the day, the patients were given instructions to measure the blood glucose 6 times a day. When diet adherence and hypoglycaemic agents were in an optimal steady state the patients could perform a glucose profile of 6 measurements over 2 consecutively days at every 14^{th} day and depending on their needs [appendix 2]. The percentage of patients obtaining an HbA1c level below 6.5% during and at the end of the study was used as an indicator of success. Both HbA1c and FPG were used as powerful feedback parameters towards the patients to increase the level of motivation, compliance, and adherence to therapy.

Treatment of hypertension and blood pressure control

Great effort was invested in the combination of the most appropriate therapy in the treatment of arterial hypertension. When ever possible long-acting combinations and combination of antihypertensive medications such as ACEI or ARA combined with a diuretics or a calcium-channel antagonist were preferred to improve patient compliance to medication and daily pill count. Figure 4.1 shows an example of a treatment algorithm initiated in the hypertensive patients not using any antihypertensive agents at referral. Many of the patients in the DANSUK study were at referral already in some kind of medical treatment due to their pre-existing cardiac disease and depending of diagnosis and symptoms, different algorithms were created. Thus beta-blockers may be substituted for calcium channel blockers if the patient was in a post-MI phase, had angina, heart failure or arrhythmia. A nurse controlled blood pressure regularly every 2-3 weeks using a standard sphygmomanometer until the treatment goal was reached. If there were signs of treatment failure, a 24-hour measurement was frequently performed.

Treatment of dyslipidaemia and lipid control

Therapeutic lifestyle change remains the keystone of lipid management for patients with T2DM requiring lipid therapy but in the DANSUK study all the patients with T2DM or IGT in the unit of CR were started treatment with a statin early in the study period not awaiting results of nutritional changes or exercise. Measurement of adherence to treatment was based on regularly lipid profiles. The use of fibrates in the DANSUK study was limited. Patients with T2DM or IGT were treated with a statin, irrespective of the values of total cholesterol, LDL cholesterol and HDL cholesterol or history of cardiac disease.

Other pharmacological treatment modalities

As part of the predefined treatment goals in the DANSUK study (table 4.3), all patients with T2DM or IGT in the CR group had to receive treatment with ASA independently of co-existing vascular disease.

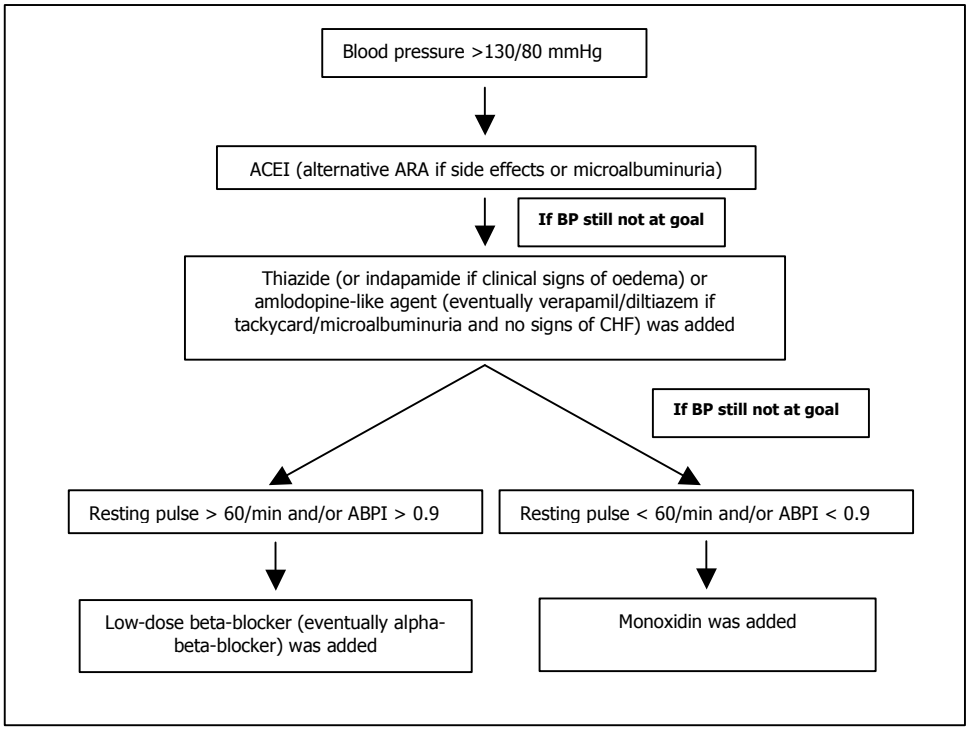

Figure 4.1. Treatment algorithme used in the DANSUK study to obtain the predefined treatment goal of arterial hypertension. BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARA, angiotensin receptor-II antagonist; ABPI, ankle/brachial pressure index

Patients who had been revascularized involving coronary stenting also received treatment with clopidogrel. Patients in the CR were all screened for mental depression and were offered medical treatment if needed. There was no use of weight loss inducing pharmacological treatment.

Behavioural care and self-care

Apart from the prescheduled assessment visits, the patients in the CR group could consult the dieticians, nurses, physiotherapists and the physicians on request. At these visits the patients received brief supportive advice, reinforcing them to continue their change of lifestyle. At every consultation in the unit of CR, smokers were encouraged to give up smoking and the patients were constantly inspired to increase the level of physical activity. The physicians were responsibly of emphasizing the significant contribution of nutritional counselling and physical exercise towards the patients. Consultation by a dietician is of great necessity in patients with T2DM with IHD and has been shown to cause an 8.6% reduction in hospitalization and a 16.9% reduction in physician visits [287]. Behavioural changes and adherence to pharmacological treatment are essential for improving the prognosis in T2DM patients with or without cardiac disease. But T2DM in combination with CVD contains many aspects that make compliance and adherence to therapy difficult. Being a chronic disorder, lifestyle changes are required, and the treatment is often complex, intrusive and inconvenient in demanding, besides motivation, some degree of self-discipline. Many of the patients took two tablets plus maybe insulin for control of their blood glucose, one tablet for dyslipidaemia, and two maybe 3 agents for hypertension, in addition to a low-dose ASA and maybe a clopidogrel each day. Thus the need for continued and individualized education and en-

couragement was in focus throughout the study period to maintain the patients motivated and self-assured in the hope of increasing adherence to the programme.

4.4. Statistical methods

All test were made by SAS statistical systems. The power calculation of the DANSUK study was based on the primary end point. The mean baseline HbA1c-value in the patients with KT2DM included within the first two years of the main study (N = 114) was 8% ± 1.75% [257]. With the intention of reducing the mean HbA1c from a mean of 8% to a mean of less than 6.5% over the study period of 1 year, each treatment group had to consist of at least 21 patients with T2DM with a power of 80% and a type I error of 0.05. Baseline and follow-up characteristics were compared between the groups using t-test for continuous variables and X^2 test for categorical variables. Results are shown as means ± SD for continuous variables and as number and percent for categorical variables. Intergroup comparisons were made by parred t-test for normally distrubuted variables and by Wilcoxon two-sample test for variables with a skewed distribution. Analyses were made separately for men and women when appropriate. Verification of normal distribution of data was accomplished with histograms. Kruskal-Wallis test was used to test for difference between two or more independent groups in non-parametric data. McNemar's test was used to test changes in pharmacological use from baseline to end of study. For the analyses of independent predictors of glucose intolerance two different comparisons were made: T2DM versus NGT and IGT versus NGT. Two models were analysed using logistic regression. Model 1 included all predictors known at baseline that were significantly related to IGT in bivariate analyses. In model 2, variables believed to be mediators or intermediate variables of the relation between predictors and IGT were removed (FPG, HbA1c and HOMA-IR). Statistical significance was defined as a two-sided $p<0.05$.

Part III: Prevalence of IGM in the DANSUK study

5. Results – DANSUK 1 (Article 1, appendix 3)

5.1. Baseline characteristics of the study population

The study population comprised 201 patients with a mean age of 62.5 ± 11.0 years. Women constituted 30% of the patients included. Apart from lipid control, the risk profile was worse in patients with KT2DM compared to the patients undergoing screening for IGM (table 5.1). There was no significant difference in age and cardiac disease stratification in patients with KT2DM and patients with no previously known glucometabolic abnormality. An underutilisation of cardiovascular pharmacotherapy in the patients with

Table 5.1. Patients characteristics of the DANSUK study (N = 201)

	KT2DM N = 42	**Patients to screen N = 159**	**P****
Demographic			
Age [years/range]	63.5 [42-82]	62.3 [37-89]	NS
Women	38%	28%	NS
Stratification			
Congestive Heart Failure	2 (5)	14 (9)	NS
Ischemic Heart Disease	26 (62)	95 (60)	NS
High-Risk patients	14 (33)	50 (31)	NS
Previous history			
Myocardial Infarction	9 (21)	32 (20)	NS
Revascularization	16 (38)	82 (52)	NS
Known systemic hypertension	31 (74)	85 (53)	**0.018**
Known hypercholesterolemia	32 (76)	119 (75)	NS
Cerebrovascular events	7 (17)	20 (13)	NS
Intermittens clautication	8 (19)	20 (13)	NS
Clinical			
Ambulatory systolic blood pressure (mmHg)	131.5 (20.5)	124.9 (18.4)	**0.048**
Ambulatory diastolic blood pressure (mmHg)	73.0 (9.2)	73.7 (9.2)	NS
Physical inactive (< 30 min/day)	23 (55)	72 (45)	NS
Body Mass Index (kg/m^2)	32.7 (6.9)	28.1 (4.9)	**0.001**
Ancle-Brachial Pressure Index < 0.9	16 (38)	36 (23)	**0.042**
Exercise capacity (mets)	5.53 (1.0)	6.36 (1.5)	**0.004**
Biochemical			
Total cholesterol (mmol/l)	4.17 (1.1)	4.83 (1.1)	**0.001**
HDL cholesterol (mmol/l)	1.17 (0.4)	1.31 (0.4)	**0.027**
LDL cholesterol (mmol/l)	2.17 (0.9)	2.81 (1.0)	**0.0002**
VLDL cholesterol (mmol/l)	0.72 (0.4)	0.67 (0.3)	NS
Triglycerides (mmol/l)	1.83 (1.3)	1.57 (0.9)	NS
Fasting plasma glucose (mmol/l)	8.20 (2.1)	5.91 (1.1)	**< 0.0001**
HbA1C (%)	7.35 (1.3)	5.95 (0.6)	**< 0.0001**
Hyperinsulinemia (≥ 51 pmol/l)	26 (62)	76 (48)	NS
Microalbuminuria (2,5-25 mg/mmol)	11 (26)	14 (9)	**< 0.002**
Cardiovascular medication			
ASA	29 (69)	120 (75)	NS
ACEI/ARA	20 (47)	59 (37)	NS
β-blockers	19 (45)	78 (62)	NS
Statins	31 (74)	99 (62)	NS

Mean values or exact numbers. Brackets are 1 SD or %. KT2DM, known type 2 diabetes at baseline, ACEI, converting enzyme inhibitor, ARA, angiotensin receptor-II antagonist

** p values for difference between groups

T2DM compared to the patients with no previously glucometabolic abnormality, was not observed. Table 5.2 shows baseline characteristics of the patients sub grouped by the result of the OGTT and FPG values. A worsening of the risk profile followed increasing disturbance in glucose metabolism. The fasting values of plasma C-peptide and insulin were also markedly higher in patients with glucose intolerance although nearly one third of the patients with a normal glucose metabolism were hyperinsulinemic compared to the background population. As the glucose tolerance deteriorates, values of fasting plasma insulin tends to decrease as a manifestation of failing beta-cell function.

Table 5.2. Baseline characteristics in patients sub grouped by outcome of an oral glucose tolerance test

The DANSUK study (N = 201)	**KT2DM** N = 42	**ST2DM** N = 26	**IGT** N = 36	**IFG** N = 19	**NGT** N = 78	P**
Demographic						
Age (years*/range)	63.5 (42-82)	63.4 (50-81)	64.8 (45-89)	63.2 (50-80)	60.5 (37-87)	NS
Women	38	27	36	21	27	NS
Clinical						
Systolic blood pressure (mmHg)*	131.5 (20.5)	132.2 (21.0)	125.0 (21.6)	121.7 (12.6)	123.1 (16.7)	NS
Diastolic blood pressure (mmHg)*	73.0 (9.2)	74.2 (10.1)	72.1 (10.3)	74.5 (7.3)	74.0 (8.9)	NS
Physical inactive (< 30 min/day)	23 (55)	16 (62)	16 (44)	9 (53)	31 (40)	NS
Ex-smokers	15 (36)	17 (65)	22 (61)	14 (74)	37 (47)	NS
Current smoking	13 (31)	6 (23)	7 (19)	5 (26)	28 (36)	NS
Body mass index (kg/m^2)*						
Women	32.7 (6.9)	37.2 (7.4)	27.5 (4.7)	30.0 (8.3)	27.6 (4.6)	**< 0.005**
Men	29.86 (4.3)	29.1 (4.4)	27.5 (4.0)	29.8 (4.2)	26.5 (3.6)	**< 0.005**
Waist circumference (cm)*						
Women	107.3 (3.1)	110.7 (9.5)	91.3 (12.5)	104.8 (25.6)	94.3 (13.8)	**< 0.01**
Men	107.5 (11.7)	105.5 (10.8)	101.0 (12.4)	107.5 (10.4)	98.9 (11.0)	**< 0.01**
Ankle/brachial pressure index < 0.9	16 (38)	8 (31)	9 (25)	7 (37)	12 (15)	NS
Exercise capacity (Mets)*	5.53 (1.0)	5.68 (1.2)	6.40 (1.3)	5.73 (1.5)	6.73 (1.6)	**< 0.001**
Biochemical						
Total cholesterol (mmol/l)*	4.17 (1.1)	4.70 (1.3)	4.75 (1.3)	4.98 (1.3)	4.85 (1.0)	**< 0.05**
HDL-cholesterol (mmol/l)*	1.17 (0.4)	1.21 (0.3)	1.36 (0.5)	1.28 (0.4)	1.33 (0.3)	NS
LDL-cholesterol (mmol/l)*	2.17 (0.9)	2.57 (1.0)	2.74 (1.1)	2.88 (1.2)	2.89 (0.9)	**< 0.005**
VLDL-cholesterol (mmol/l)*	0.72 (0.4)	0.82 (0.39)	0.66 (0.3)	0.82 (0.4)	0.59 (0.3)	**< 0.01**
Triglycerides (mmol/l)*	1.83 (1.3)	1.81 (0.9)	1.47 (0.6)	1.80 (0.9)	1.48 (1.0)	NS
Fasting plasma glucose (mmol/l)*	8.20 (2.3)	7.76 (1.1)	5.64 (0.7)	6.24 (0.4)	5.34 (0.5)	**< 0.0001**
HbA1C (%)* (range)	7.35 (5.1-11.0)	6.55 (5.0-7.8)	5.94 (5.1-6.9)	6.02 (5.2-6.8)	5.73 (5.0-6.7)	**< 0.0001**
Hyperinsulinemia (>51 pmol/L)	26 (62)	22 (85)	18 (50)	11 (58)	25 (32)	**< 0.0001**
HOMA-IR*	5.73 (6.6)	4.67 (1.6)	2.34 (1.5)	2.85 (1.1)	1.83 (1.2)	**< 0.0001**
Fasting plasma C-peptide (pmol/l)*	1069.4 (513.7)	1256.6 (438.2)	1017.0 (490.9)	1031.3 (322.0)	837.2 (426.8)	**< 0.05**
Microalbuminuria (2,5-25 mg/mmol)*	11 (26)	3 (12)	3 (8)	2 (11)	6 (8)	**< 0.05**
Macroalbuminuria (>25 mg/mmol)*	7 (17)	0	0	1 (5)	0	**< 0.0001**

* Mean (SD). Data are number (%) unless otherwise indicated. ** p values are for the difference between the groups.
NGT, patients with no glucometabolic abnormality according to the WHO definition; IFG, Impaired fasting glucose according to the WHO definition; IGT, Impaired glucose tolerance; ST2DM, Screen-detected type 2 diabetes; KT2DM, known type 2 diabetes at baseline.

5.2. Prevalence of IGM in the DANSUK study

Besides the 42 patients (42/201, 21%; 95% CI:15%;27%) who had KT2DM, 26 patients (26/201, 13%; 95% CI:8%;18%) had screen detected type 2 diabetes (ST2DM), 36 patients (36/201, 18%; 95%

CI:13%;23%) had IGT and 19 patients (19/201, 9%; 95% CI:5%;13%) had isolated IFG. Thus 123 patients of the patients in the DANSUK study had glucose intolerance (123/201, 61%, 95% CI:54%;68%) according to the WHO definitions (table 4.2). Overall 38% (26/68, 95% CI:29%;47%) of the patients with T2DM had ST2DM.

5.3. Age-and sex specific prevalence of IGM

In the DANSUK study, significantly more patients above the age of 50 years had IGM (65%, 95% CI:58%; 72%) compared to the patients below 50 years (32%, 95% CI:14%; 50%) ($p<0.009$) and in the middle-aged group more than 15% (95% CI:9%;21%) of the patients had ST2DM. Only the prevalence of IFG varied between the three age groups ($p<0.002$). There was no statistically significant difference in the prevalence of IGM between women and men. Nearly 67% (95% CI:55%; 79%) of the women and 59% (95% CI:51%; 67%) of the men had IGM.

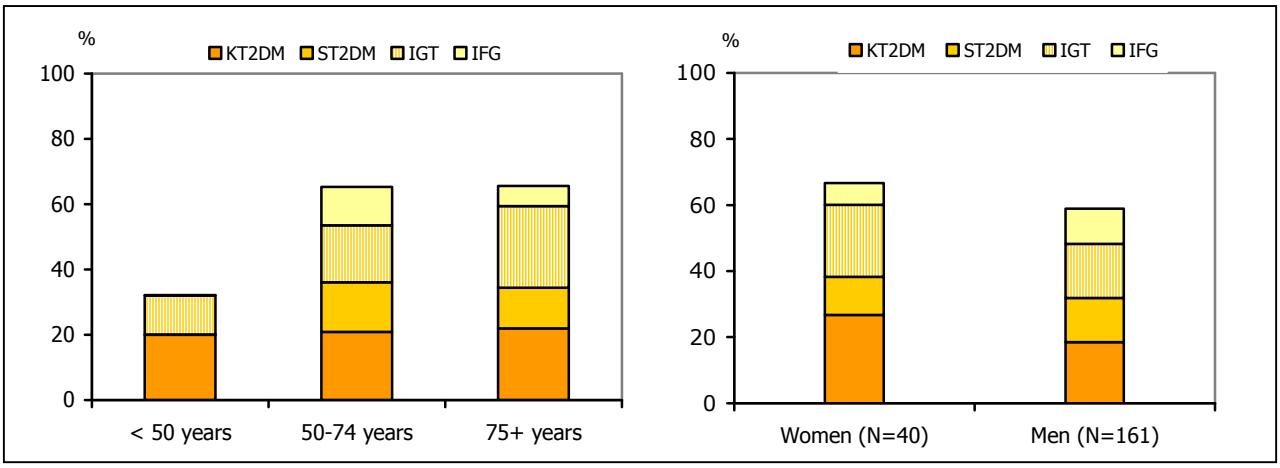

Figure 5.1. Sex- and age specific prevalence of IGM in the DANSUK study

5.4. IGM and cardiac disease group assignment

There was no statistical significant difference in the prevalence of IGM between the three groups in the DANSUK study (figure 5.2). Within the group of IHD, IGT was significantly more prevalent than T2DM and IFG ($p<0.02$).

5.5. The WHO definition compared to the ADA criteria

Using the ADA criteria (table 4.2), 36% (73/201) of the DANSUK population would be characterized as IFG thus increasing the prevalence by 100% compared to the 18% (36/201) according to the WHO definition. But the IFG category according to the ADA criteria would contain 19% (5/26) of the patients with ST2DM and fasting normoglycaemia and 37% (29/78) of the patients diagnosed as NGT according to the WHO definition (figure 5.3). Likewise 44% of the patients with IGT would be characterized as having NGT.

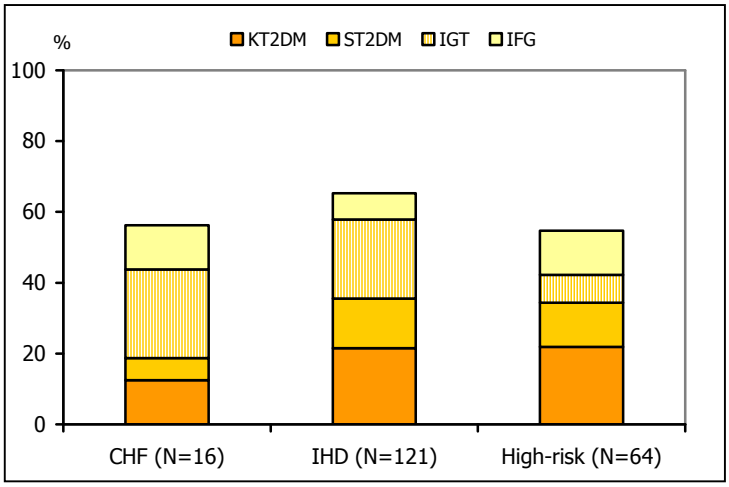

Figure 5.2. Prevalence of IGM according to cardiac disease group

In the DANSUK study all the patients with fasting normoglycaemic ST2DM had plasma glucose levels between 6.1-6.9 mmol/l and therefore would had been detected if an OGTT was performed in patients with IFG [69] (table 5.3).

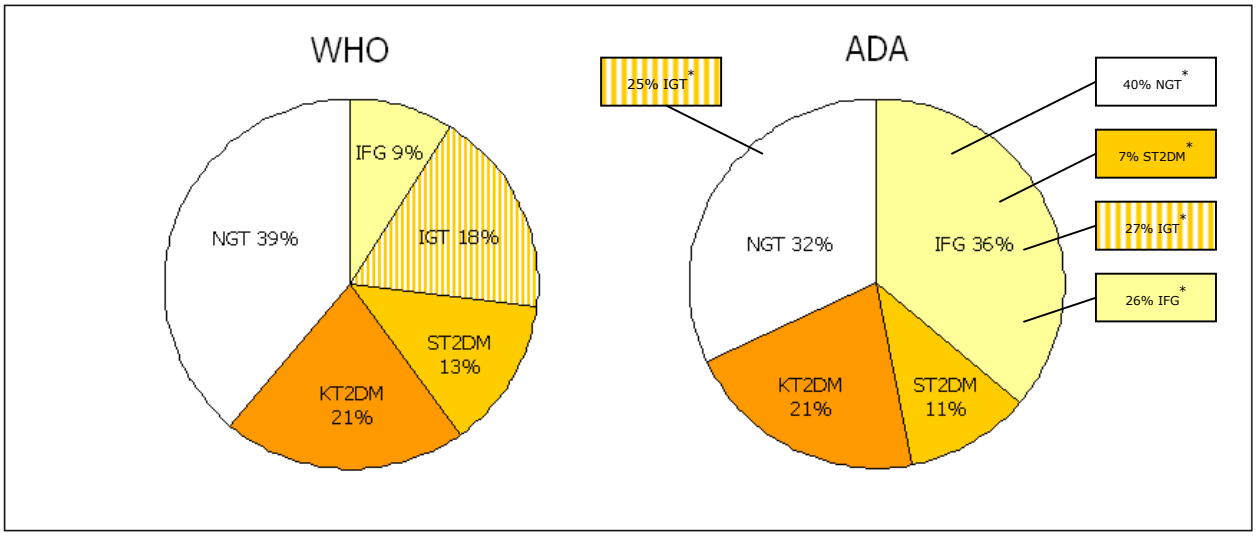

Figure 5.3. Metabolic group assignment in the DANSUK study according to the WHO definition and the ADA criteria.
*compared to the WHO definition

5.6. FPG as a screening tool

In clinical practice, IFG is much easier to diagnose than IGT so in the efforts of trying to limit the need for OGTTs, it is interesting to determine how efficient the condition of IFG is to predict IGT according to both the WHO and the ADA definitions. Table 5.3 illustrates the concordance rate between the OGTT and FPG-values in diagnosing IGM both according to the WHO definition and the ADA criteria. The majority of the patients diagnosed with NGT had a referral value of FPG below 7.0 mmol/l. Thus it is reasonable to believe that the patients in the DANSUK study were truly fasting.

		OGTT			
		NGT < 7.8 mmol/L	IGT 7.8-11.0 mmol/L	T2DM ≥ 11.1 mmol/L	Total
FPG	NGT (< 6.1/< 5.6 mmol/L)	78/49	**24/16**	0/0	102/65
	IFG (6.1-6.9/5.6-6.9 mmol/L)	19/48	12/20	**5/5**	36/73
	T2DM (≥ 7.0 mmol/L)	0/0	4/4	17/17	21/21
	Total	97/97	40/40	22/22	159

Table 5.3. Distribution and concordance of the exact number of glucometabolic abnormalities in the DANSUK study according to the diagnostic criteria defined by the WHO and the ADA (WHO/ADA). The final metabolic classification was based on the outcome of the OGTT and on ***two*** independently taken FPG values. Bolded numbers denotes the patients overlooked or misclassified if an OGTT is omitted.

The sensitivity of a screening test is the proportion of diseased individuals who test positive on the screening test. The specificity is the proportions of non-diseased individuals who test negative on a screening test. The predictive values refer to the probability of being non-diseased given a negative test (PV-) or the probability of being diseased given a positive test (PV+). The predictive values rely on the prevalence of the disease seen in the population. This is part of the rationale for targeted screening in high-risk populations. Table 5.4 shows the evaluation of test performance when using IFG in predicting T2DM or IGT. Increasing the sensitivity of a test, by lowering the cut-off for positivity, as in the latest ADA criteria, results in a classical example of diminishing test specificity. And even more important is the hereby lack of improvement of the negative predictive value, which is unchanged as well as an inappropriate decrease of the positive predictive value.

	Sensitivity	Specificity	PV-	PV+
WHO	61 (38/62)	80 (78/97)	76 (78/102)	67 (38/57)
ADA	74 (46/62)	51 (49/97)	75 (49/65)	49 (46/94)

Table 5.4. Evaluation of IFG according to the WHO definition and ADA criteria in predicting IGM (T2DM or IGT) in the DANSUK study. PV-, negative predictive value; PV+, positive predictive value. Numbers taken from table 5.3.

The classification in table 5.3 and 5.4 is based upon two consequtively taken FPG-values. Lowering the FPG-level according to the ADA criteria only improves the sensitivity by 21%, but the specificity drops by one-third and the negative predictive value remains unchanged (table 5.4). If the metabolic classification were to be based upon a single FPG-value, the classification would have another appearance (table 5.5). To simplify the process of screening in the settings of CR, another approach could have been to combine single values of FPG and HbA1c at referral also seen in table 5.5. Classifying the patients only using a single FPG-value result in an immediate overestimation of IGM. By the performance of an OGTT only in

the patients that could be classified as metabolic uncertain (FPG-values between 5.6 mmol/l to 6.9 mmol/l), more than half of the OGTTs could be omitted at the expense of 44% (16/36) of the patients with IGT being misclassified as having NGT. If the WHO definition is used in the same way, 75% of the OGTTs could have been spared overlooking 67% (24/36) of the patients with IGT.

Table 5.5. Evaluation of using IFG defined by a ***single*** FPG-value according to the WHO and the ADA criteria alone or in combination with an HbA1c-value in the proces of screening for IGM (T2DM or IGT) in the DANSUK study

Screening criteria	*Sensibility*	*Specificity*	*PV-*	*PV+*
IFG(WHO) (single FPG-value)	**41** (33/33+48)	**94** (73/73+5)	**60** (73/73+48)	**87** (33/33+5)
IFG(ADA) (single FPG-value)	**53** (43/43+38)	**63** (49/49+29)	**56** (49/49+38)	**60** (43/43+29)
IFG(WHO) + HbA1c>6.4%	**9** (7/7+74)	**99** (77/77+1)	**51** (77/77+74)	**88** (7/7+1)
IFG(ADA) + HbA1c>6.4%	**9** (7/7+74)	**95** (74/74+4)	**50** (74/74+74)	**64** (7/7+4)

Values are percentage. Absolute number of patients in brackets.
PV-, negative predictive value; PV+, positive predictive value; FPG, fasting plasma glucose

The sensitivity of all the screening proposals in table 5.5 is considered low for a high-risk population. While there is no improvement in the predictive value of a negative test (PV-), the specificity is relatively high. The sensitivity is increased by 29% when using a single FPG-value according to the ADA criteria compared to the WHO definition with no improvement in predictive values or specificity. The attribution of the HbA1c to a single FPG-value in the screening process seems useless in the DANSUK population.

5.7. Cardiovascular risk profile

The baseline cardiovascular risk profile of the patients additionally diagnosed with IFG according to the ADA criteria (FPG between 5.6 mmol/l and 6.0 mmol/l) differed significantly in insulin resistance, HbA1c and BMI which were all worse compared to the patients diagnosed with NGT (FPG<5.6 mmol/l) according to the same criteria (all $p<0.02$). The additionally diagnosed IFG patients were also less insulin resistant and had fewer signs of PAD and a better exercise capacity compared to the patients with FPG values between 6.1 mmol/l and 6.9 mmol/l (all $p<0.05$). The patients with IGT and IFG according to both the WHO and the ADA criteria were more insulin resistant, more obese and had suffered more myocardial infarctions than the patients with IGT and normal FPG values (all $p<0.03$) who again had a worse risk profile compared to the patients with NGT (all $p<0.05$). The patients with ST2DM had significantly lower HbA1c, higher plasma insulin levels, and they had suffered fewer myocardial infarctions compared to the patients with KT2DM (all $p<0.05$).

5.8. Predictors of IGT and T2DM

In a univariate analysis, nearly all the baseline variables inserted (age, gender, arterial hypertension, dyslipidemia, waist circumference, BMI>25 kg/m^2, FPG>6.9 mmol/l, HbA1c>6.4%, ABPI<0.9, hyperinsulinemia, microalbuminuria, HOMA-IR>1.76) were predictors of T2DM. Haemoglobin A1c above 6.4%, FPG above 5.5 mmol/l and waist circumference were predictive of IGT. In model 1 where the possible

mediators of glucose intolerance were allowed to enter, FPG and HbA1c stayed as the only and strongest predictors of IGT and T2DM. In model 2 where all the possible mediators were withdrawn, only arterial hypertension remained an independent predictor of IGT (OR: 2.9, 95% CI: 1.1-5.9, $p<0.05$). In model 2, age (OR: 1.1, 95% CI: 1.0-1.2, $p<0.05$), BMI above 25 kg/m^2 (OR: 1.22, 95% CI: 1.1-1.3, $p<0.0001$), arterial hypertension (OR: 2.9, 95% CI: 1.1-6.3, $p<0.01$) and low exercise capacity (OR: 0.6, 95% CI: 0.4-0.8, $p<0.0001$) emerged as strong independent predictors of T2DM. Unfortunately the collection of data on family history of diabetes was incomplete and could not be used in the analysis of variance.

5.9. Discussion

The DANSUK study has shown that the prevalence of IGM in a broad group of patients eligible for CR is high. More than 40% of the patients had a previously unrecognized glucometabolic abnormality according to the WHO definition. The prevalence of the different metabolic groups in the IHD group in the DANSUK study is in accordance with the elective group in the European Heart Survey. In the DANSUK study there were fewer patients with KT2DM and more patients with isolated IFG reflecting a less diseased population [27]. The prevalence of glucose intolerance in patients with CHF is known to be high [288-290] but this was not the case in the DANSUK study most obvious due to a small sample size since only 16 patients (8%) were stratified to the CHF group.

The proportion of ST2DM was relatively high especially in the middle-aged group and among men (figure 5.1), which coincide with the findings in the Inter99 study [61]. The high ratio between ST2DM and KT2DM in the DANSUK study was surprising when taking into account that the patients had just been discharged from a department specialized in cardiology undergoing intensive observation for CVD. On the other hand, selection bias could have occurred due to selective non-participation of individuals with long-standing KT2DM with severe co-morbidities (mean duration of KT2DM in non-participants was not registered). Most likely it reflects selective overrepresentation of overweight and obese patients in the DANSUK study. It is note worthy that the mean BMI in the patients with KT2DM was 33 kg/m^2 at baseline in the DANSUK study (table 5.1). Comparing this to the BMI values shown for the different populations in table 2.1, it is obvious that CR programmes draw the attentions from the most obese. Thus the high ratio between ST2DM and KT2DM reflects the continued screening potential for T2DM in departments of cardiology and that it should be done also in the younger patients. The crude prevalence of ST2DM in the DANSUK study is less than in other studies of patients with CVD [87,88], which is partly explained again by the heterogeneity of the DANSUK population including 30% high-risk individuals. This could also explain the relatively high concordance rate of IGT and IFG between the DANSUK study and the Inter99 population [61]. In the Inter99 study the crude prevalence of IGT among the patients in the sixties was 17.5%, and nearly 34% of the women and 50% of the men had glucose intolerance by the age of 60 [61].

Even if one-third of the patients diagnosed with NGT according to the WHO definition, had hyperinsulinaemia at baseline (table 5.2) they were in general less obese, had lower blood pressure, lower levels of VLDL-cholesterol and fewer signs of PAD. There was also a considerable difference in the

baseline exercise capacity and in the level of insulin resistance between the patients with NGT and the patients with glucose intolerance. The exercise capacity seemed inverse proportional to the insulin resistance. The patients with ST2DM and KT2DM had very high levels of insulin resistance compared to both the patients with prediabetes and the patients with NGT but at least part of this difference could be due to the use of insulin in the patients with KT2DM making the HOMA-IR less reliable in this population. The difference in cardiovascular risk profile between the patients with isolated IFG and IGT deserves some comments. Impaired glucose tolerance and IFG represent two different stages in the glucose continuum without them necessary preceeding each other or T2DM. Impaired glucose tolerance is still considered more hazardous with regard to the development of CVD and T2DM. Although the group was relatively small (N=19) the patients with isolated IFG in the DANSUK study exhibited a worse cardiovascular risk profile than the patients with IGT. These findings both disagree and coincide with the findings in different population-based studies [291,292]. The patients with isolated IFG had a more sedentary life style, they were more obese and insulin resistant and had as low exercise capacity as the patients with ST2DM and the same high prevalence of PAD. A sample of cardiovascular risk factors that make them very suitable for CR even though there is no evidens from randomized controlled trials that they benefit the same as patients with IGT. Thus in the DANSUK study, the cardiovascular risk profile associated with IFG defined by both definitions was statistically different from that associated with isolated IGT and NGT. This may justifie the use of the ADA criteria of IFG as an independent category of the glucose homeostasis although obviously not suitable as a screening tool for IGT. Many of the patients with IGT had normal FPG values and the majority were still normoglycaemic when repeating the tests (89%) emphazising the continued need of the OGTT regardless of FPG-values.

Unlike the DECODE study [62], IFG was efficient in predicting T2DM in the DANSUK study since all the patients with ST2DM were classified as IFG. No other risk factors or symptoms were conspicuous and would single them out from the rest of the patients diagnosed with IFG. Only an OGTT would finally reveil the diagnosis and would induce the patients to enter a surveillance programme for retinopathy and nephropathy much less cause referral to a patient education programme. Using HbA1c as a screening tool is questionable. The cut-off value of the used HbA1c in the DANSUK study is relatively high and caused a low sensitivity and low positive predictive value when used alone as a screening tool. Nothing was gained by ascribing HbA1c to a single FPG-value in the process of screening and metabolic classification upon a single FPG-value overestimated the prevalence of IGM in the DANSUK study.

5.10. Conclusions (DANSUK 1)

- More than 60% of the patients in the DANSUK study had impaired glucose metabolism and 38% of the patients with type 2 diabetes had screen detected type 2 diabetes.

- Omitting the oral glucose tolerance test, 19% of the patients with screen detected type 2 diabetes would have been misclassified as impaired fasting glucose.

- The prevalence of impaired glucose tolerance was high emphasizing the great potentials in preventing type 2 diabetes in the settings of cardiac rehabilitation.

- Concordance rate between the WHO and the ADA criteria was low in the DANSUK study.

- Cardiovascular risk profile in means of metabolic parameters and body mass index was worse in the patients additionally diagnosed with impaired fasting glucose according to the ADA criteria compared to the patients who remained normal glucose tolerant.

- In the DANSUK study known arterial hypertension at baseline was a predictor of impaired glucose tolerance and age, a body mass index above 25 kg/m^2, arterial hypertension and a low physical exercise capacity were independent predictors of type 2 diabetes.

- If not performed at referral to the unit of cardiac rehabilitation, an oral glucose tolerance test should be performed to establish a proper risk factor profile considering both cardiovascular and diabetic risk factors with the possibility of adjusting actions of behavioural interventions and treatment goals.

- A combined stepwise screening method using impaired fasting glucose according to the ADA criteria and HbA1c to limit the need of an oral glucose tolerance test was inefficient in classifying patients with impaired glucose tolerance.

- The prevalence of impaired glucose metabolism is overestimated in the DANSUK population if single fasting plasma glucose values are used.

Part IV: Intensive multifactorial intervention towards patients with IGM

6. Results – DANSUK 2 (Article 2, appendix 4)

6.1. Baseline characteristics of the two study groups

Of the patients included in the DANSUK study, 53 patients (52%) randomized to UC had T2DM (KT2DM=20; ST2DM=14) or IGT (19 patients) and 51 patients (52%) randomized to CR had T2DM (KT2DM= 22; ST2DM=12) or IGT (17 patients). Table 6.1 depicts the demographic and clinical characteristics upon entry into the study in the patients with IGM (T2DM or IGT).

Table 6.1. Patients characteristics of the DANSUK study (N = 104)

	Usual care (N = 53)	**Cardiac rehabilitation** (N = 51)
Demographic		
Age (years/range)	65.5 (42-89)	62.3 (43-81)
Women	36	33
Stratification		
Congestive heart disease	3 (6)	4 (8)
Ischemic Heart Disease	35 (66)	35 (69)
High-Risk patients	15 (28)	12 (23)
Previous history		
Myocardial Infarction	10 (19)	11 (22)
Revascularization	28 (53)	24 (47)
Known systemic hypertension	39 (74)	35 (69)
Known hypercholesterolemia	45 (85)	37 (73)
Clinical		
Ambulatory systolic bloodpressure (mmHg)	129.5 (21.9)	129.3 (20.3)
Ambulatory diastolic bloodpressure (mmHg)	71.1 (9.4)	74.2 (10.1)
Physical inactive (< 4 h/week)	21 (40)	28 (55)
Body mass index (kg/m^2)		
Women	31.7 (6.5)	31.8 (7.6)
Men	28.8 (3.9)	28.8 (4.6)
Waist circumference (cm)		
Women	102.4 (14.1)	101.9 (15.5)
Men	103.9 (12.7)	105.6 (11.1)
Ancle-Brachial Pressure Index < 0.9	22 (42)	11 (22)
Metabolic equivalents	5.9 (1.2)	5.9 (1.3)
Biochemical		
Total cholesterole (mmol/l)	4.60 (1.3)	4.43 (1.1)
HDL cholesterole (mmol/l)	1.25 (0.3)	1.24 (0.5)
LDL cholesterole (mmol/l)	2.56 (1.1)	2.37 (0.9)
VLDL cholesterole (mmol/l)	0.69 (0.4)	0.76 (0.3)
Triglycerides (mmol/l)	1.69 (1.2)	1.71 (0.8)
Fasting plasma glucose (mmol/l)	8.20 (2.1)	5.91 (1.1)
HbA1C (%)	7.35 (1.3)	5.95 (0.6)
Hyperinsulinemia (≥ 51 pmol/L)	26 (62)	76 (48)
Microalbuminuria (2,5-25 mg/mmol)	11 (26)	14 (9)
Cardiovascular medication		
Aspirin	29 (69)	120 (75)
ACEI/ARA	20 (47)	59 (37)
β-blockers	19 (45)	78 (62)
Statins	31 (74)	99 (62)

Mean values or exact numbers. Brackets are 1 SD or %. ACEI, angiotensin-converting Inhibitor; ARA, angiotensin receptor-II antagonist

The randomization was well balanced with no statistical difference at baseline between the two intervention groups. At baseline there was also no significant difference between the two treatment groups in the use of oral hypoglycaemic agents or insulin. Overall the population was a fairly well treated group of mostly ischemic obese patients half of them with a history of revascularization.

6.2. Main results

The main results of the multifactorial intervention on clinical, biochemical, and behavioural outcome in the CR compared to UC are shown in table 6.2 and in table 6.4. The patients with IGM in the CR group obtained a significantly greater mean change in HbA1c, FPG, insulin resistance, systolic and diastolic blood pressure compared to usual care. The exercise capacity also improved significantly in the patients with IGM.

Table 6.2. Changes at the end of the study in clinical, biochemical and behavioural variables

	Impaired glucose metabolism						**Normal glucose tolerance**	
	IGT/UC (N=18)	**IGT/CR** (N=17)	**T2DM/UC** (N=29)	**T2DM/CR** (N=32)	**IGM/UC** (N=47)	**IGM/CR** (N=49)	**UC** (N=47)	**CR** (N=44)
Clinical								
Systolic blood pressure (mmHg)*	-1.33 (24.3)	-1.68 (14.9)¥	-0.80 (15.6)	**-8.40 (15.3)†**	-0.09 (19.5)	**-6.04 (15.3)†**	0.43 (10.7)	-0.34 (14.0)¥
Diastolic blood pressure (mmHg) *	0.94 (10.7)	-1.88 (7.7)¥	-0.20 (6.7)	**-4.87 (8.7)†**	0.28 (8.5)	**-3.83 (8.4)†**	-0.70 (11.5)	0.24 (8.4)
Body mass index (kg/m^2)*	0.85 (1.6)†	0.07 (1.3)	-0.09 (1.8)	-0.18 (1.7)	0.27 (1.8)	-0.11 (1.6)	0.43 (2.0)	-0.04 (1.7)
Waist circumference (cm)*	-1.67 (7.8)	-0.17 (4.7)	-3.13 (5.2)†	-3.72 (6.9)†	-2.55 (6.3)†	-2.45 (6.5)†	-0.61 (6.2)	-3.22 (6.1)†
Weight changes (kilo pounds)*	2.5 (4.8)†	0.20 (3.5)	-0.18 (5.1)	-0.36 (4.9)	0.88 (5.1)	0.17 (4.5)	1.4 (5.8)	-0.03 (5.4)
Weight (mean in kilo pounds)**	76.6/79.2	79.1/79.3	87.4/89.2	89.6/89.6	83.5/85.3	86.1/86.0	79.7/81.0	86.3/86.1
Current smokers**	2/2	5/4	9/9	10/8	11/11	15/12	18/15	15/14
Exercise < 30 min/day**	10/10	6/3	22/17	17/11	32/27	23/14†	15/15	**25/10†**
Exercise capacity (Mets)*	-0.48 (0.6)†	**0.06 (0.8)**	0.07 (0.8)	0.31 (0.8)¥	-0.18 (0.8)	**0.21 (0.8)†**	-0.17 (1.1)	**0.39 (0.8)†**
HOMA-IR	1.52 (4.8)	0.26 (1.3)	0.62 (4.1)	-0.52 (2.9)†	0.97 (4.3)†	**-0.26 (2.5)†**	0.04 (1.1)	0.26 (1.8)
Biochemical								
HbA1C*	-0.02 (0.3)	0.01 (0.4)	-0.08 (0.7)	**-0.65 (0.9)†**	-0.06 (0.6)	**-0.42 (0.8)†**	-0.10 (0.4)	-0.14 (0.4)
Fasting plasmaglucose (mmol/l)*	0.54 (0.6)†	**0.09 (0.5)**	0.38 (2.1)	**-0.97 (2.2)†**	-0.01 (1.9)	**-0.60 (1.8)†**	-0.03 (0.7)	-0.15 (1.0)
Total cholesterol (mmol/l)*	-0.12 (0.7)	-0.26 (1.0)†	0.16 (1.0)	-0.13 (0.8)¥	0.04 (0.9)	-0.18 (0.9)	0.03 (0.8)	-0.25 (1.1)†
HDL cholesterol (mmol/l)*	0.24 (0.3)†	0.19 (0.3)†	0.19 (0.3)†	0.21 (0.2)†	0.21 (0.3)†	0.20 (0.2)†	0.16 (0.2)†	0.22 (0.2)†
LDL cholesterol (mmol/l)*	-0.44 (0.7)†	-0.62 (1.0)†	-0.08 (0.7)	-0.22 (0.7)¥	-0.24 (0.7)†	-0.37 (0.8)†	-0.21 (0.7)†	-0.47 (1.0)†
Triglycerides (mmol/l)*	0.14 (0.7)	0.28 (0.7)	0.18 (1.0)	0.03 (0.7)	0.16 (0.8)	0.12 (0.7)	0.20 (0.8)	-0.04 (0.9)

Impaired glucose metabolism (IGM) denotes type 2 diabetes (T2DM) and impaired glucose tolerance (IGT); UC, Usual care; CR, Cardiac rehabilitation
One Mets, resting metabolic rate at 3.5 ml O^2/kg/min; *Plus-minus values are means ± SD; ** at baseline and at the end of the study; bolded values denotes p<0.05 versus usual care; † p<0.05 versus baseline; ¥ p<0.06 versus baseline and usual care

In spite of the lack of standardized questionnaires concerning hypoglycaeminc events in the DANSUK study, only a few reported having experienced light to moderate symptoms of hypoglycaemia (1 patient in the CR group and 2 patients in UC group). No significant difference from usual care was obtained in total-, LDL-, HDL- cholesterol or triglycerides, BMI, waist circumference, total body weight or in the number of ex-smokers. The patients with T2DM had the greatest improvements in glycaemic parameters, blood pressure, LDL- and VLDL-cholesterol. The HbA1c decreased more than 9% during the study period compared to a decrease of little more than 1% in the usual care group (table 6.4).

Table 6.3 shows where the treatment and follow-up visits of the patients in the usual care group took place during the study. In the following the difference in the primary and secondary endpoint will be discussed in details. Data of the effect of CR in patients with IGT is very limited, so many of the comparisons to other trials will mainly concern the patients with T2DM.

Table 6.3. Follow-up during study period in the usual care group

	Diabetes care*	Cardiac care
General practitioner	56%	15%
Specialized department	44%	85%

38% of the patients had 1-2 visits at the outpatients clinic before referral to the general practitioner; Diabetes care, department of endocrinology at Bispebjerg University Hospital or Steno Diabetes Center; Cardiac care, department of cardiology at Bispebjerg University Hospital; *only patients with T2DM

6.3. Discussion

6.3.1. Intensive treatment of hyperglycaemia (primary endpoint)

The mean change of HbA1c in the patients with IGM randomized to CR was significantly greater than the mean change obtained in the UC group (table 6.2). The decline in the HbA1c was even greater in the patients with T2DM and most pronounced in the patients with KT2DM attending CR (figure 6.1).

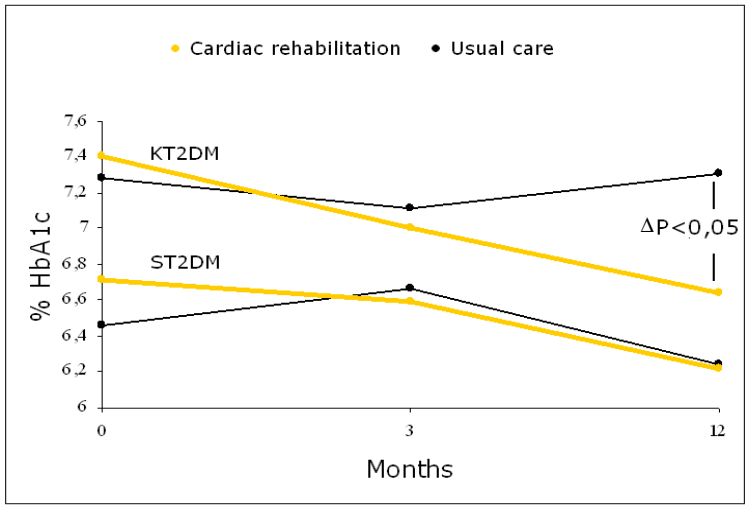

Figure 6.1. Changes over time in HbA1c in patients with KT2DM and ST2DM in both treatment groups (UC: N = 34/29; CR: N = 34/32)

The patients and the caretakers in the UC group had access to the test results and the patients in the UC group also received written information of the result of the OGTT and how to react if they had been diagnosed with glucose intolerance (the patients were advised to contact their physician). The OGTT was performed 3 months after inclusion. Hereafter the HbA1c declines in both treatment groups in the patients with ST2DM, reflecting patients and caretakers action upon the new knowledge. It is highly possible that the decline of the HbA1c in the UC group would have failed to appear, if the test result had not been accessible. In the CR group the mean HbA1c in the patients with ST2DM starts to decline before

the metabolic diagnosis was known (figure 6.1). This could reflect the 'pure' effect of comprehensive CR upon glycaemic control, although the decline was not statistically different from the change in the UC group (p=0.16). In all patients with T2DM, the mean decline of HbA1c after 3 months of follow-up in the CR group was significantly different from the UC group (p=0.02). Being an open randomised study physicians in the UC group knew that their therapy and efforts would be compared with a more intensive treatment. This could have influenzed the initial although limited decline in the HbA1c in the patients with KT2DM in the UC group. As time went by, the results from the obligatory assessments visits in the UC group stopped followed by deterioration in HbA1c (figure 6.1).

The mean decline in HbA1c of -0.65 % (9% improvement) in the patients with T2DM in the CR group after one year is comparable with the results obtained in the STENO 2 study (study duration: 7.8 years; mean HbA1c decline: -0.5%; percentage improvement: 13%) [105], the DIGAMI I (study duration: one year; mean HbA1c decline: -0.3%; percentage improvement: 4%) [156] and the DIGAMI II study (study duration: two years; mean HbA1c decline: 0.5%; percentage improvement: 7%) [161] (table 2.4). In the STENO 2 study, the greatest decline in HbA1c appeared within the first year of intensive treatment. In the following years and until the end of the study, HbA1c stabilized itself around a mean of 7.6% [105]. The relatively impressive decline in HbA1c with 0.9% (13% improvement) in the UKPDS was only maintained for a short period. During the following 9 years the HbA1c increased to a mean of 8%.

Table 6.4. Mean values of different risk factors at baseline, after 12 months of follow-up, and as percentage change of baseline values in the patients with T2DM in the two study groups

	Usual care			**Cardiac rehabilitation**		
	Baseline (N = 34)	Follow-up (N = 29)	% change from baseline	Baseline (N = 34)	Follow-up (N = 32)	% change from baseline
Clinical						
Systolic blood pressure (mmHg)	131 (21)	129 (23)	-1.4	132 (21)	125 (16)	**-5.4**†
Diastolic blood pressure (mmHg)	72 (9)	71 (11)	-0.7	75 (10)	70 (7)	**-7.3**†
Body mass index (kg/m^2)						
Women	34.8 (5.7)	36.8 (4.3)	5,6	33.4 (8.0)	32.6 (8.3)	-2.4
Men	29.4 (4.8)	29.4 (6.0)	0	29.5 (3.8)	29.7 (4.1)	0.7
Body weight (kg)						
Women	87.4 (14.8)	92.6 (12.0)	6.0	88.0 (23.2)	85.8 (23.9)	-2.5
Men	87.4 (17.5)	87.6 (21.4)	0.2	90.4 (11.1)	91.5 (12.5)	1.2
Waist circumference (cm)						
Women	110.2 (9.8)	109.1 (8.8)	-1.0†	106.3 (14.2)	101.9 (16.0)	-3.9†
Men	105.3 (12.0)	103.1 (15.4)	-2.1†	108.0 (10.6)	105.1 (10.9)	-2.7†
Exercise capacity (Mets)	5.6 (1.2)	5.6 (1.6)	0	5.7 (1.0)	5.9 (1.1)	3.5
Biochemical						
Total cholesterol (mmol/l)	4.4 (1.4)	4.5 (1.2)	2.3	4.4 (1.0)	4.3 (0.7)	-2.3
HDL cholesterol (mmol/l)	1.2 (0.3)	1.3 (0.4)	8.3†	1.2 (0.4)	1.4 (0.4)	16.7†
LDL cholesterol (mmol/l)	2.3 (1.1)	2.2 (1.0)	-4.5	2.3 (0.9)	2.1 (0.5)	-8.7
VLDL cholesterol (mmol/l)	0.7 (0.4)	0.8 (0.3)	14.3	0.8 (0.4)	0.7 (0.3)	-12.5
Triglyceride (mmol/l)	1.9 (1.3)	2.2 (1.3)	15.8	1.8 (1.0)	1.8 (1.2)	0
Fasting plasma glucose (mmol/l)	7.9 (1.6)	8.2 (2.1)	3.8	8.2 (2.2)	7.3 (1.8)	**-11.0**†
HbA1C (%)	6.95 (1.1)	6.87 (1.2)	-1.2	7.13 (1.2)	6.48 (0.8)	**-9.1**†

Brackets are 1 SD. Bolded values denotes p<0.05 versus usual care. † p<0.05 versus baseline
One Mets, resting metabolic rate at 3.5 ml O^2/kg/min

There are very limited data on the effect of CR in patients with T2DM. The few existing studies are not randomized [26,55,56] and the information of any change in glycaemic control is often not available [55,56]. In one study of comprehensive CR including both patients with T2DM and patients with NGT, the only significant improvement obtained in the diabetic population, was in exercise capacity while the HbA1c increased 3% although not significantly [25].

6.3.2. Intensive treatment of blood pressure and lipids (secondary endpoints)

Nearly 75% of the patients with IGM in the DANSUK study were registered as having arterial hypertension at baseline or as having had two measurements equal to or above 140/90 mmHg during admission (table 6.1). Looking at the 24-hour blood pressure measurement done at baseline in the patients with T2DM, 53% of the patients had a blood pressure equal to or above the intended treatment goal of 130/80 mmHg. The decline of the systolic blood pressure in the patients with IGM randomized to CR was significantly greater than the decline obtained in the usual care group (table 6.2). The decline of the systolic blood pressure was greatest in the patients with T2DM as seen in figure 6.2 and in table 6.4.

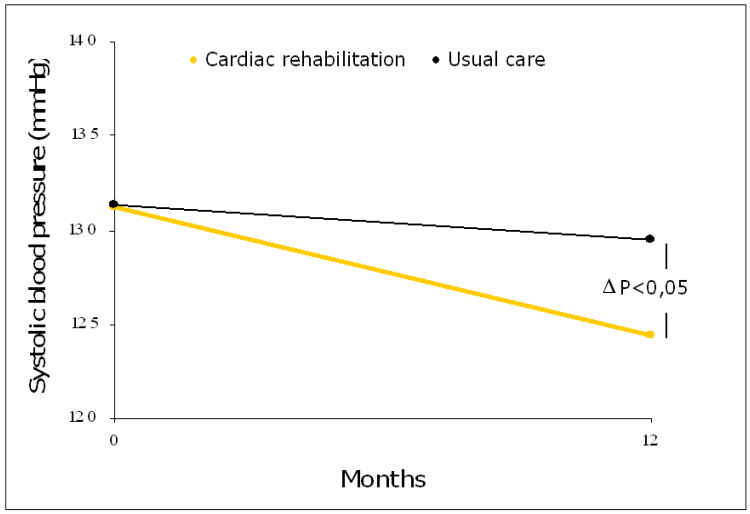

Figure 6.2. Changes over time in systolic blood pressure in patients with T2DM (K2DM + ST2DM) in both treatment groups (UC = 34/29; CR = 34/32)

A mean decline of the systolic blood pressure of 8.4 mmHg in the T2DM patients in the CR group is remarkable. The measurements were done as 24-hour measurements considered being a more valid method than means of single sphygmomanometer measurements. The decline in the diastolic blood pressure was also significantly greater in the CR group compared to the UC group (mean difference: -4.9 mmHg versus –0.2 mmHg, $p<0.05$) in the T2DM patients. Although measured in the supine position, it is difficult to compare mean blood pressure changes in the STENO 2 study to the mean changes obtained in the DANSUK study because measurements were performed with different methods. The mean change in the systolic blood pressure within the first year of the STENO 2 study in the intensively treated group was close to 8.0 mmHg. During the rest of the study period (mean 7.8 years) the systolic blood pressure kept on declining reaching a mean decline of 14.0 mmHg [105].

When comparing the follow-up blood pressure in the patients with T2DM in the DANSUK with the follow-up measurements in the studies shown in table 2.5, none of these studies obtained a mean blood pressure below 130/80 mmHg. Although the baseline values are considerable higher than in the DANSUK study, improvements of 4-8% in the systolic blood pressure resulted in a relative risk reduction in major cardiovascular events of 30-50% [202,199]. In the HOT study, small differences in follow-up blood pressures of 3-4% (144/85 mmHg vs 140/81 mmHg) in the patients with T2DM diminished the relative risk reduction for major cardiovascular events by one half [207] (table 2.5). The majority of the patients in the blood pressure-lowering trials shown in table 2.5 had no history of CVD. In the DANSUK study nearly half of the patients with T2DM had been revascularized and 15% had suffered an acute MI. Thus as they possess a higher absolute risk of cardiovascular events, a percentage improvement of 5% and 7% in systolic and diastolic blood pressure most likely is beneficial.

Although not significantly different from UC, all the lipids exept from triglyceride, showed an improvement from baseline of 2-17% with the improvement of LDL-cholesterol being nearly 9% (table 6.4). In the trials shown in table 2.6, the percentage improvement of LDL-cholesterol using statins in the treatment of dyslipidaemia in patients with T2DM, varied from 20-35% with a mean baseline LDL-cholesterol level of 3.55 mmol/l. These reductions in LDL-cholesterol induced a relative risk reduction of 20-50% in major cardiovascular events. The improvements in total-, LDL-, and HDL-cholesterol in the DANSUK study coinside with the findings in other trials investigating the effect of comprehensive CR in patients with T2DM [25,55,56] (table 6.5). In the DANSUK study, both treatment groups had already at baseline a mean value of LDL-cholesterol (2.32 mmol/l) that had reached the predefined treatment goal (<2.50 mmol/l). A further lowering of 9% was possible although the size of the population was under-powered to obtain significant differences.

6.3.3. Intensive treatment of behavioral modifications (secondary endpoints)

There was no significant change in BMI or total body weight within or between the two treatment groups in the DANSUK study. Waist circumference was significantly reduced during the study period among the patients with T2DM in both the CR and the UC group (table 6.3 and 6.4). It is remarkable that the patients in the CR group obtained an improved glycaemic control without gaining weight. But due to a small number of patients a significant improvement in BMI and total body weight compared to usual care may have been missed. Gaining weight is a common and inappropriate side effect when improving metabolic control and is often due to the increased use of hypoglycaemic drugs. In the UKPDS [168], the DCCT [171], the Kumamoto [170], and the STENO 2 study [104] the patients in the intensively treated groups gained weight. In the STENO 2 study the mean weight gain over the study period of 7.8 years was 3.7 kg in the intensively treated group compared to a mean weight gain of 0.5 kg in the control group ($p=0.001$). In the same study, the mean increase in hip circumference was 5 cm in the intensively treated group compared to a mean decline of 1 cm in the control group ($p=0.048$). Even if the intensively treated group in the Steno-2 study did not obtain a weightloss, they experienced a greater reduction in the ratio of daily intake of saturated and unsaturated fatty acids compared to the control group [104].

Although not significantly different, all 4 metabolic group assignments in the CR group in the DANSUK study maintained their weight compared to a weight increase in all 4 groups in the UC group (table 6.2). One randomized controlled trial assessing the effect of a multifaceted intervention towards patients with T2DM in primary care also succeed in a metabolic improvement without the adverse weight gain [106].

In the patients with IGM, the CR group achieved a significant improvement of exercise capacity compared to a decrease in the UC group ($p<0.05$). There was also a significant difference in HOMA-IR between the 2 treatment groups ($p<0.01$)(table 6.2). Improving exercise capacity is beneficial in many aspects especially in patients with glucose intolerance. In the settings of CR, exercise training and individual physical guidance is one of the most established and substantial forms of treatment in patients with IHD. It improves both exercise capacity and the functional well being of the patients [114,293]. It also reduces re-hospitalizations and revascularizations [294]. After 1 year, the exercise capacity in the patients with T2DM in the CR group was almost significantly different from UC ($p=0.067$). Infact, the only group of patients receiving UC, who showed a trend towards an improvement in exercise capacity, were the patients with T2DM (table 6.2). It can only be speculated why the exercise capacity in the patients with T2DM in the CR group was only improved 3.5% compared to other trials obtaining an improvement of 26-38% [25,55,56]. The comprehensive CR programmes including the exercise programme are very similar in all three non-randomized studies but compared to the DANSUK study, they had a longer period of supervised exercise training (10-12 week) and a more intensive programme of three training lesions a week of 40-50 minuts. The most obvious reason for the difference between the above mentioned studies and the DANSUK study is, that the data from the DANSUK study is after 1 year of follow-up and not immidately after the intensive exercise period. In the Extensive Lifestyle Management Intervention study (ELMI) where 20% of the patients had T2DM, there was a non-significant improvement of 1.0% in exercise capacity in the overall population compared to UC where the exercise capacity decreased 1.0% in one year [295].

Of the 15 patients with IGM in the CR group that were smoking at baseline, 3 patients (20%) stopped smoking during the study period. None of the 11 patients with IGM in the UC group stopped smoking during the same period [table 6.2.]. A lack of difference could be due to the small number of patients in the DANSUK study. A greater study has shown that having suffered an acute MI and not attending a CR programme is an independent predictor of continued smoking ($p=0.0008$) [296]. A recent meta-analysis has also shown that CR creates more ex-smokers than usual care [31]. Thus, expectations of a higher smoking cessation rate than 20% during a comprehensive CR programme may be excessive [297]. In the randomized Extensive Lifestyle Management Intervention study (ELMI) including 302 patients, no difference in the cessation rate between the UC group and CR group was found [295].

6.4. Obtaining treatment goals

In the DANSUK study, there was a trend towards a higher degree of reaching the pre-defined treatment goals among the patients with T2DM in the CR group compared to UC (figure 6.3). The percentage of

patients in the intensively treated group in the STENO 2 study who obtained the treatment goal of HbA1c below 6.5% at the end of the study was 15% [105] compared to 66% in the CR group and 45% in the UC group in the DANSUK study. The percentage of patients with T2DM obtaining the other treatment goals was all close to the results of the STENO 2 study [105]. Obtaining a BMI below 25 kg/m^2 was often more illustrative than realistic as it was never a goal by itself in the very obese. The lack of a weight loss in the patients with IGM may seem disappointing compared to the great effort that was put into the nutritional counselling. Obtaining an ideal metabolic control and healthier exercise behaviour may compensate for the lack of weight reduction. We may also argue, that the stable body weight could be due to a serious change of life style motivated by the supervised exercise training programme. This seems possible since there was no weight increase in any of the 4 metabolic groups in the CR group.

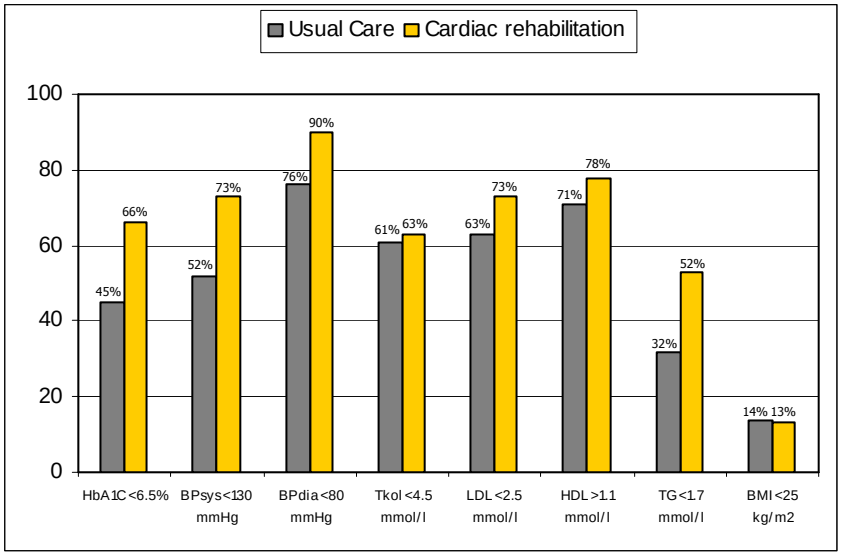

Figure 6.3. Percentage of patients with T2DM who obtained the intensive predefined treatment goals in the CR group (N = 32) and in the UC group (N = 29). No statistical difference between treatment groups was obtained.

For some reason, achieving the pre-defined treatment goals in the patients diagnosed with IGT was a more difficult task than in the patients with T2DM (figure 6.4). At baseline this group later diagnosed with IGT seemed less metabolic deteriorated being the leanest of the 4 metabolic groups (mean BMI: 27.5 kg/m^2), less glycaemic deteriorated (mean HbA1c: 5.94%; mean FPG: 5.64 mmol/l) and having nearly as high a physical exercise capacity (mean mets: 6.40) as the patients diagnosed with NGT. The mean decline in systolic blood pressure in the IGT patients in the CR group almost reached statistical significance (p=0.057). In the CR group, the mean FPG value fell during treatment and physical capacity improved in the patients with IGT compared to UC. The mean decline in systolic blood pressure almost reached statistically significance in the patients with NGT in the CR group compared to UC (p=0.054).

6.4.1. Pharmacological treatment

After 12 months of follow-up the use of ASA, statin, ACEI/ARA, Ca-channel antagonists and diuretics had increased in the patients with T2DM in the CR group. The increased use of ACEI/ARA and Ca-channel antagonists was statistically different from the UC group (figure 6.5). Only a few patients with T2DM in the CR treatment group did not take ASA or statin at the end of the study due to intolerable side effects. The use of ACEI/ARA in the UC group also increased significantly during the study period. This was

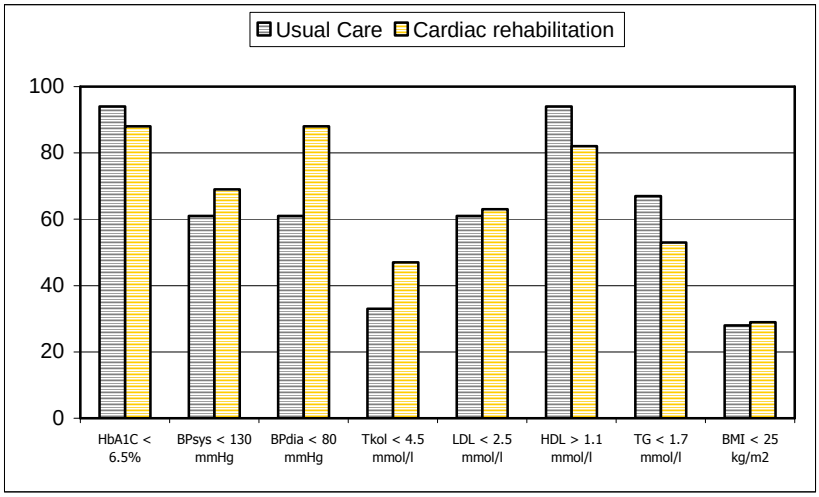

Figure 6.4. Percentage of patients with IGT who obtained the intensive pre-defined treatment goals in the CR group (N=17) and in the UC group (N=18). No statistical difference between treatment groups was obtained.

mainly among the patients who were followed in the out patient clinic at the department of cardiology. At the end of study period, 88% of the patients with T2DM in the CR group had a daily intake of 2-4 blood pressure lowering medications compared to 71% in the UC group.

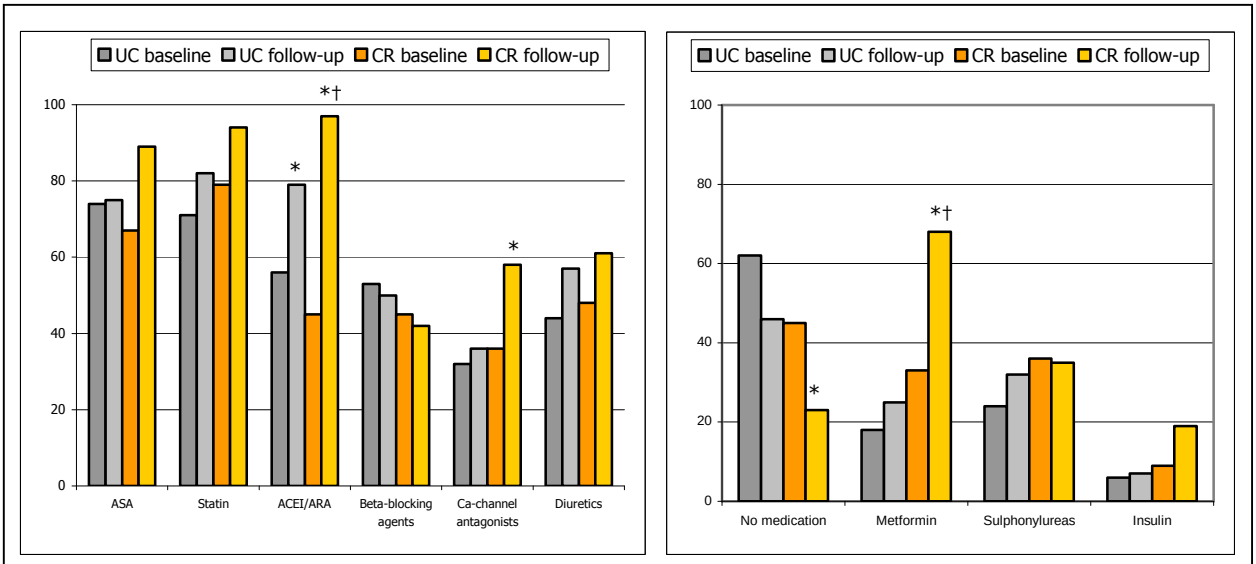

Figure 6.5. – Proportion of patients with T2DM using cardiovascular and hypoglycaemic drugs at baseline and at the end of study in the two intervention groups (CR: N = 34/32; UC: N=34/29).

* p< 0.05 versus baseline; † p< 0.05 versus usual care

Corresponding numbers for patients with IGT was 59% in the CR group and 67% in the UC group. As seen in figure 6.5, many of the patients with T2DM were already being treated with ASA, ACEI/ARA and statins at baseline and the ones who were not, were mainly high-risk patients. In many of these patients the arguments for installing such a treatment was often obvious because of arterial hypertension, microalbuminuria or dyslipidemia. Mean intake of antihypertensive drugs by the patients with T2DM at baseline and at the end of study in the 2 study groups are shown in figure 6.6.

Metformin was used to improve metabolic control in many of the patients because they were obese. It was well tolerated but because of the risk of the severe but rare lactic acidosis [298], the use of metformin was limited in the patients with CHF, although these patients seem to benefit when treated [299]. The use of ACEI/ARA, statin and ASA in the patients with IGT was not as intensive as in the patients with T2DM especially in the high-risk group. It was difficult in this group to overcome the barrier of starting a lifelong relatively expensive treatment with ACEI/ARA and statin in patients who neither were or felt themselves immediate cardiac or true metabolic diseased (figure 6.7).

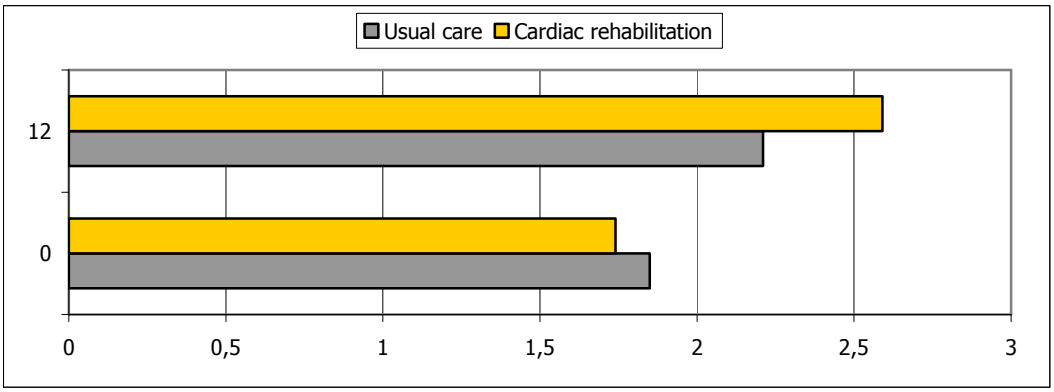

Figure 6.6. Average number of antihypertensive agents (ACEI, ARA, β-blockers, ca-channel antagonists, diuretics) taken by the patients with T2DM at baseline (0) and at the end of the study (12) in the two study groups (UC: N = 34/29; CR: N = 34/32). No statistical difference was found.

6.4.2. Adherence to polypharmacy

The patients in the DANSUK study were educated in the rationale for the prescribed polypharmacy. But it is well known that even when symptoms are present, start of new treatment may not always relieve these, and change of lifestyle can lead to improvements as well as reduction in quality of life, the latter being a potential barrier to adherence to medical therapy [300]. The successful polypharmacy obtained among the patients with T2DM in the DANSUK study were labour intensive and time consuming for the care providers. At times, it seemed difficult to comprehend that failure to achieve treatment goals could be related to inadequate self-management and often the pitfall was to intensify the pharmacological therapy to even more inconvenience for the patients. It was also very challenging to organize the therapy in high-risk symptom-less patients with multiple risk factors for CVD and newly diagnosed with T2DM. It often became a delicate balance between the threat of loosing a patient or creating a successful and self-aware patient.

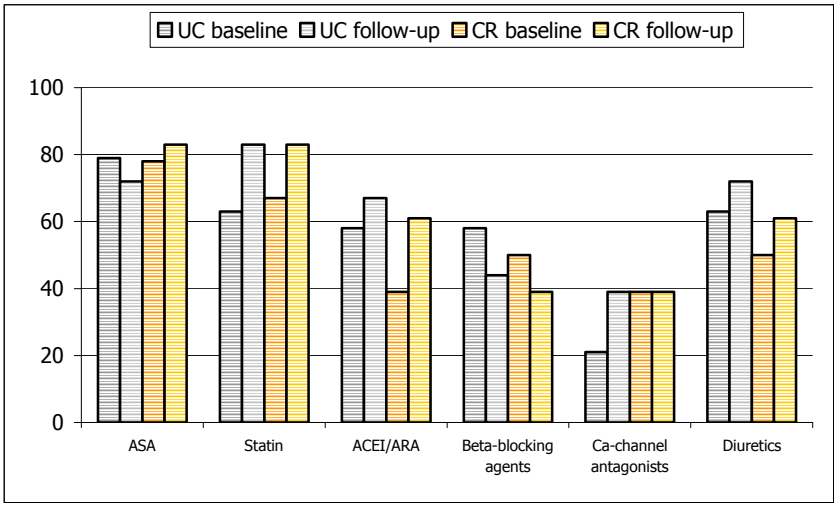

Figure 6.7. Proportion of patients with IGT using cardiovascular drugs at baseline and at the end of study. (CR: N=17; UC: N=18). No statistical difference between treatment groups was obtained.

6.5. Conclusions (DANSUK 2)

- Compared to usual care, an intensified comprehensive cardiac rehabilitation with an integrated diabetes module is more efficient in improving glycaemic and blood pressure control, exercise capacity and insulin resistance in patients diagnosed with impaired glucose metabolism.

- In patients with type 2 diabetes randomized to comprehensive cardiac rehabilitation, the value of HbA1c was brought below a level that has been shown to reduce diabetic complications.

- In patients with type 2 diabetes randomized to comprehensive cardiac rehabilitation, the blood pressure was treated to below a level that has been shown to reduce both diabetic and cardiovascular complications.

- Compared to usual care, improvement of metabolic control was obtained without weight increase and with no increase in hypoglycaemic events in the patients with type 2 diabetes randomized to cardiac rehabilitation.

7. Final comments

New knowledge from the DANSUK study

The DANSUK study has emphasized the need to identify patients with glucose intolerance in the settings of CR and target them for an aggressive program of multidisciplinary risk factor management, including exercise training. A correctly metabolic classification of these patients is important because of the possible difference in behavioural characteristics between patients with and without T2DM following major cardiovascular events. These behavioural differences may in fact contribute to the higher rate of future cardiovascular events. As in other studies, the patients with glucose intolerance had a worse cardiovascular risk profile at baseline than their metabolic normal counterparts. Thus from the beginning of the CR programme, patients with glucose intolerance have greater barriers to overcome to obtain the pre-defined treatment goals that are often more strict than the ones outlined for patients with NGT.

By showing flaws in the metabolic classification by the use of FPG values alone, the DANSUK study have emphasized the necessity of screening all high-risk cardiac patients without a history of T2DM for glucose intolerance by the performance of an OGTT.

The DANSUK study has reveiled that the patients additionally diagnosed with IFG by lowering the FPG threshold of NGT to 5.5 mmol/l did have a worse cardiovascular risk profile compared to the patients that remained normoglycaemic. Thus a new kind of glycaemic intolerant patients has evolved but whether the diagnosis will benefit them by participation in CR remains to be seen. Besides having an awareness of the IFG-condition, it is difficult to assign further initiatives than usual general risk factor management, until it is established how well IFG predict the subsequent development of T2DM and CVD. Is may be logical but is it certain that intervention that prevent the progression of IFG to T2DM (or IGT) also prevent the development of arterial hypertension and dyslipidaemia or CVD?

In accordance with the DIGAMI II and the GAMI study [161,47], the DANSUK study have shown, that acute cardiac events are common also in fairly well glycaemic regulated patients. Encouragement to follow the current intensive ADA lifestyle and hypoglycaemic treatment regimes is therefore obvious.

Although fairly well treated at referral, the majority of the patients in the DANSUK study were at higher risk for late diabetic and cardiovascular complications than the patients in the other randomized studies comparing intensive multifactorial threatment to usual care [105-111]. The DANSUK study is the first randomized controlled trial in the settings of comprehensive CR to obtain a mean HbA1c-value below 6.5% in the intensively treated group (table 6.4). The patients with T2DM in the UC group also obtained a close to acceptable mean HbA1c-value below 7.0% after 12 months of follow-up, which is far better than control groups in other studies [105,170]. The DANSUK study have shown that intensive treatment of chronic hyperglycaemia in already fairly well treated patients with T2DM is possible and can be accomplished without severe side effects.

An additional important aspect of the DANSUK study is the concept of adherence to therapy. Having suffered a cardiac event is a motivating factor itself to induce a lifestyle change. Being

offered comprehensive CR may further induce help to selfcare principals that the patients have to rely on and live by for the rest of their life.

It was possible to develop and integrate a diabetes module in the programme of comprehensive CR by a team not specialized in endocrinology and diabetes care. It was feasible to obtain a significantly improvement of glycaemic and blood pressure control that in other studies have shown to be beneficial in reducing the risk of cardiac relaps. Comparing the outcome of the DANSUK study to other trials of CR rehabilitation, it is obvious that much is gained by focusing on glycaemic control also when comparing the lipid profiles, which is often improved when the hyperglycaemia is under control (table 7.1).

Table 7.1. Effect of comprehensive CR on clinical outcome in patients with T2DM

	Main cardiac disease	No. of patients	Mean age	Male %	Mean BMI	% improvement/change							
						HbA1c	FPG	TC	HDL	LDL	TG	METs	BMI
Hindman et al.[56]	IHD	292	63	73	32	NA	**-3.7**	**-3.6**	**-2.1**	**-4.8**	-3.8	**26.3**	**-0.02**
Milani et al.[26]	IHD	70	64	73	29	3.0	-6.0	-2.0	0	-3.0	-13.0	**38.0**	-1.0
The DANSUK study	IHD	32	62	70	31	**-9.0**	**-11.0**	-2.3	4.5	-8.7	0	3.5	-1.2
Banzer et al.[55]	IHD	250	62	54	34	NA	NA	NA	NA	NA	NA	**26.0**	0

Bolded numbers denotes a significant change from baseline

METs, metabolic equivalents (1 MET=3.5 ml O2/kg/minute); NA, not available; IHD, ischemic heart disease; BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride

7.1. Study limitations and representativity

Representativity of the DANSUK population

As a randomized trial unbiased allocation of treatment was assured in the best possible way, but the nature of an open trial may have non-intended excluded those patients unwilling to consider adapting their lifestyle habits to the proposed intervention. Thus the following questions deserves some attention:

- Does the DANSUK population represent a typical group of cardiac patients eligible for CR?
- Are the two study groups altogether comparable?

Predefined in- and exclusion criteria and a low participation rate (of 47%) could question the representativeness of the DANSUK population and the data collected on the excluded patients is not entirely sufficient to answer the first question. The excluded patients had a higher degree of co-morbidities but the prevalence of known T2DM was similar in consenters as in non-consenters. Selection bias may affect the prevalence of IGM and risk factors and associations between these in both directions as illustrated in the following. Patients that were highly motivated for changing their lifestyle could have been more willing to consent. In the entire DANSUK population, 43% were overweight (BMI between 25-30 kg/m^2) and 33% were obese (BMI above 30 kg/m^2). This may reflect an overrepresentation of obese patients and therefore an expected overestimation of IGM in the DANSUK study. Many patients of other ethnic origin, known to be prone for IGM, were excluded because of linguistic problems thereby possibly causing an underestimation of the true prevalence of IGM in this hospital population. Even though the program was highly individually tailored, the rather physical demanding exercise program could have

accomplished many older and physically more disabled patients not to consent. The non-consenters also had a higher degree of co-morbidities so the patients who finally consented to the DANSUK study may have been the healthiest. When adjusting for age, no difference in participation rate was found between men and women.

Limitations of the study

Limitations to the DANSUK study are divisible into general limitations related to study design and validity and to method specific limitations. As mentioned, randomization gives raise to an optimal comparability between study groups but it also bears the limitations of creating a highly selective population because of narrow in- and exclusion criteria. Baseline data was collected before randomization. The same kind of blinding was not possible in data collection during the study period. Knowledge of the glycaemic status in the patients at the time of referral to Bispebjerg University Hospital is partly incomplete. Although access to FPG during hospital admission and at the time of referral, the performance of an OGTT at the time of referral was not possible due to logistic difficulties. The OGTT was performed 3 months after randomization and after completion of the initial comprehensive rehabilitation programme that could have influenced the outcome although there was no statistically difference in metabolic subgroup assignment between the two study groups. Measurement of insulin resistance in patients with T2DM on the basis of the homeostasis model is not satisfactory but insulin clamp studies were never an opportunity. Finally the DANSUK study did not elaborate standardized questionnaires in collecting data on hypoglycaemic events that could have caused an underestimation of light and moderate experiences.

Part V: Implications from the DANSUK study

8. Future prospects in CR of patients with IGM

With IGM being more common among cardiac patients than NGT it is an absolute necessity for cardiologists to break down professional barriers and for endocrinologists to do the same facing a threatening future epidemic of T2DM and obesity. Units of CR should only serve as the 'last line of defence' in the effort to oppose this development. Efforts should be put in solving the questions in best performance of optimal cardiovascular risk stratification for myocardial ischemia in newly diagnosed T2DM. But fortunately the intensity of the glycemic control has increased during the last decade as seen in the difference in the baseline HbA1c in the DIGAMI studies [156,161].

Questions as to what kind of specialists and critical core of knowledge is needed to manage intensified treatment of patients with IGM in future CR programmes are discussable? Given the complexity of T2DM management the ADA recommends that patients with T2DM should receive medical care from a physician-coordinated team [301]. The DANSUK study has shown that integrating a diabetes module into an ongoing trial of comprehensive CR is feasible. The patients with T2DM or IGT obtained a higher degree of improved outcome compared to the patients with NGT. As in many single risk factor trials, the patients having the highest risk of disease often obtains the greatest benefit from treatment. The DANSUK study was no exception. In patients with T2DM or IGT and CVD, the CR programme should focus on a very aggressive risk factor control and enhancement of exercise capacity. Screening the referred patients for IGM seems inevitable and the OGTT is a vital necessity in doing so. The diabetes care in the DANSUK study was performed by physicians and nurses not specialized in diabetology and anyway all the type 2 patients underwent surveillance for retinopathy, nephropathy and foot ulcers as prescribed. If it is not possible to affiliate diabetologists to the settings of CR, the education of future cardiologists should contain at least some minimal educational skills in handling these patients. Diabetologists should also, as part of their specialization, obtain knowledge in suspecting myocardial ischemia, cardiac neuropathy, and in the treatment of other cardiovascular risk factors. Diagnosing T2DM in the unit of CR does not necessary oblige for a referral to a specialist. But because of the patient also being cardiac diseased certain clinical examinations and precautions as well as adjustments may have to be taken especially before exercising (figure 8.1).

In contrary to the treatment of hypertension and dyslipidaemia, the treatment of hyperglycaemia is often a more challenging assignment for the caretaker. Because of the progressive nature of diabetes and the frequent variability of outcome measurements, it demands a more intense and continued intervention strategi and survaillance. Special considerations have to be taken in these patients because they may have more difficulties in losing weight than their metabolic normal counterpart because of metabolic differences, fear of hypoglycaemia, hypoglycaemic agents, limited physical activity, depressions and diet fatigue.

The STENO 2 study concluded that there was a limited impact of lifestyle education in patients with T2DM [104]. There are several differences between the DANSUK study and the STENO 2 study. Besides being a healthier and more homogeneous population the educational programme in the

intensively treated group was quite different in the STENO 2 study. The physical exercise was not supervised by a physiotherapist and the number of patients (incl. spouses) in the group sessions were relatively large compared to the DANSUK study.

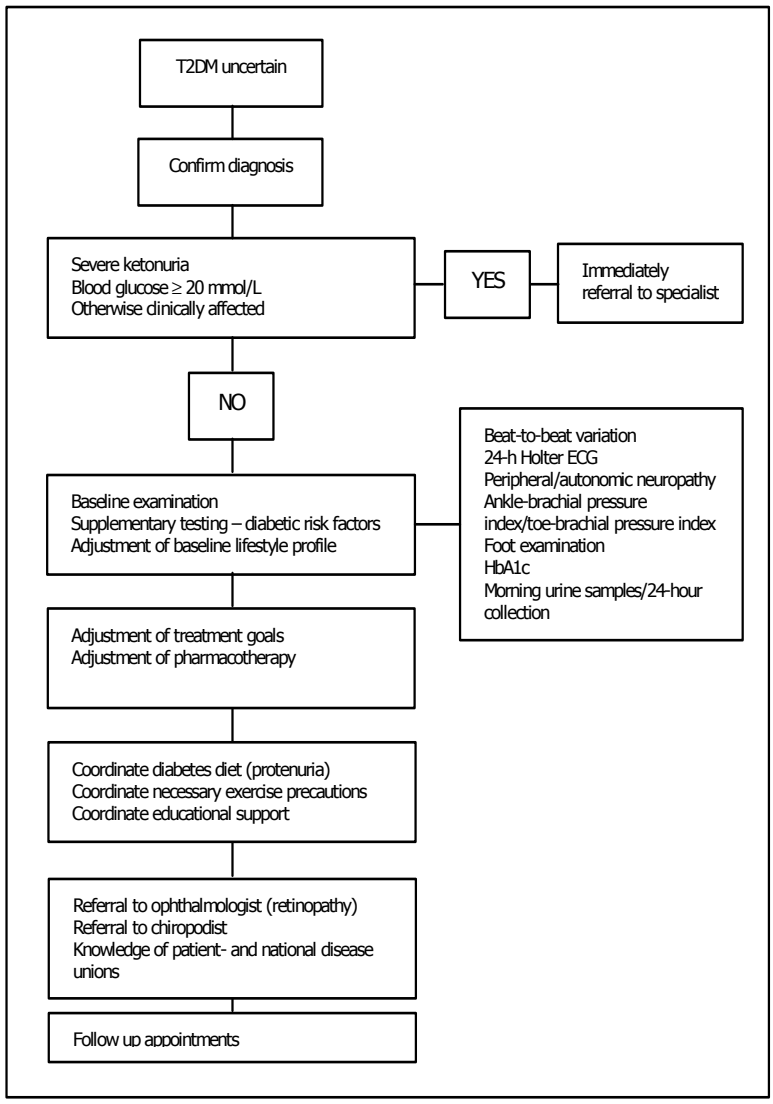

Figure 8.1. - Initial examination and treatment of ST2DM in patients referred to CR

8.1. Barriers for implementation and success

The reactions of the patients, when told that they suffer from a chronic disease, were very diversified. In some of the patients in the DANSUK study who had just survived an AMI, also being diagnosed with T2DM could be overwhelming. In other patients the diagnosis was almost neclectable compared to their cardiac disease. This was especially pronounced in patients with no symptoms of hyperglycaemia which was the majority of the patients. The patient education had to be highly adjusted to this diversity in pattern of reaction to information and this was a great challenge for the caretakers and the outcome depended of course of the characteristics of providers and provider-patient relationships. This emphasise the great challenge in chronic disease management. In the DANSUK study, 30% of the patients were stratified as HR patients. In consenting to the DANSUK study and being diagnosed with T2DM, many

types of intervention were offered and it had to be done with great caution and often over a long period. Many of these patients thought themselves to be relatively healthy and many frontiers had to be crossed from feeling healthy to become a candidate of 4-5 tablets a day. Very few of the patients with ST2DM had experienced symptoms directly related to hyperglycaemia such as polyuria, tactile disturbances, blurred vision etc. If the symptoms were present they were often neglected by the patients and considered of minor important compared to the symptoms of their cardiac disease. This was also a great challenge to the caretaker. It required great motivation to induce lifestyle changes and at the same time slowly persuade and implement 1 or 2 tablets.

8.2. Concluding remarks

The DANSUK study clearly demonstrates that the prevalence of IGM is high among patients referred to CR and that the classification disagreement between the WHO definition and the ADA criteria is considerable also in this kind of population. Without interfering with the overall comprehensive CR programme it was feasible to integrate a diabetes module, consolidate a need for focus on glucose intolerance and to create improved outcome in metabolic and blood pressure control that was superior to usual care. From the design of the DANSUK study, it is not possible to draw any conclusions to which of the treatment components were the most effective in producing the improvements that in other studies have been proven to reduce complications. But it would be headlong to conclude, that a difference in pharmacological treatment explain it all. The obtained improvements in all the metabolic groups randomized to CR may still justify the concept of nutritional guidance, a school kitchen, the supervised physical exercise training and the other core components used in the DANSUK study.

Summary

The prevalence of glucose intolerance is common among patients with acute myocardial infarction. The European Heart Survey recently revealed that having suffered an ischemic event it is more common to be glucose intolerant than having normal glucose tolerance. Whether the prevalence of impaired glucose metabolism in patients referred to cardiac rehabilitation is of the same magnitude is unclear as is the effect of comprehensive cardiac rehabilitation in patients with type 2 diabetes.

First part of the dissertation reviews randomized controlled trials in diabetes prevention, treatment of hyperglycaemia, arterial hypertension, dyslipidemia and multifactorial intenvention.

Second part describes the DANSUK study developed as a substudy to the larger DANREHAB trial that randomized 770 patients over a 3-year period to compare comprehensive cardiac rehabilitation to usual care. As part also of the DANSUK study the last 201 included patients were also metabolic classified (DANSUK 1) and the intensively treatment of patients with type 2 diabetes or impaired glucose tolerance in the cardiac rehabilitation was compared to usual care (DANSUK 2).

Third part concerns the results of DANSUK 1 where 42 patients (21%) had known type 2 diabetes and the remaining 159 patients were metabolic classified according to the outcome of an oral glucose tolerance test (OGTT) and fasting plasma glucose values. Twenty-six patients (13%) had screen-detected type 2 diabetes, 18% had impaired glucose tolerance, 9% isolated impaired fasting glucose and the remaining 39% had normal glucose tolerance. If an oral glucose tolerance test is omitted 18% of the patients with impaired glucose metabolism in the OGTT-cohorte are overlooked including 19% of the patients with screen-detected type 2 diabetes. Classification according to the American Diabetes Association criteria in the attempt to spare the oral glucose tolerance test increased the population with impaired glucose metabolism to 68% with only a minor improvement in classifying impaired glucose tolerance as impaired fasting glucose. The performance of an oral glucose tolerance test was essential in correctly classifying the patients in the DANSUK study.

The fourth part describes the results of the intensified treatment compared to usual care where the patients with type 2 diabetes or impaired glucose tolerance in the cardiac rehabilitation group obtained a significantly greater reduction in mean HbA1c, blood pressure as well as an improvement of exercise capacity and insulin resistance after 12 months of follow-up. The patients with type 2 diabetes obtained a mean decline of HbA1c at 0.64% without weight increase and a mean decline in blood pressure at 8.4/4.9 mmHg. Both improvements were significantly different from the changes obtained in the usual care group. Until now the DANSUK study is the only study in the settings of comprehensive cardiac rehabilitation to obtain a mean HbA1c below 6.5% in the intensively treated group. As the prevalence of T2DM is increasing in Denmark, future comprehensive CR programmes must adopt a holistic approach to chronic disease management.

Resumé

Forekomsten af glukose intolerance er høj blandt patienter med hjerteinfarkt. En større europæisk prævalensundersøgelse har nyligt dokumenteret, at glukose intolerance blandt infarktpatienter er mere almindeligt end normal glukose tolerance. Hyppigheden af glukose intolerance blandt patienter henvist til hjerterehabilitering er dårligt belyst i litteraturen ligesom der er begrænset viden om effekten af intensiv hjerterehabilitering hos patienter med type 2 diabetes endsige nedsat glukose tolerance.

Første del af afhandlingen beskriver udfaldet af forskellige diabetesforbyggende randomiserede studier og giver en summarisk beskrivelse af studier over forekomsten af glukose intolerance blandt patienter med hjerteinfarkt. Den videnskabelige dokumentation for intensiv behandling af dyslipidæmi og arteriel hypertension hos patienter med type 2 diabetes gennemgås. Oversigten redegører desuden for evidensen for at aggressiv hypoglykæmisk behandling har betydning for forløbet af makrovaskulær sygdom.

Anden del af afhandlingen beskriver DANSUK studiet. Undersøgelsen var designet som et substudium til det store hjerterehabiliteringsprojekt DANREHAB på Bispebjergs Universitets Hospital, hvor 770 patienter med iskæmisk hjertesygdom eller risiko herfor over en treårig periode blev inkluderet og randomiseret til henholdsvis intensiv hjerterehabilitering eller til sædvanlig efterbehandling (kontrolgruppen). De sidste 201 randomiserede patienter indgik i DANSUK studiet, der havde til formål at belyse 1) Graden af glukose intolerance blandt hjertepatienter og patienter i risiko for hjertesygdom som var egnet til hjerterehabilitering (DANSUK 1) og 2) at vurdere effekten af en intensiveret hjerterehabilitering af patienter med type 2 diabetes eller nedsat glukose tolerance sammenlignet med sædvanlige efterbehandling. Opfølgning af kontrolgruppen foregik efter vanlige retningslinier i speciallæge ambulatorium eller i almen praksis (DANSUK 2).

Tredje del af afhandlingen beskriver prævalensdelen af DANSUK studiet, hvor alle patienter uden kendt type 2 diabetes blev inviteret til en oral glukose belastningstest 3 måneder efter inklusionen. To og fyrre patienter (21%) havde kendt type 2 diabetes og de resterende 159 patienter blev på basis af en oral glukose belastningstest (OGTT) og faste plasma glukose-værdier inddelt i yderligere 4 metaboliske grupper efter WHOs definition som nydiagnosticeret type 2 diabetes, nedsat glukose tolerance, isoleret faste hyperglykæmi eller normal glukose tolerance. Seks og tyve (13%) havde nydiagnosticeret type 2 diabetes, 36 patienter (18%) havde nedsat glukose tolerance, 19 patienter (9%) havde isoleret faste hyperglykæmi og 78 patienter (39%) havde normal glukose tolerance. Hvis man helt undlod at udføre en oral glukose belastningstest, ville 18% af patienterne i OGTT-kohorten med glukose intolerance efter WHO definitionen overses eller misklassificeres heriblandt 19% af patienterne med nydiagnosticeret type 2 diabetes. Patienterne blev reklassificeret i henhold til ADA kriterierne. Disse kriterier er nyligt anvendt for at simplificere diagnosticeringen af patienter med nedsat glukose tolerance med minimal brug af oral glukosebelastning. Anvendelsen af denne klassifikation af patienterne medførte en forøgelse af popula-tionen af glukose intolerante til 68% med en kun beskeden forbedret klassificering af nedsat glukose tolerante som havende faste hyperglykæmi. En helt ny gruppe patienter med isoleret faste hyperglykæmi, som efter WHO definitionen tidligere havde haft normal glukose tolerance, blev

introduceret. For korrekt diagnostik af type 2 diabetes og nedsat glukose tolerance i DANSUK populationen krævedes således udførelsen af en oral glukose belastningstest.

Fjerde del af afhandlingen beskriver interventionsdelen af DANSUK studiet. Patienter randomiseret til intensiv hjerterehabilitering med type 2 diabetes eller nedsat glukose tolerans blev over 12 måneder tilbudt intensiv hjerterehabilitering med et integreret diabetes modul. Diabetesmodulet bestod af såvel gruppeundervisning som individuel opfølgning sideløbende med det etablerede intensive rehabiliteringsprogram. Efter 12 måneder havde patienterne med glukose intolerance opnået en signifikant bedre glykæmisk og blodtryksmæssig kontrol ligesom de havde forbedret deres fysiske kapacitet og mindsket deres insulinresistens i højere grad end de glukose intolerante patienter, der havde modtaget sædvanlig efterbehandling. Patienterne med type 2 diabetes randomiseret til hjerterehabiliteringsenheden havde et gennemsnitligt fald i det systoliske og diastoliske blodtryk på henholdsvis 8.4 mmHg og 4.9 mmHg, hvilket var signifikant større end kontrolgruppen ($p<0.05$). Det gennemsnitlige fald i HbA1c var 0.65% hvilket ligeledes var signifikant forskelligt fra den sædvanlige efterbehandling ($p<0.05$) og 66% af patienter med type 2 diabetes i den intensivt behandlede gruppe opnåede en HbA1c på mindre end 6.5% efter 1 år. Resultaterne fra DANSUK studiet giver overvejelser omkring nødvendigheden af at implementere og integrere et diabetes modul i fremtidens hjerterehabiliteringskoncept.

References:

1. The World Health Organization. Diabetes: the cost of diabetes. http://www.who.int/mediacentre/factsheets/fs236/en/, accessed 2005.12.31).

2. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414-1431.

3. Boyle JP, Honeycutt AA, Narayan KM, et al. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. Diabetes Care 2001;24:1936-1940.

4. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002;288:1723-1727.

5. Crespo CJ, Keteyian SJ, Heath GW, et al. Leisure-time physical activity among US adults. Results of the Third National Health and nutrition Examination Survey. Arch Intern Med 1996;156:93-98.

6. Stern MP. Glycaemia and cardiovascular risk. Diabet Care 1997;1501-1502.

7. Unwin N, Shaw J, Zimmet P, et al. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabet Med 2002;19:708-723.

8. Zimmet P. Globalization, coca-colonization and the chronic disease epidemic: can the Doomsday scenario be averted? J Intern Med 2000;247:301-310.

9. International Diabetes Federation. Position statement: diabetes and cardiovascular disease 2005. Available at www.idf.org/home/index.cfm?node=1075.

10. Stampler J, Vaccaro O, Neaton JD, et al for the Multiple Risk Factor Intervention Trial Research Group. Diabetes, other risk factors and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434-44.

11. Kannell WB. Lipids, diabetes, and coronary heart disease: insight from the Framingham Study. Am Heart J 1985;110:1100-1107.

12. Miettinen H, Lehto S, Salomaa V, et al. Impact of diabetes on mortality after the first myocardial infarction: the FINMONICA Myocardial Infarction register Study Group. Diabetes Care 1998;21:69-75.

13. Lundberg V, Stegmayr B, Asplund K, et al. Diabetes as a risk factor for myocardial infarction: population and gender perspectives. J Intern Med 1997;241:485-492.

14. Hu FB, Stampfer MU, Solomon CG, et al. The impact of diabetes mellitus on mortality on all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med 2001;161:1717-1723.

15. Liao Y, Cooper RS, Ghali JK, et al. Sex differences in the impact of coexistent diabetes on survival in patients with coronary heart disease. Diabetes Care 1993; 16:708-713.

16. Steinberg HO, Paradisi G, Cronin J, et al. Type II diabetes abrogates sex difference in endothelial function in premenopausal women. Circulation 2000;101:2040-2046.

17. Stein B, Weintraub WS, Gebhart SSP, et al. Influence of diabetes mellitus on early and late outcome after percoutaneus transluminal coronary angioplasty. Circulation 1995; 91:979-89.

18. Kuntz RE. Importance of considering atherosclerosis progression when choosing a coronary revasculari-zation strategy. The diabetes-percoutaneus transluminal coronary angioplasty dilemma. Circulation 1999;99:847-851.

19. Herlitz J, Karlson BW, Wognsen GB, et al. Mortality and morbidity in diabetic and non-diabetic patients during a 2-year period after coronary artery bypass grafting. Diabetes Care 1996;19:698-703.

20. Barness GW, Peterson ED, Ohman EM, et al. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. Circulation 1997;96:2551-2556.

21. Herlitz J, Dellborg M, Karlson BW, et al. Prognosis after acute myocardial infarction continues to improve in the reperfusion era in the community of Goteborg. Am Heart J 2002;144:89-94.

22. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. N Engl J Med 2001;345:892-902.

23. World Health Organization Expert Committee. Rehabilitation after cardiovascular disease, with special emphasis on developing countries. WHO, Geneva, 1993.

24. Cardiac rehabilitation programs: a statement for health care professionals from the American Heart Association. Circulation. 1994;90:1602-1610.

25. Lear SA, Ignaszewski A, Linden W, et al. A randomized controlled trial of an extensive lifestyle management intervention (ELMI) following cardiac rehabilitation: study design and baseline data. Curr Control Trials Cardiovasc Med 2002;3:9-23.

26. Milani R V, Lavie C J. Behavioral differences and effects of cardiac rehabilitation in diabetic patients following cardiac events. Am J Med 1996;100:517-523.

27. Bartnik M, Rydén L, Ferrari R, et al for the Euro Heart Survey Investigators. The prevalence of abnormal glucose regulation in the patients with coronary artery disease across Europe. The Euro heart Survey on diabetes and the heart. Euro Heart J 2004;25:1880-1890.

28. Pyörälä K, Lehto S, De Bacquer D for the EUROASPIRE I Group, EUROASPIRE II Group. Risk factor management in diabetic and non-diabetic patients with coronary heart disease. Findings from the EUROASPIRE I and II surveys. Diabetologia 2004;47:1257-1265.

29. Brandi JW, Jacobsen SJ, Weston SA, et al. Cardiac rehabilitation after myocardial infarction in the community. Am Coll Cardiol 2004;44:988-996.

30. Oldrigde NB, Guyatt GH, Fischer ME, et al. Cardiac rehabilitation after myocardial infarction: combined experience of randomized controlled trials. JAMA 1988;260:945-950.

31. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med 2004;116:682-692.

32. O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation 1989;80:234-244.

33. Yu C-M, Lau C-P, Cheung BM-Y, et al. Clinical predictors of morbidity and mortality in patients with myocardial infarction or revascularization who underwent cardiac rehabilitation, and importance of diabetes mellitus and exercise capacity. Am J Cardiol 2000;85:344-349.

34. Norhammar A, Malmberg K, Rydén L, et al for the register of Information and knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). Under utilisation of evidence-based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction. Eu Heart J 2003;24:838-844.

35. Suresh V, Harrison RA, Houghton P, et al. Standard cardiac rehabilitation is less effective for diabetics. Int J Clin Pract 2001;55(7):445-448.

36. Massing MW, Sueta CA, Chowdhury M, et al. Lipid management among coronary artery disease patients with diabetes mellitus or advanced age. Am J Cardiol. 2001;87:646-649.

37. George PB, Tobin KJ, Corpus RA, et al. Treatment of cardiac risk factors in diabetic patients: how well do we follow the guidelines? Am Heart J. 2001;142:857-863.

38. Merz CN, Buse JB, Tuncer D, et al. Physician attitudes and practices and patients awareness of the cardiovascular complications of diabetes. J Am Coll Cardiol 2002;40:1877-1881.

39. Coutinho M, Gerstein HC, Wang Y, et al. The relationship between glucose and incident cardiovascular events: a metaregression analysis of publiched data from 20 studies of 95.783 individuals followed for 12.4 years. Diabetes Care 1999;22:233-240.

40. Eschwêge E, Richard JL, Thibult N, et al. Coronary heart disease mortality in relation with diabetes, blood glucose and plasma insulin levels: the Paris Prospective Study, ten years later. Horm Metab res 1985;15(suppl):41-46.

41. Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in US. Diabetes Care 2001;24:447-453.

42. Spijkerman AM, Dekker JM, Nijpels G, et al. Impact of diabetes duration and cardiovascular risk factors on mortality in type 2 patients: the Hoorn Study. Eur J Clin Invest 2002;32:924-930.

43. Cruikshank N. Coronary thrombosis and myocardial infarction, with glucosuria. BMJ 1931;1:618-619.

44. Yudkin JS, Oswald GA. Hyperglycemia, diabetes and myocardial infarction. Diabetes Med 1987;4;13-18.

45. Department of Health and Human service. Centers for Disease Control and Prevention. Receipt of cardiac rehabilitation services among heart attack survivors --- 19 States and the District of Columbia, MMWR Morb Mortality Wkly 2003;52(44):1072-1075.

46. Farrer M, Fulcher G, Albers CJ, et al. Patients undergoing coronary artery bypass graft surgery are at high risk of impaired glucose tolerance and diabetes mellitus during the first postoperative year. Metabolism 1995;44(8):1016-1027.

47. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet 2002;359:2140-2144.

48. Conaway DG, O'Keefe JH, Reid KJ, et al. Frequency of undiagnosed diabetes mellitus in patients with acute coronary syndrome. Am J Cardiol 2005;96:363-365.

49. Fujiwara R, Kutsumi Y, Hayashi T, et al. Relation of angiographically defined coronary artery disease and plasma concentrations of insulin, lipid, and apolipoprotein in normolipidemic subjects with varying degrees og glucose tolerance. Am J Cardiol 1995;75:122-126.

50. Seibaek M, Sloth C, Vallebo L, et al. Glucose tolerance status and severity of coronary artery disease in men referred to coronary arteriography. Am Heart J 1997;133:622-629.

51. Natali A, Vichi S, Landi P, et al. Coronary atherosclerosis in type II diabetes: angiographic findings and clinical outcome. Diabetologia 2000;43:632-641.

52. Kowalska I, Prokop J, Bachórzewska-Gajewska H, et al. Disturbances of glucose metabolism in men referred for coronary arteriography. Diabetes Care 2001;24:897-901.

53. Taubert G, Winkelmann BR, Schleiffer T, et al. Prevalence, predictors, and consequences of unrecognized diabetes mellitus in 3266 patients scheduled for coronary angiography. Am Heart J 2003;145:285-291.

54. Wascher TC, Sourij H, Roth M, et al. Prevalence of pathological glucose metabolism in patients undergoing elective coronary angiography. Atherosclerosis 2004;176:419-421

55. Banzer JA, Maguire TE, Kennedy CM, et al. Results of cardiac rehabilitation in patients with diabetes mellitus. Am J Cardiol 2004;93:81-84.

56. Hindman L, Falko JM, Lalonde M, et al. Clinical profile and outcomes of diabetic and nondiabetic patients in cardiac rehabilitation. Am Heart J 2005;150:1046-1051.

57. Sasaki M, Saito T, Kubo N, et al. Alteration in risk factor accumulations of acute myocardial infarction during the last one decade: Analysis of patients admitted in Coronary Care Unit. Diabetes Res Clin Pract 2006;71(3):339-344.

58. Malmberg K, Rydén L. Myocardial infarction in patients with diabetes mellitus. Eur Heart J 1988;9:259-264.

59. Lomuscio A, Castagnone M, Vergani D, et al. Clinical correlation between diabetic and non-diabetic patients with myocardial infarction. Acta Cardiologica 1991;46:543-554.

60. Drivsholm T, Ibsen H, Schroll M, et al. Increasing prevalence of diabetes mellitus and impaired glucose tolerance among 60-year old Danes. Diabet Med 2001;18:126-132.

61. Glümer C, Jørgensesn T, Borch-Johnsen K. Prevalences of diabetes and impaired glucose regulation in a Danish population. The Inter99 study. Diabetes Care 2003; 26:2335-2340.

62. The DECODE study group on behalf of the European Diabetes Epidemiology Group. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. BMJ 1998;317:371-375.

63. Jarret RJ, McCartney P, Keen H. The Bedford Study: ten years mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycemic controls and risk indices for coronary heart disease in borderline diabetics. Diabetologia 1982;22(2):79-84.

64. Tominaga M, Eguchi H, Manaka H, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Funagata Diabetes Study. Diabetes Care 1999;22:920-924.

65. Hu FB, Stampfer MJ, Haffner SM, et al. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. Diabetes Care 2002;285:2486-2497.

66. Edelstein SL, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes 1997;4:701-710.

67. de Vegt F, Dekker JM, Jager A, et al. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. JAMA 2001;16:2109-2113.

68. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537-544.

69. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Programme Research Group. Reduction in the incidencee of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.

70. Tuomilehto J, Lindström J, Eriksson JG, et al. Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifesstyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-1350.

71. Boule NG, Haddad E, Kenny GP, et al. Effects of exercise on glycemic control and body mass index in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 2001;286:1218-1227.

72. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. Med Sci Sports Exerc 2001;33:754-761.

73. Lee IM, Skerrett PJ. Physical activity and all-cause mortality: what is the dose-response relation? Med Sci Sports Exerc 2001;33:S459-S471.

74. Tanasescu M, Leitzmann MF, Rimm EB, et al. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation 2003;107:2435-2439.

75. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 2002;51:2796-2803.

76. Chaisson JL, Josse RG, Gomis R, et al. Arcobase for prevention of type 2 diabetes: the STOP-NIDDM rando-mized trial. Lancet 2002;359:2072-2077.

77. Torgerson JS, Hauptman J, Boldrin MN, et al. XENical in the prevention of diabetes in obese subjects (XEN-DOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese. Diabetes Care 2004;27:155-161.

78. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur J Cardiovasc Pre Rehabil 2003;10(Suppl 1):S1-81.

79. Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modelling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland and the United Kingdom. Clin Ther 2004;26(2):304-321.

80. Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. JAMA 2001;286:1882-1885.

81. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium blocker vs diuretics: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial (ALLHAT). JAMA 2002;288:2981-2997.

82. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002;359:995-1003.

83. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence or a protective treatment effect in the Weat of Scotland Coronary Prevention study. Circulation 2001;103:357-362.

84. The Expert committee on the Diagnosis and Classification of diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 20:1183-1197, 1997.

85. Alberti KG, Zimmet PZ. Definitions, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15:539-553, 1998.

86. American Diabetes Association: Clinical practice recommendations 2005. Diabetes Care 2005;28 suppl. 1.

87. Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study group on behalf of the Diabetes Epidemiology Group. Glucose tolerance and mortality: comparisons of WHO and American Diabetes Association diagnostic criteria. Lancet 1999;354;617-621.

88. Meigs JB, Nathan DM, D'Agostino RB Sr, et al. Fasting and post-challenge glycaemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care 2002; 25:1845-1850.

89. W, Yano K. Impaired glucose tolerance, diabetes, and cardiovascular disease risk factor profiles in the elderly: the Honolulu Heart Program. Diabetes Care 1996;19:587-590.

90. McPhillips JB, Barrett-Connor E, Wingard DL. Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a community of older adults. Am J Epidemiol 1990;131:443-453.

91. Stratton IM, Adler AI, Neil HA, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-412.

92. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulphonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005-2012.

93. Wei M, Gaskill SP, Haffner SM, et al. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. Diabetes Care 1998; 21 (7):1167-1172.

94. Laakso M. Hyperglycemia and cardiovascular disease in diabetes. Diabetes 1999;48:937-942.

95. Khaw K-T, Wareham N, Bingham S, et al. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European Prospective Investigation into Cancer in Norfolk. Ann Intern Med 2004;141:413-420.

96. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141: 421-431.

97. Khaw K-T, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). BMJ 2001;322:15-18.

98. Assmann G, Carmena R, Cullen P, et al for the International Task Force for the Prevention of Coronary Heart Disease. Coronary heart disease: reducing the risk. A worldwide view. Circulation 1999;100:1930-1938.

99. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-234.

100. Executive Summary of The third report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult treatment Panel III). JAMA 2001;285:2486-2497.

101. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) registry. Circulation 2000;102:1014-1019.

102. Evans JMM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had a myocardial infarction: cross sectional and cohort studies. BMJ 2002;324:939-942.

103. Gæde P, Vedel P, Parving HH, et al. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno 2 randomised study. Lancet 1999;353:617-622.

104. Gæde P, Beck M, Vedel P, et al. Limited impact of lifestyle education in patients with type 2 diabetes mellitus and microalbuminuria: results from a randomized intervention study. Diabet Med 2001;18:104-108.

105. Gæde P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-393.

106. Olivarius N de Fine, Beck-Nielsen H, Andreasen HA, et al. Randomised controlled trial of structured personal care of type 2 diabetes mellitus. BMJ 2001;323:1-9.

107. Hanefeld M, Fischer S, Schmechel H, et al. Diabetes Intervention Study. Multiintervention trial in newly diagnosed NIDDM. Diabet Care 1991;14:308-317.

108. Ménard J, Payette H, Baillargeon J-P, et al. Efficacy of intensive multitherapy for patients with type 2 diabetes mellitus: a randomized controlled trial. Can Med Assoc J 2005;173(12):1457-1466……

109. Rachmani R, Slavachevski I, Berla M, et al. Teaching and motivationg patients to control their risk factors retards progression of cardiovascular as well as microvascular sequelae of type 2 diabetes mellitus – a randomized prospective 8 years follow-up study. Diabetic Medicine 2005;22:410-414.

110. Joss N, Ferguson C, Brown C, et al. Intensified treatment of patients with type 2 diabetes mellitus and overt nephropathy. QJMed 2004;97:219-227.

111. Tranche S, Galgo A, Mundet X, et al on behalf of Karen AP Study Investigators. Cardiovascular risk factors in type 2 diabetic patients: multifactorial intervention in primary care. Kidney Int Suppl 2005;S55-S62.

112. Turner RC, Mills H, Neil HAW, et al for the United Kingdom Prospective Diabetes Study Group. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23). BMJ 1998;316:823-828.

113. Nawaz H, Katz DL. American College of Preventive Medicine Practice policy statement: weight management counselling of overweight adults. Am J Prev Med 2001;21:73-78.

114. Hu FB, Willett WC, Optimal diets for prevention of coronary heart disease. JAMA 2002;288:2569-2578.

115. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99:779-785.

116. Franz MJ, Bantle JP, Beebe CA, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care 2002;25:148-198.

117. [Cardiac Rehabilitation at hospitals]. Copenhagen, National Network of Health Promoting Hospitals in Denmark, Danish Society of Cardiology and Danish Heart Foundation; 2004. (www.forebyggendesygehuse.dk/pdf/hjerterehabilitering%20Final.pdf, accesses February 2006).

118. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. UKPDS Group. Metabolism 1990;39:905-912.

119. Howard BV, Abbott WG, Swinburn BA. Evaluation of metabolic effects of substitution of complex carbohydrates for saturated fat in individuals with obesity and NIDDM. Diabet Care 1991;14:786-795.

120. Grundy SM, Balady GJ, Criqui MH et al. When to start cholesterol-lowering therapy in patients with coronary heart disease. A statement for healthcare professionals from the American Heart Association Task Force on Risk Reduction. Circulation 1997;95:1683-1685.

121. Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. Am J Clin Nutr 1997;65:643S-651S.

122. Howard G, Wagenknecht LE, Burke GL, et al. Cigarette smoking and progression of atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. JAMA 1998;279:119-124.

123. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. Diabet Care 1999;22:1887-1898……

124. Al Delaimy WK, Willett WC, Manson JE, et al. Smoking and mortality among women with type 2 diabetes: The Nurses' Health Study cohort. Diabet Care 2001;24:2043-2048.

125. Chaturvedi N, Stevens L, Fuller JH. Which features of smoking determine mortality risk in former cigarette smokers with diabetes? The World Health Organization Multinational Study Group. Diabet Care 1997;20:1266-1272.

126. Rigotti Na, Monafo MR, Murphy MF, et al. Interventions for smoking cessation in hospitalised patients. Cochrane Database Syst Rev 2003; CD001837.

127. Hajek P,Taylor TZ, Mills P. Brief intervention during hospital admission to help patients to give up smoking after myocardial infarction and by pass surgery: randomized controlled trial. BMJ 2002;324:87-89.

128. American Diabetes Association. Diabetes mellitus and exercise. Diabetes care 2002;25(suppl 1):S64-S68.

129. Castaneda C, Layne JE, Munoz-Orians L, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care 2002;25:2335-2341.

130. McAuley KA, Williams SM, Mann JI, et al. Intensive lifestyle changes are necessary to improve insulin sensitivity: A randomized controlled trial. Diabetes Care 2002;25:445-452.

131. Brandenburg SL, Reusch JE, Bauer TA, et al. Efforts of exercise training on oxygen uptake kinetic responces in women with type 2 diabetes. Diabetes Care 1999;22:1640-1646.

132. Wannamethee SG, Shaper AG, Walker M. Physical activity and mortality in older men with diagnosed coronary heart disease. Circulation 2000;102:1358-1363.

133. Diabetes. Special considerations. In Guidelines for cardiac rehabilitation and secondary prevention programmes. AACVPR. American Association of cardiovascular and pulmonary rehabilitatin 2004,165-169.

134. Anderson JW, Kendell CWC, Jenkins DJA. Importance of weight management in type 2 diabetes: Review with meta-analysis of clinical studies. J Am Coll Nutri 2003;22:331-339.

135. Anderson JW, Konz EC. Obesity and disease management: Effects of weight loss on co-morbid conditions. Obes Res 2001;9:326S-334S.

136. Maggio C, Pi-Sunyer F. The prevention and treatment of obesity. Application to type 2 diabetes. Diabetes Care 1997;20:1744-1766.

137. Henry R, Gumbiner B. Benefits and limitations of very-low-calorie diet therapy in obese NIDDM. Diabetes Care 1991;14:802-823.

138. Sjöström CD, Lissner L, Wedel H, et al. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS intervention study. Obes Res 1999;7:477-484.

139. UK Prospective Diabetes Study 7. Response of fasting plasma glucoseto diet therapy in newly presenting type II diabetic patients. UKPDS Group. Metabolism 1990;39:905-912.

140. Nelson KM, Reiber G, Boyko EJ. Diet and exercise among adults with type 2 diabetes: findings from the third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care 2002;25:1722-1728.

141. Gavard JA, Lustman PJ, Clouse RE. Prevalence of depression in adults with diabetes: an epidemiological evaluation. Diabetes Care 1993;16:1167-1178.

142. Lavie CJ, Milani RV. Effects of cardiac rehabilitation programs on exercise capacity, coronary risk factors, behavioural characteristics, and quality of life in a large elderly cohort. Am J Cardiol 1995;76:177-179.

143. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function and costs. Arch Intern Med 2000;160:3278-3285.

144. Sodi-Pallares D, Testelli MR, Fishleder BL, et al. Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. A preliminary clinical report. Am J Cardiol 1962;9:166-181.

145. Opie LH. The glucose hypothesis: its relation to acute myocardial ischemia. J Moll Cell Cardiol 1970;1:107-115.

146. Medical Research Council Working Party on the treatment of Myocardial Infarction. Potassium, glucose, and insulin treatment for acute myocardial infarction. Lancet. 1968;2:1355-1360.

147. Mittra B. Potassium, glucose, and insulin in treatment of myocardial infarction. Lancet. 1965;2:607-609.

148. Pentecost BL, Mayne NM, Lamb P. Controlled trial of intravenous glucose, potassium, and insulin in acute myocardial infarction. Lancet. 1968;1:946-948.

149. Pilcher J, Etishamudin M, Exon P, et al. Potassium, glucose and insulin in myocardial infarction. Lancet. 1967;1:1109.

150. Hjermann I. A controlled study of peroral glucose, insulin and potassium treatment in myocardial infarction. Acta Med Scand. 1971;190:213-218.

151. Heng MK, Norris RM, Singh BN, et al. Effects of glucose and glucose-insulin-potassium on haemodynamics and enzyme release after myocardial infarction. Br Heart J. 1977;39:748-757.

152. Stanley AWH, Prather JW. Glucose-insulin-potassium, patient mortality and the acute myocardial infarction; results from a prospective randomized study. Circulation. 1978;57(suppl II):II-62. Abstract.

153. Rogers WJ, McDaniel HG, Mantle JA, et al. Prospective randomized trial of glucose-insulin-potassium in acute myocardial infarction: effects of hemodynamics, short and long-term survival. J AM Coll Cardiol. 1983;1:628. Abstract.

154. Satler LF, Green CE, Kent KM, et al. Metabolic support during coronary reperfusion. Am Heart J. 1987;114:54-58.

155. Fath-Ordoubadi F, BeattKJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. Circulation 1997;96:1152-1156.

156. Malmberg K, Rydén L, Efendic S, et al on behalf of the DIGAMI Study Group. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI): effect on mortality at 1 year. J Am Coll Cardiol. 1995;26:57-65.

157. Diaz R, Paolasso EA, Piegas LS, et al. The ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group. Metabolic modulation of acute myocardial infarction. Circulation 1998;98:2227-2234.

158. Ceremuzynski L, Budaj A, Czepiel A, et al for the Pol-GIK Trial Investigators. Low-dose Glucose-Insulin-Potassium is ineffective in acute myocardial infarction: Results of a randomized Multicenter Pol-GIK Trial. Cardiovasc Drugs Ther 1999;13:191-200.

159. van der Horst IC, Zijlstra F, van't Hof AW, et al. Glucose-insulin-potassium infusion in patients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study (GIPS-1): a randomized trial. J Am Coll Cardiol 2003;42:784-791.

160. The CREATE-ECLA Trial Group Investigators. Effect of glucose-Insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction. JAMA. 2005;293:437-446.

161. Malmberg K, Rydén L, Wedel H, et al for the DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005;26:650-661.

162. Yusuf S, Metha SR, Diaz Rafael, et al for the CREATE-ECLA Investigators and Steering Committee. Challenges in the conduct of large simple trials of important generic questions in resource-poor settings: The CREATE and ECLA trial program evaluating GIK (glucose, insulin and potassium) and low-molecular-weight heparin in acute myocardial infarction. Am Heart J2004;148:1068-1078.

163. Diaz-Araya G, Nettle D, Castro P, et al. Oxidative stress after reperfusion with primary coronary angioplasty: lack of effect of glucose-insulin-potassium infusion. Crit Care Med 2002;30:417-421.

164. Mantle JA, Rogers WJ, Smith R, et al. Clinical effects of glucose-insulin-potassium on left ventricular function in acute myocardial infarction: results from a randomized clinical trial. Am Heart J 1981;102:313-324.

165. Whitlow PL, Rogers WJ, Smith LR, et al. Enhancement of left ventricular function by glucose-insulin-potassium infusion in acute myocardial infarction. Am Heart J 1982;49:811-820.

166. Apstein CS. The benefits of glucose-insulin-potassium for acute myocardial infarction. J AM Coll Cardiol 2003;42:792-795.

167. van der Horst IC, Timmer JR, Ottervangen JP, et al. Glucose-insulin-potassium and reperfusion in acute myocardial infarction: Rationale and design of the Glucose-Insulin-Potassium Study-2 (GIPS). Am Heart J 2005;149:585-91.

168. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulfphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-853.

169. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-117.

170. Shichiri M, Ohkubo Y, Kishikawa H, et al. Long-term results of the Kumamoto study on the optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000;23 (suppl. 2):B21-B29.

171. The Diabetes Control and Complication Trial Research Group: The effect of intensive treatment and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986.

172. Groeneveld Y, Petri H, Hermans J, et al. Relationship between blood glucose level and mortality in type 2 diabetes mellitus: a systematic review. Diabet Med 1999;16:2-13.

173. Capes S, Hunt D, Malmberg K, et al. Stress hyperglycaemia and increased risk of death of myocardial infarction in patients with and without diabetes: a systemic review. Lancet 2000;355:773-778.

174. Bulk J van de Ploeg T, Cornel JH, Arnold AE, et al. Impaired glucose metabolism predicts mortality after a myocardial infarction. Int J Cardiol 2001;79:207-214.

175. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 2003;348:2294-2303.

176. Nathan DM, Cleary PA, Backlund JY, et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643-2653.

177. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-865.

178. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care 1995;18:258-268.

179. Abraira C, Colwell J, Nuttall F, et al and the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VACSDM) Group. Cardiovascular events and correlates in the Veteran Affairs Diabetes Feasibility Trial. Arch Intern Med 1997;157:181-188.

180. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, et al. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin-dependent diabetes mellitus: the Oslo Study. BMJ 1985;290:811-815.

181. Abraira C, Duckworth, McCarren M, et al for the participants of the VA Cooperative Study of glycemic Control and Complications in Diabetes Mellitus Type 2. J Diabet Compli 2003;17:314-322.

182. Kullberg CE, Bergström A, Dinesen B, et al. Comparision of studies on diabetic complications hampered by differences in HbA1c measurements. Diabetes Care 1996;19:726-729.

183. Vijan S, Hofer T, Hayward R. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med 1997;127:788-795.

184. American College of Endocrinology: Consensus statement on guidelines for glycemic control. Endocrine Pract 2002;8 (suppl. 1):5-11.

185. International Diabetes Federation, Clinical Guidelines Task Force. 2005;26-28.

186. American Diabetes Association. Standards of medical care for patients with diabetes mellitus (Position statement). Diabetes Care 2003;26 (Suppl. 1):S33-S50.

187. Ezzati M, Lopez AD, Rodgers A, et al. Selected major risk factors and global and regional burden of disease. Lancet 2002;360:1347-1360.

188. Tarnow L, Rossing P, Gall MA, et al. Prevalence of arterial hypertension in diabetic patients before and after the JNC-V. Diabetes Care 1994;17:1247-1251.

189. Hypertension in Diabetes Study Group. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. J Hypertens 1993;309-317.

190. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and treatment of high blood pressure. The JNC 7 Report. JAMA 2003;289:2560-2572.

191. Guidelines Committee 2003 European Society of Hypertension – European Society of Cardiology Guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011-1053.

192. American Diabetes Association. Hypertension management in adults with diabetes. Diabetes Care 2004;27(Suppl 1):S65-67.

193. Kannel WB, Wilson PW, Zhang TJ. The epidemiology of impaired glucose tolerance and hypertension. Am Heart J 1991;121:1268-1273.

194. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities: role of insulin resistance and the sympathoadrenal system. N Engl J Med 1996;334:374-381.

195. Fuller JF, Shipley MJ, Rose G, et al. Mortality from coronary heart disease and stroke in relation to the degree of glycaemia: the Whitehall study. Br Med J 1983;287:867-870.

196. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979;59:8-13.

197. UK Prospective Diabetes Study group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes:UKPDS 38. BMJ 1998;317:307-713.

198. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. New Engl J Med 1998;338:645-652.

199. Tatti P, Pahor M, Byington RP, et al. Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597-603.

200. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Eldery Program Cooperative Research group. JAMA 1996;276:1886-1892.

201. Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effect of calcium channel blockage in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. N Engl J Med 1999;340:677-684.

202. Niskanen L, Hedner T, Hansson L, et al for the CAPPP Study Group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen. Diabetes Care 2001;24:2091-2096.

203. Lindholm LH, Hansson L, Ekbom T, et al for the STOP Hypertension-2 Study Group. Comparison of antihypertensive treatment in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with hypertension-2. J Hypertens 2000;18:1671-1675.

204. Brown MJ, Palmer CR, Casaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a ling-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000;356:366-372.

205. Lindholm LH, Ibsen H, Dahlöf B, et al for the LIFE study group. Cardiovascular morbidity and mortality in patients with diabetes in the Lorsatan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:1004-1010.

206. Whelton PK, Barzilay J, Cushman WC, et al for the ALLHAT Collaborative Research Group. Clinical outcomes in Antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normaglycemia. Arch Intern Med 2005;165:1401-1409.

207. Hansson L, Zanchetti A, Carruthers SG, et al for the HOT Study Group. Effects of intensive blood-pressure loweing and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755-1762.

208. Dahlöf B, Sever PS, Poulter NR, et al for the ASCOT investigators. Prevention of cardiovascular events with an hypertensive regimen of amlodipine adding perindopril as required versus atenolol adding

bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT_BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895-906.

209. UK Prospective Diabetes Study group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998;317:713-720.

210. Adler AI, Stratton IM, Neil AW, et al on behalf of the UK Prospective Diabetes Study Group. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321:412-419.

211. Zanchetti A, Ruilope L. Antihypertensive treatment in patients with type-2 diabetes mellitus: what guidance from recent controlled randomized trials? J Hypertens 2002;20:2099-2110.

212. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimes on major cardiovascular events in individuals with and without diabetes mellitus. Arch Intern Med 2005;165:1410-1419.

213. Guidelines Committee. 2003. European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011-1053.

214. Chobian AV et al. The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. JAMA 2003;289:2560-2572.

215. American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2002;25(Suppl 1):S71-73.

216. Levey AS, Beto JA, Coronado BE, et al., for the National Kidney Foundation Task Force on Cardiovascular Disease. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? Am J Kidney Dis 1998;32:853-906.

217. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-259.

218. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbsartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-860.

219. Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with typr 2 diabetes. N Engl J Med 2001;345:870-878.

220. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-869.

221. Klingbeil AU, Schneider M, Martus P, et al. A mata-analysis of the effect of treatment on left-ventricular mass in essential hypertension. Am J Med 2003;115:41-46.

222. Malmqvist K, Kahan T, Edner M, et al. Regression of left-ventricular hypertrophy in human hypertension with irbesartan. J Hypertens 2001;19:1167-1176.

223. Williams B. Recent hypertension trials. Implications and controversies. J Am Cill Cardiol 2005;45:813-827.

224. Mancia G, Grassi G, Zanchetti A. New-onset diabetes and hypertensive drugs. J Hypertens 2006;24:3-10.

225. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. Review. Diabetologia 2003;46:733-749.

226. Howard BV, Robbins DC, Sivers MI, et al. LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: the Strong Heart Study. Arterioscl Thromb Vasc Biol 2000;20:830.

227. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin and cardiovascular disease. Subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med 2002;162:2597-2604.

228. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study (DAIS), a randomised study. Lancet 2001;357:905-910.

229. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849-1861.

230. The Diabetes Atorvastatin Lipid Intervention (DALI) Study Group. The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia. Diabetes Care 2001;24:1335-1341.

231. Downs JR, Clearfield M, Weis S, et al for the AFCAPS/TexCAPS Research Group. Primary Prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. JAMA 1998;279(20):1615-1622.

232. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. JAMA 2002;288(23):2998-3007.

233. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of the cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005-2016.

234. Sever PS, Poulter NR, Dahlöf B, et al for the ASCOT Investigators. Reduction in cardiovascular events with atorvastatin in 2532 patients with type 2 diabetes. Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering ARM (ASCOT-LLA). Diabetes Care 2005;28:1151-1157.

235. Colhoun HM, Betteridge DJ, Durrington PN, et al on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685-696.

236. Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997;20:614-620.

237. Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol And Recurrent Events (CARE) trial. Circulation 1998;98:2513-2519.

238. Keech A, Colquhoun D, Best J, et al for the Lipid study group. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose. Diabetes Care 2003;26:2713-2721.

239. Arampatzis CA, Goedhart D, Serruys PW, et al on behalf of the LIPS Investigators. Fluvastatin reduces the impact of diabetes on long-term outcome after coronary intervention- A Lescol Intervention Prevention Study (LIPS) substudy. Am Heart J 2005;149:329-335.

240. Hoogwerf BJ, Waness A, Cressman M, et al for the Post CABG Study Investigators. Effects of aggressive cholesterol lowering and low-dose anticoagulation on clinical and angiographic Outcomes in patients with diabetes. Diabetes 1999;48:1289-1294.

241. Shepard J, Blauw GJ, Bollen ELEM, et al om behalf of the PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-1630.

242. Abbott RD, Donahue RP, Kannel WB, et al. The impact of diabetes on survival following myocardial infarction in men versus women. JAMA 1998;260:3456-3460.

243. Brown AS. Lipid management in patients with diabetes mellitus. Am J Cardiol 2005;96 (Suppl):26E-32E.

244. American Diabetes Associaltion. Position statement. Dyslipidemia management in adults with diabetes. Diabetes Care 2004;(Suppl 1):S68-S71.l

245. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program. Adult Treatment Panel III guidelines. Circulation 2002;106:3143-3421.

246. Cannon CP, Braunwald E, McCabe CH, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-1504.

247. Cheung BMY, Lauder IJ, Lau C-P, et al. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. Br J Clin Pharmacol 2004;57(5):640-651.

248. Vijan S, Hayward RA. Pharmacological lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. Ann Intern Med 2004;140:650-658.

249. Koskinen P, Manttari M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. Diabetes Care 1992;15:820-825.

250. Law Mr, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326:1423.

251. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panal III Guidelines. Circulation 2004;110:227-239.

252. Jolliffe JA, Rees K, Taylor RS, et al. Exercise-based rehabilitation for coronary disease (review). The Cochrane Collaboration. The Cochrane Library 2005, Issue 4.

253. Brown A, Taylor R, Noorani H et al. Exercise-based cardiac rehabilitation programs for coronary artery disease: a systematic clinical and economic review. Ottawa, Canadian Coordinating Office for Health Technology Assessment;2003,3.

254. Vergés B, Patois-Vergés B, Cohen M, et al. Effects of cardiac rehabilitation on exercise capacity in type 2 diabetic patients with coronary artery disease. Diabet Med 2004;21;889-895.

255. Hedbäck B, Perk J, Wodlin P. Long-term reduction of cardiac mortality after myocardial infarction: 10-year results of the comprehensive rehabilitation programme. Eur Heart J 1993;14:831-835.

256. Danish Heart Foundation and Danish Society of Cardiology. Rehabilitering af hjertepatienter. Retningslinjer [Rehabilitation of cardiac patients. Guidelines]. Copenhagen, Danish Heart Foundation, 1997.

257. Zwisler ADO, Schou L, Soja AMB, et al and the DANREHAB group. A randomized clinical trial of hospital-based, comprehensive cardiac rehabilitation versus usual care for patients with congestive heart failure, ischemic heart disease, or high risk of ischemic heart disease (the DANREHAB trial) – design, intervention and population. Am Heart J 2005;150:899.e7-8999.e16.

258. Soja AMB, Zwisler ADO, Melchior T, et al. Prevalence and characteristics of unrecognized type 2 diabetes and impaired glucose tolerance in patients referred to cardiac rehabilitation – The DANSUK study. Eur J Cardiovasc Pre Rehabil 2006;13:784-790.

259. Soja AMB, Zwisler ADO, Frederiksen M, et al M. Use of intensified comprehensive cardiac rehabilitation to improve risk factor control in patients with type 2 diabetes or impaired glucose tolerance – the randomized DANSUK study. Accepted Am Heart J January 2007.

260. Borg G. Perceived exertion as indicator of somatic stress. Scand J Rehabil Med 1970;2:92-98.

261. Frederiksen M, Kriegsbaum P. [Individually tailored rehabilitation] in: Zwisler ADO, Schou L, Vind-Sørensen, L. [Cardiac rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital]. Copenhagen,

Bispebjerg Hospital; National Institute of Public Health, 2003;(49-68).
(http://www.cardiacrehabilitation.dk/rehab_uk/html/index6.html, accessed 2005.12.31).

262. Brunse L. [Patient education] in: Zwisler ADO, Schou L, Vind-Sørensen, L. [Cardiac rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital]. Copenhagen, Bispebjerg Hospital; National Institute of Public Health, 2003;(69-82).

(http://www.cardiacrehabilitation.dk/rehab_uk/html/index7.html, accessed 2005.12.31).

263. Villadsen TH, Kristensen J. [Physical exercise] in: Zwisler ADO, Schou L, Vind-Sørensen, L. [Cardiac rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital]. Copenhagen, Bispebjerg Hospital; National Institute of Public Health, 2003;(83-96).
(http://www.cardiacrehabilitation.dk/rehab_uk/html/index8.html, accessed 2005.12.31).

264. Larsen J. [Support for smoking cessation] in: Zwisler ADO, Schou L, Vind-Sørensen, L. [Cardiac rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital]. Copenhagen, Bispebjerg Hospital; National Institute of Public Health, 2003;(109-118).
(http://www.cardiacrehabilitation.dk/rehab_uk/html/index10.html, accessed 2005.12.31).

265. Brunse L, Birket-Smith M. [Psykosocial support] in: Zwisler ADO, Schou L, Vind-Sørensen, L. [Cardiac rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital]. Copenhagen, Bispebjerg Hospital; National Institute of Public Health, 2003;(119-130).
(http://www.cardiacrehabilitation.dk/rehab_uk/html/index11.html, accessed 2005.12.31).

266. Soja AMB, Frederiksen M. [Systematic risk factor management and clinical assessment] in: Zwisler ADO, Schou L, Vind-Sørensen, L. [Cardiac rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital]. Copenhagen, Bispebjerg Hospital; National Institute of Public Health, 2003;(131-138).
(http://www.cardiacrehabilitation.dk/rehab_uk/html/index12.html, accessed 2005.12.31).

267. Soja AMB, Ejlertsen M. [Type 2 diabetes mellitus] in: Zwisler ADO, Schou L, Vind-Sørensen, L. [Cardiac rehabilitation. Rationale, methods and experiences from Bispebjerg Hospital]. Copenhagen, Bispebjerg Hospital; National Institute of Public Health, 2003;(139-151).
(http://www.cardiacrehabilitation.dk/rehab_uk/html/index13.html, accessed 2005.12.31).

268. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: towards an integrative model of change. J Consult Clin Psychol 1983;51:390-395.

269. Executive summary of the clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults. Arch Intern Med. 1998;68:1855-1865.

270. Orchard TSD. Assessment of peripheral vascular disease in diabetics: report and recommendations of an international workshop sponsored by the American Diabetes Association and the American Heart Association, September 18-20, 1992, New Orleans, Louisiana. Circulation 1993;88:819-828.

271. Peterson JI, Young DA. Evaluation of the hexokinase-glucose-6-phosphate dehydrogenase method of determination of glucose in urine. Anal Biochem 1968;23:301-316.

272. The DECODE study group on behalf of the European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and non-cardiovascular disease? Diabetes Care 2003;26:688-696.

273. Ellis G, Diamandis EP, Giesbrechts EE et al. An automated high pressure liquid-chromatographic assay for hemoglobin A1c. Clin Chem 1984;30:1746-1752.

274. Warnick GR. Enzymatic methods for quantification of lipoprotein lipids. Methods Enzymol 1986;129:101-123.

275. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-509.

276. Mogensen CE, Keane WF, Bennett PH et al. Prevention of diabetic renal disease with special reference to microalbuminuria. Lancet 1995;346:1080-1084.

277. Smulders YM, Slaats EH, Rakic M, et al. Shortterm variability and sampling distribution of various parameters of urinary albumin excretion in oatients with non-insulin-dependent diabetes mellitus. J Lab Clin Med 1998;132:39-46.

278. Myocardial infarction redefined: a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 2000;36:959-969.

279. Remme WJ, Svedberg K, Cleland et al. Task force of the ESC: Guideline for the diagnosis and treatment of chronic heart failure. Eur Heart J. 2001;22:1527-1560.

280. Lean MEJ, Han TS, Seidell JC. Impairment of health and quality of life in people with large waist circumference. Lancet 1998;351:863-866.

281. Balkau B and Charles MA for the European Group for the Study of Insulin Resistance (EGIR). Comment on the provisional report from the WHO consultation. Diabet Med 1999;16:442-443.

282. Balkau B, Charles MA, Drivsholm T, et al. Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. Diabetes Metab 2002;28:364-376.

283. Lau C, Færch K, Glümer C, et al. Inter99 Study. Dietary Glycemic Index, Glycemic Load, Fiber, Simple Sugars, and Insulin resistance – The Inter99 study. Diabetes Care 2005;28:1397-1403.

284. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-419.

285. Albareda M, Rodriquez-Espinosa J, Murugo M, et al. Assessment of insulin sensitivity and beta-cell function from measurements in the fasting state and during an oral glucose tolerance test. Diabetologia 2000;43:1507-1511.

286. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care 2003;26:881-885.

287. Sheils JF, Rubin R, Stapleton DC. The estimated costs and savings of medical nutrition therapy. The Medicare population. J Am Diet Assoc 1999;99:428-435.

288. Kannell WB, McGee DL. Diabetes and cardiovascular disease: the Framingham Study. JAMA 1979;241:2305-2308.

289. Nichols GA, Hillier TA, Erbey JR, et al. Congestive Heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care 2001;24:1614-1619.

290. Kistorp C, Galatius, Gustafsson F, et al. Prevalence and characteristics of diabetic patients in a chronic heart failure population. Inter J Cardiol 2005;100:281-287.

291. Blake D, Meigs J, Muller D, et al. Impaired glucose tolerance, but not impaired fasting glucose, is associated with increased levels of coronary heart disease risk factors: results from the Baltimore Longitudinal Study on Aging. Diabetes 2004;53:2095-2100.

292. Novoa FJ, Boronat M, Saavedra P, et al. Differendes in cardiovascular risk factors, insulin resistance, and insulin secretion in individuals with normal glucose tolerance and in subjects with impaired glucose regulation. The Telde Study. Diabetes Care 2005;28:2388-2393.

293. Beniamini Y, Rubenstein JJ, Zaichkowsky LD, et al. Effects of high-intensity strength training on quality-of-life parameters in cardiac rehabilitation patients. Am J Cardiol 1997;80:841-846.

294. Hambrecht R, Walther C, Möbius-Winkler S, et al. Percoutaneous coronary Angioplasty compared with exercise training in patients with stable coronary artery disease. Circulation 2004;109:1371-1378.

295. Lear SA, Ignaszewski A, Linden W, et al. The extensive lifestyle management intervention (ELMI) following cardiac rehabilitation trial. Eur Heart J 2003;24:1920-1927.

296. Attebring MF, Hartford M, Hjalmarson A, et al. Smoking habits and predictors of continued smoking in patients with acute coronary syndromes. J Adv Nurs 2004;46(6):614-23.

297. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. JAMA 2003;290:86-97.

298. Sulkin TV, Bosman, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. Diabetes Care 1997;20:925-928.

299. Eurich TD, Majumdar SR, McAlister FA, et al. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. Diabetes Care 2005;28:2345-2351.

300. Hiss RG. Barriers to care in non-insulin-dependent diabetes mellitus: the Michigan experience. Ann Intern Med 1996;124:146-148.

301. ADA: Standards of medical care in diabetes. Diabetes Care 2005;28:S4-S36.