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Heart Disease and Diabetes

Edited by

MILES FISHER

SECOND EDITION · 2 · SECOND EDITION ·

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SECOND EDITION

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Preface

The management of people with type 1 and type 2 diabetes has improved following the results of large multi-centre trials. The microvascular complications of retinopathy, nephropathy, and neuropathy can all be reduced by intensive glycaemic control. Long-term epidemiological follow-up from trials has now shown that intensive glycaemic control reduces macrovascular complications, especially coronary events.

The focus has therefore shifted from whether improved glycaemic control reduces cardiovascular events, to identifying the safest treatment regimen for improving glycaemic control without unacceptable weight gain or hypoglycaemia.

Further advances have also been made in the management of dyslipidaemia and hypertension in diabetes, and there have been several well designed and well-conducted studies examining the most appropriate cardiovascular intervention for diabetic patients with established coronary heart disease.

This second edition of the book remains a concise and practical guide to reducing cardiovascular risk and in particular heart disease in people with diabetes. It will be of interest to GPs and practice nurses, hospital specialists, and specialist nurses in diabetes and cardiology, and has been extensively up-dated to reflect the results of recent trials.

As for the first edition I am extremely grateful to the other authors for their contributions to this book. Stephen Wheatcroft and his cardiology colleagues from Leeds have provided the more cardiological chapters, and Chapter 7 on coronary revascularization in the patient with diabetes has been heavily revised. Again my diabetes work colleague Ken Paterson, along with clinical pharmacology colleagues has produced a very useful and understandable guide to the heath economic aspects of treating cardiovascular disease in diabetes.

In producing this second edition my wife Margaret and son Marc have caught me sneaking off to work on the laptop at weekends and evenings, and I thank them for their continuing support and patience.

Miles Fisher, December 2010

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ADVANCE	Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation
ACCOMPLISH	Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension
ACCORD	Action to Control Cardiovascular Risk in Diabetes
AGE	Advanced glycation end products
ALLHAT	Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial
ARA	Angiotensin-II receptor antagonists
ARTS	Arterial Revascularization Therapies Study
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ATP	Adult Treatment Panel
AWESOME	Angina With Extremely Serious Operative Mortality Evaluation
BARI	Bypass Angioplasty Revascularization
BARI 2-D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass graft
CABRI	Coronary Angioplasty versus Bypass Revascularization Investigation
CANOE	Canadian Normoglycaemia Outcomes Evaluation
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CARDS	Collaborative AtoRvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CHD	Coronary heart disease

CHF	Chronic heart failure
CIMT	Carotid intima-media thickness
CKD	Chronic kidney disease
CORE	Centre for Outcomes Research
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CRP	C-reactive protein
CTT	Cholesterol Treatment Trialists
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events'
CVD	Cerebrovascular disease
DCCT	Diabetes Control and Complications Trial
DETAIL	Diabetics Exposed to Telmisartan and Enalapril
DIABHYCAR	Diabetes, Hypertension, cardiovascular events, and Ramipril
DIAD	Detection of Silent Myocardial Ischaemic in Asymptomatic Diabetics
DIGAMI	Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction
DiGEM	Diabetes glycaemic education and monitoring
DPP	Diabetes Prevention Program
DPS	Diabetes Prevention Study
DREAM	Diabetes Reduction Assessment with ramipril and rosiglitazone Medication
EAST	Emory Angioplasty versus Surgery Trial
EBCT	Electron-beam computed tomography
ECG	Electrocardiography
ED	Erectile dysfunction
EDIC	Epidemiology of Diabetes Interventions and Complications
ESRD	End-stage renal disease
EUROPA	EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease
FDA	Federal Drug Administration
GIP	Glucose-dependent insulinotropic peptide
GIST-UK	UK Glucose Insulin in Stroke Trial
GRACE	Global Registry of Acute Coronary Events
HDL	High-density lipoprotein

HDS	Hypertension in Diabetes Study
HI-5	Hyperglycemia Intensive Insulin Infusion in Infarction
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment trial
HPS	Heart Protection Study
HR	Hazard ratios
HYVET	Hypertension in the Very Elderly Trial
ICD	Implantable cardiac defibrillators
ICER	Incremental cost-effectiveness ratio
IDNT	Irbesartan Diabetic Nephropathy Trial
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IRMA-2	Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study
JBS 2	Joint British Societies' Guidelines on prevention of cardiovascular disease in clinical practice
JUPITER	Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LAGB	Laparoscopic adjustable gastric banding
LDL	Low-density lipoprotein
LIFE	Losartan Intervention For Endpoint reduction in hypertension
LIPID	Long-Term Intervention with Pravastatin in Ischaemic Disease
LMWH	Low molecular weight heparins
LVSD	Left ventricular systolic dysfunction
MARVAL	Microalbuminuria Reduction with Valsartan
MI	Myocardial infarction
MIBG	Meta-iodobenzylguanidine
MICRO-HOPE	Microalbuminuria, Cardiovascular and Renal Outcomes-Heart Outcomes Prevention Evaluation
MRI	Magnetic resonance imaging
MSCT	Multi-slice computed tomography
NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research
NICE	National Institute for Health and Clinical Excellence

NO	Nitric oxide
NOD	New-onset diabetes
NYHA	New York Heart Association
OGTT	Oral glucose tolerance test
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PCI-CURE	Clopidogrel in Unstable angina to Reduce Recurrent Events (CURE) trial of patients with acute coronary syndromes undergoing PCI
PEACE	Prevention of Events with Angiotensin Converting Enzyme inhibition
PPAR	Peroxisome proliferator-activated receptor
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events
PROGRESS	Perindopril Protection against Recurrent Stroke Study
PROVE-IT TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infraction 22
PTCA	Percutaneous Transluminal Coronary Angioplasty
QALY	Quality adjusted life year
RCT	Randomized controlled trial
REACH	Reduction of Atherthrombosis for Continued Health
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
SCOUT	Sibutramine Cardiovascular Outcomes Trial
SHEP	Systolic Hypertension in the Elderly Program
SMC	Scottish Medicines Consortium
SOS	Stents or Surgery
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SPECT	Single-photon emission computed tomography
STOP-NIDDM	Study to Prevent Non-Insulin-Dependent Diabetes Mellitus
SYNTAX	SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery

TIA	Transient ischaemic attacks
TNT	Treatment to New Targets
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38
TZD	Thiazolidinedione
UFH	Unfractionated heparin
UKPDS	United Kingdom Prospective Diabetes Study
VLDL	Very low-density lipoprotein
WHO	World Health Organization
WOSCOPS	West of Scotland Coronary Prevention Study
XENDOS	XENical in the prevention of Diabetes in Obese Subjects

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Chapter 1

Introduction, epidemiology, and cardiovascular risk factors

Miles Fisher

Diabetes is a state of premature cardiovascular death which is associated with chronic hyperglycaemia and may also be associated with blindness and renal failure

Miles Fisher, British Diabetic Association meeting Dublin 1996.

Key points

- Cardiovascular disease is a common cause of morbidity and mortality in people with type 2 diabetes. Some guidelines define diabetes as a coronary heart disease equivalent, requiring multiple cardiovascular risk factor reduction
- In addition to diabetes the WHO has defined impaired glucose tolerance and impaired fasting glucose as intermediate hyperglycaemia. Subjects with intermediate hyperglycaemia have an increased risk of cardiovascular disease, and of progression to diabetes
- The presence of the metabolic syndrome (abdominal obesity, diabetes or impaired fasting glucose, raised blood pressure, and dyslipidaemia) predicts subsequent development of diabetes and vascular disease, but is not a separate target for intervention
- The relative risk of cardiovascular disease is greatly increased in people with type 1 diabetes, but the absolute risk is not particularly high. Components of the metabolic syndrome predict cardiovascular risk in type 1 diabetes.

1.1 Introduction

When I suggested the above re-definition of diabetes, which was prior to the publication of the results of the United Kingdom Prospective Diabetes Study (UKPDS), only the treatment of hypercholesterolaemia and hypertension, plus the use of antiplatelet drugs in certain high-risk patients, were of proven benefit in reducing cardiovascular events in people with diabetes. The purpose of the re-definition was to awaken healthcare professionals caring for people with diabetes to the fact that clinical management needed to embrace the prevention, detection and treatment of macrovascular disease in addition to microvascular disease.

1.2 Epidemiology

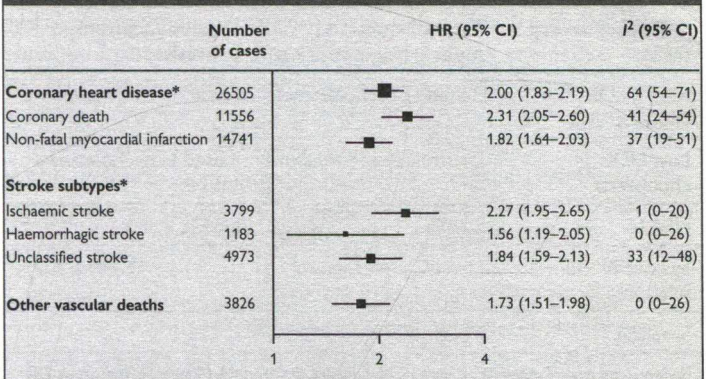
The Framingham study was one of the first to quantify the increased risk of cardiovascular morbidity and mortality in people with diabetes, and showed that there was an excess of cardiovascular disease in people with diabetes (predominantly type 2 diabetes) compared to non-diabetic people. This could not be fully explained by conventional cardiovascular risk factors of blood pressure, cholesterol, smoking, or obesity. Excesses were demonstrated in coronary heart disease, congestive cardiac failure, strokes, peripheral vascular disease and cardiovascular deaths (Table 1.1). In particular, an excess cardiovascular morbidity and mortality was seen in women with diabetes, and the rates of vascular disease in diabetic women approached the rates of vascular disease in men with diabetes.

In a population-based study from Finland it was shown that people with type 2 diabetes, who had no known cardiac disease, had the same incidence of myocardial infarction and cardiovascular death on 7-year follow-up as people without diabetes who had sustained

Table 1.1 Increased risk of cardiovascular disease in diabetic subjects compared to non-diabetic subjects in the Framingham study

	Relative risk men	Relative risk women
Coronary heart disease	2	3
Stroke	2	4
Peripheral arterial disease	4	6
Congestive heart failure	2	5
Any cardiovascular disease	2	3
Cardiovascular death	2	5

Figure 1.1 Hazard ratios (HRs) for vascular outcomes in people with diabetes at baseline versus those without diabetes from the Emerging Risk Factors Collaboration



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a myocardial infarction. Similar results were obtained on 18-year follow-up. Others later challenged the suggestion that diabetes is a true coronary heart disease equivalent, pointing out that while the event rate in people with diabetes who are completely free of vascular disease at baseline is increased compared to non-diabetic subjects, the event rate is not as high as in survivors of myocardial infarction.

A recent meta-analysis from the Emerging Risk Factors Collaboration has been performed of 102 prospective studies containing 698,782 people without initial vascular disease. Risks for coronary heart disease were doubled in people with diabetes (Figure 1.1), and for women with diabetes the risk was greatest.

1.2.1 **Risk factors for coronary heart disease in diabetes**

The UKPDS was a large randomized trial of intensive versus conventional treatment of blood glucose in recently diagnosed patients with type 2 diabetes. A large amount of epidemiological data has been obtained from the study. In the UKPDS at baseline the traditional risk markers of hypertension, dyslipidaemia, and smoking, as well as HbA1c were independent risk factors for subsequent coronary events, indicating a potential for risk factor intervention in people with type 2 diabetes (Table 1.2). The importance of HbA1c as a risk factor is that it indicated that it was not just the presence of diabetes but the degree of hyperglycaemia as measured by HbA1c that was important. Variation in fasting blood glucose and HbA1c within the normal range has been shown to predict cardiovascular risk within