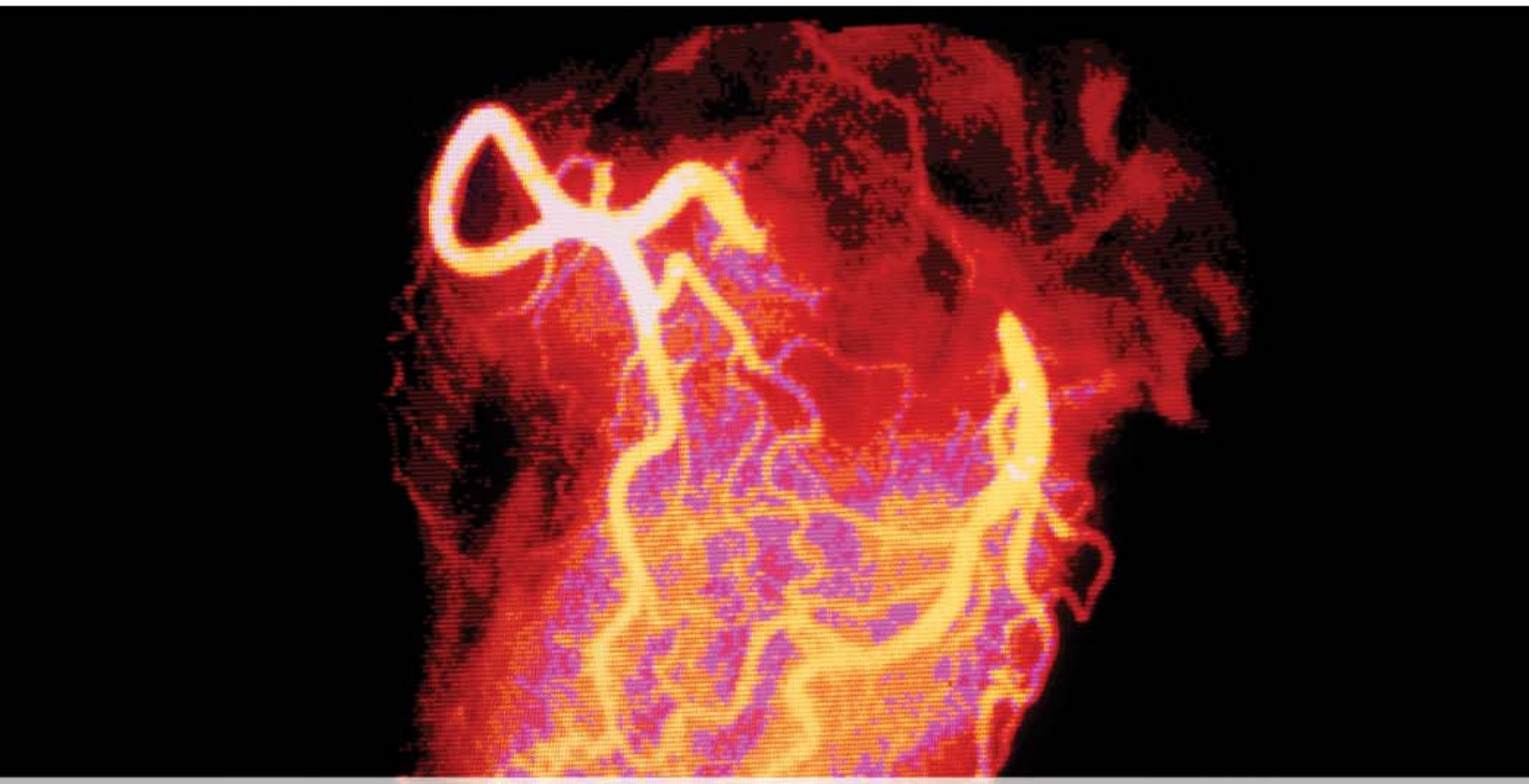
ABC of Interventional Cardiology

SECOND EDITION

Ever D. Grech



WILEY-BLACKWELL www.abcbookseries.com BMJ Books

Contents

ABC of

Interventional Cardiology

Second Edition

Ever D. Grech
Consultant Cardiologist
South Yorkshire Cardiothoracic Centre, Northern General Hospital, Sheffield, UK

WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

BMJ Books

This edition first published 2011, © 2011 by Ever D. Grech

Previous edition: 2003

BMJ Books is an imprint of BMJ Publishing Group Limited, used under licence by Blackwell Publishing which was acquired by John Wiley & Sons in February 2007. Blackwell's publishing programme has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK

The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell

Library of Congress Cataloging-in-Publication Data

ABC of interventional cardiology / Ever D. Grech. – 2nd ed.

p.; cm.

Includes bibliographical references and index.

ISBN 978-1-4051-7067-3 (pbk.: alk. paper)

1. Heart – Diseases – Treatment. 2. Coronary heart disease – Surgery. I. Grech, Ever D.

[DNLM: 1. Cardiovascular Diseases – therapy. WG 120]

RC683.8.A33 2010

616.1′2-dc22

2010039150

ISBN: 978-1-4051-7067-3

List of Contributors

Abdallah Al-Mohammad
Consultant Cardiologist, South Yorkshire Cardiothoracic Centre, Northern General Hospital, Sheffield, UK

Kevin S. Channer
Professor of Cardiovascular Medicine, Royal Hallamshire Hospital, Sheffield, UK

Ever D. Grech
Consultant Cardiologist, South Yorkshire Cardiothoracic Centre, Northern General Hospital, Sheffield, UK

Julian Gunn
Senior Lecturer and Honorary Consultant Cardiologist, University of Sheffield, Sheffield, UK

Gerald C. Kaye
Consultant Cardiac Interventional Electrophysiologist, Princess Alexandra Hospital, Woolloongabba, Brisbane, QLD, Australia

Damien Kenny
Specialist Registrar in Paediatric Cardiology, Bristol Royal Hospital for Children, Bristol, UK

Laurence O'Toole
Consultant Cardiologist, South Yorkshire Cardiothoracic Centre, Northern General Hospital, Sheffield, UK

Jonathan Sahu

Consultant Cardiologist, South Yorkshire Cardiothoracic Centre, Northern General Hospital, Sheffield, UK

Robert F. Storey
Reader and Honorary Consultant Cardiologist, University of Sheffield, Sheffield, UK

Kevin P. Walsh
Consultant Paediatric Cardiologist, Our Lady’s Hospital for Sick Children, Dublin, UK

Preface

It is only 33 years since the first percutaneous transluminal coronary angioplasty (PTCA) was carried out by the pioneering Swiss radiologist Andreas Greuntzig in Zurich, heralding the dawn of interventional cardiology. In this short time, interventional cardiology has overcome many limitations and undergone major evolutionary changes – most notably the development of the intracoronary stent and more explicitly the drug-eluting stent. Across the world, many thousands of patients now safely undergo percutaneous coronary intervention everyday and the numbers continue to grow. In many countries, the numbers far exceed surgical bypass operations.

Although at first, PTCA was indicated only as treatment for chronic stable angina caused by a discrete, easily accessible lesion in a single coronary artery, this has now progressed enormously to encompass complex multi-lesion and multi-vessel disease. Moreover, percutaneous coronary intervention has now become widely used in the management of acute coronary syndromes (which principally include ‘heart attacks’) with definite benefits in terms of morbidity and mortality. The effectiveness and safety of these procedures has undoubtedly been enhanced by the adjunctive use of new anti-platelet and anti-thrombotic agents, and newer drugs are being evaluated. As drug-eluting stents address the Achilles’ heel of angioplasty and stents – restenosis – the huge increase in percutaneous coronary procedures seen over recent years is likely to continue.

As the indications increase and more patients are treated, so inevitably do the demands on healthcare budgets. Although percutaneous intervention is expensive, this burden must be weighed against bypass surgery which is

significantly more costly and multi-drug therapy which would be required over many years.

Although percutaneous coronary intervention has held centre stage in cardiology, major in-roads have also been made in non-coronary areas. Transcatheter valvular treatments – including actual new valve implantation, closure devices and ethanol septal ablation – have become effective and safe alternatives to surgery, as have paediatric interventional procedures. A greater understanding of cardiac electrophysiology and heart failure has led to important advances in the treatment of arrhythmias and resynchronisation therapy. Pacemakers, implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT) are benefiting ever larger numbers of patients both in terms of life quality and mortality.

Where are we heading? This is perhaps the biggest question in the minds of many interventional cardiologists. New ideas and technology generated by industry, coupled with high levels of expertise, are fuelling advances in almost all areas of interventional cardiology. The next decade promises many new (and possibly unexpected) developments in this exciting and restless field of medicine.

In writing this book, I have endeavoured to present broad (and sometimes complex) aspects of interventional cardiology in a clear, concise and balanced manner. To this end, I have concentrated on an easy-to-read style of text, avoiding jargon and exhaustive detail where possible and supplemented with many images and graphics.

Ever D. Grech

Sheffield

Acknowledgements

I have many people to thank for their help in developing and producing this book. I am very grateful to my co-authors who have all willingly contributed their time and expertise. I would also like to recognise the positive efforts and invaluable assistance of the editors and publishers at Wiley-Blackwell. These include Laura Quigley, Adam Gilbert, Carla Hodge and Karen Moore. My thanks also to Dhanya Ramesh at Laserwords.

Finally, my enduring gratitude goes to my wife Lisa and our children Alexander and Frances for their unfailing encouragement, patience and love.

List of Abbreviations

CTO	Chronic total occlusion
HRT	Hormone replacement therapy
IVUS	Intravascular ultrasound
LAD	Left anterior descending (artery)
LCx	Left circumflex (artery)
Non-STEMI Non-ST	segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
STEMI ST	segment elevation myocardial infarction

List of Trial Abbreviations

ACE	Abciximab and Carbostent Evaluation
ADMIRAL	Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up
ASSENT-4	Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction
BARI	Bypass Angioplasty Revascularisation Investigation
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CAPITAL-AMI	Combined Angioplasty and Pharmacological Intervention Versus Thrombolytics Alone in Acute Myocardial Infarction
CAPTURE C7E3	Antiplatelet Therapy in Unstable Refractory Angina
CARDia	Coronary Artery Revascularisation in Diabetes
CARE-HF	Cardiac Resynchronization – Heart Failure
CARESS-in-AMI	Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction
CHAMPION	Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance
CLARITY	Clopidogrel as Adjunctive Reperfusion Therapy
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure
COURAGE	Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation
CREDO	Clopidogrel for the Reduction of Events during Observation
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
ECSG	European Cooperative Study Group
EPIC	Evaluation of C7E3 for Prevention of Ischemic Complications
EPILOG	Evaluation in PICA to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade
EPISTENT	Evaluation of Platelet IIb/IIIa Inhibitor for Stenting
ESPRIT	Enhanced Suppression of the Platelet Glycoprotein IIb/IIIa Receptor Using Integrilin Therapy

EUROPA	European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease
EVEREST	Endovascular Valve Edge-to-Edge Repair Study
FAME FFR	Versus Angiography for Multivessel Evaluation
FINESSE	Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events
FREEDOM	Future Revascularisation Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease
FRISC II	Fast Revascularisation during Instability in Coronary Artery Disease
GISSI	Gruppo Italiano per to Studio della Sopravvivenza nell'infarto miocardico
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
GUSTO	IV ACS Global Use of Strategies to Open Occluded Arteries IV in Acute Coronary Syndrome
HOPE	Heart Outcomes Prevention Evaluation
HORIZONS-AMI	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction
ICTUS	Invasive Versus Conservative Treatment in Unstable Coronary Syndromes Investigators
IMPACT II	Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis
ISAR-COOL	Intracoronary Stenting with Antithrombotic Regimen Cooling Off
ISAR-REACT 2	Intracoronary Stenting and Antithrombotic Regimen – Rapid Early Action for Coronary Treatment 3
ISIS-2	Second International Study of Infarct Survival
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
MADIT I and II	Multicenter Automatic Defibrillator Implantation Trials. The Use of Defibrillators in Primary Prevention
MIST	Migraine Intervention with Starflex Technology
MUSTT	Multicenter Unsustained Tachycardia Trial
On-TIME 2	Ongoing Tirofiban in Myocardial Infarction Evaluation
PARAGON	Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in the Global Organization Network
PEACE	Prevention of Events with Angiotensin-Converting Enzyme Inhibition
PLATO	Platelet Inhibition and Patient Outcomes
PRISM	Platelet Receptor Inhibition in Ischemic Syndrome Management

PRISM-PLUS	Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
PROSPECT	Predictors of Response to Cardiac Resynchronization Therapy
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
RAPPORT	Reopro and Primary PTCA Organization and Randomized Trial
RAVEL	Randomised Study with the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions
RESTORE	Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis
RITA 3	Randomised Intervention Treatment of Angina
SCD-Heft	Sudden Cardiac Death in Patients with Heart Failure
SHOCK	Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock
SIRIUS	Sirolimus-Coated Velocity Stent in Treatment of Patients with De Novo Coronary Artery Lesions Trial
Stent-PAMI	Stent Primary Angioplasty in Myocardial Infarction
SYNTAX	Synergy between PCI with Taxus and Cardiac Surgery
TACTICS-TIMI 18	Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy– Thrombolysis in Myocardial Infarction TAMI Thrombolysis and Angioplasty in Myocardial Infarction
TIMIIIIB	Thrombolysis in Myocardial Infarction IIIB
TRANSFER-AMI	Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction
TRUCS	Treatment of Refractory Unstable Angina in Geographically Isolated Areas without Cardiac Surgery
VANQWISH	Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital
VINO	Value of First Day Coronary Angiography/Angioplasty in Evolving Non-ST Segment Elevation Myocardial Infarction
WHO MONICA	World Health Organisation: Monitoring Trends and Determinants in Cardiovascular Disease

CHAPTER 1

Modifying Risk Factors to Improve Prognosis

Kevin S. Channer[1] and Ever D. Grech[2]

[1]Royal Hallamshire Hospital, Sheffield, UK

[2]South Yorkshire Cardiothoracic Centre, Northern General Hospital, Sheffield, UK

OVERVIEW

- Certain personal characteristics and lifestyles point to increased likelihood of coronary heart disease and are called *risk factors*
- The three principal modifiable risk factors are smoking, hypercholesterolaemia and hypertension. Other modifiable factors linked to lifestyle include a saturated-fat-rich diet, obesity and physical inactivity
- Prevention strategies (primary or secondary prevention) aim to reduce the risk of developing or retard the progression of atheroma, to stabilise plaques and to reduce the risk of their erosion or rupture. These measures can collectively reduce the risk of future cardiovascular events (mortality, myocardial infarction and strokes) by as much as 75–80%
- Percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) revascularisation is not a cure for coronary heart disease and they are predominantly carried out to improve symptoms. They may have little or no prognostic impact in chronic stable angina. However, CABG and PCI confer significant short- and long-term mortality benefit in acute coronary syndromes and, in particular, primary PCI for acute ST segment elevation myocardial infarction

In affluent societies, coronary artery disease causes severe disability and more deaths than any other disease including cancer. It manifests itself as silent ischaemia, angina, unstable angina, myocardial infarction, arrhythmias, heart failure and sudden death. Although this is the result of atheromatous plaque formation and its effect, the actual cause of this process is not known. However, predictive variables – known as *risk factors* –have been identified which increase the chance of its early development. Risk factors can be classified as modifiable and non-modifiable (Table 1.1).

It is clearly not possible to prevent the increased risk associated with ageing, a positive family history or male gender. However, there are many factors which can be usefully ameliorated by interventions. Moreover, there are some aspects of lifestyle that have been shown to reduce the risk of an acute myocardial infarction.

Table 1.1 Risk factors for the development of premature ischaemic heart disease and acute myocardial infarction.

Risk factor	RR*	Modifiable	Not modifiable	RR for AMI†	PAR for AMI (%)†
Smoking	5.1	√	–	2.87‡	35.7‡
Age	4.7	–	√	–	–
Abnormal lipids	3.1	√	–	3.25	49.2
Hypertension	3.1	√	–	1.91	17.9
Diabetes	2.0	√	–	2.37	9.9
Male sex	2.0	–	√	–	–
Obesity	1.8	√	–	1.12	20.1
Positive family history	1.5	–	√	–	–
Psychosocial factors	–	–	√	2.67	32.5
5× daily fresh fruits/vegetables	–	√	–	0.70	13.7
Regular alcohol	–	√	–	0.91	6.7
Regular exercise	–	√	–	0.86	12.2

Uncertain risk factors include: hypertriglyceridaemia, lipoprotien (a), microalbuminuria, uric acid, renin, fibrinogen, C-reactive protien and hyperhomocyteinaemia. *From Steeds. RR, Relative risk.

†From INTERHEART case-control study. Yusuf S *et al. Lancet* 2004;**364**: 937–52.

‡For current and former smokers.

RR for AMI: Relative risk for acute myocardial infarction. PAR for AMI(%): Population attributable risk for acute myocardial infarction. *Notes*: These 9 risk factors accounted for 90% of the population attributable risk in men and 94% in women. Psychosocial factors included depression, stress at work or at home, moderate/severe financial stress, one or more recent life events, low control score. The control population was drawn from hospital in-patients with non-cardiac conditions (58%) and community-based hospital visitors (36%). A minority were WHO MONICA controls (3%) and unknown (3%).

Risk factors are not simply additive but may be synergistically cumulative. Data from epidemiological surveys have shown for some time that combinations of risk factors generate exponential risks (Figures 1.1 and 1.2). This applies to both men and women. Risk factors are not static but increase with age – this may partly explain the independent effect of age. Blood pressure increases normally with age, so whatever definition is used for hypertension, the frequency of this condition will increase with age. Cholesterol and triglycerides increase with age as do insulin resistance and body mass index.

Figure 1.1 The adverse effect of single and combined risk factors on the risk of acute myocardial infarction. Smk, smoking; DM, diabetes mellitus; HTN, hypertension; ApoB/A1, lipid abnormalities; Obes, obesity; PS, psychosocial factors; RFs, risk factors. From INTERHEART case-control study. Yusuf S *et al. Lancet* 2004;**364**:937–52.

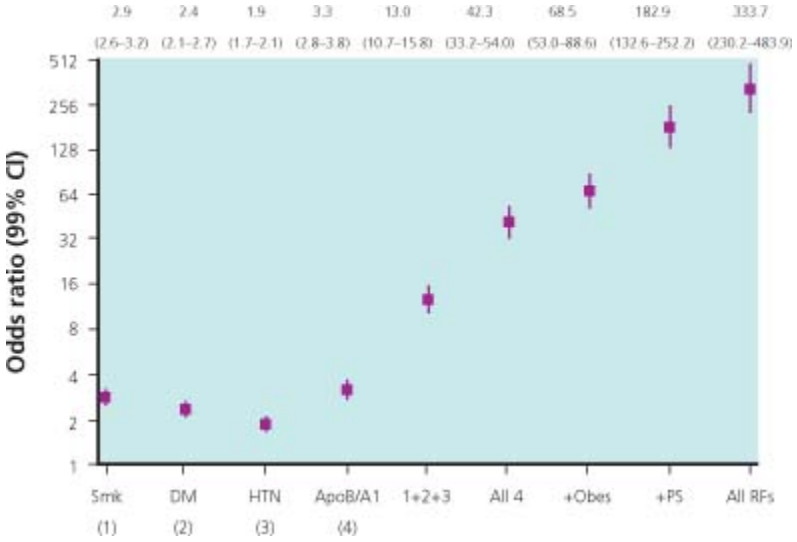
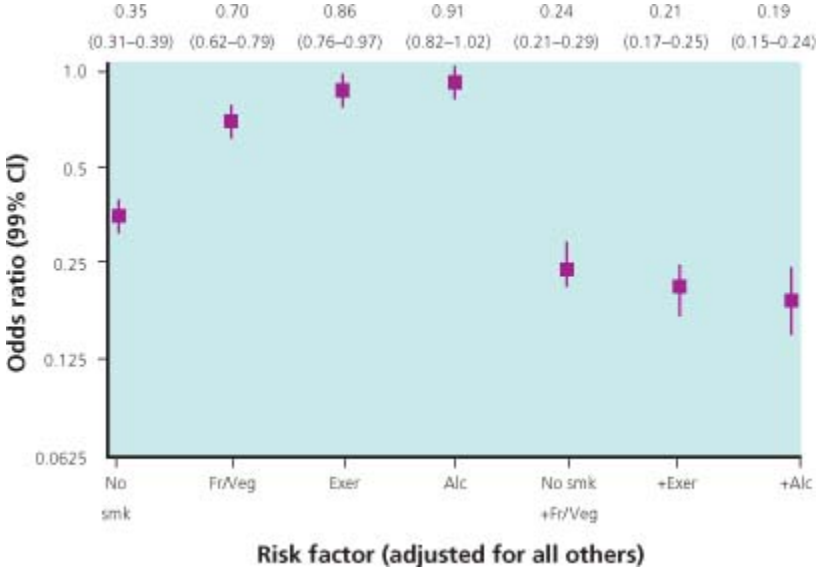


Figure 1.2 The beneficial effect of single and combined risk factors on the risk of acute myocardial infarction. No smk, no smoking; Fr/Veg, daily 5 fresh fruits/vegetables; Exer, regular exercise; Alc, regular alcohol. From INTERHEART case-control study. Yusuf S *et al. Lancet* 2004;**364**:937–52.



Impact of risk factors

Smoking

Smoking confers a fivefold relative risk for acute myocardial infarction and cardiovascular death. By comparison, stopping smoking has an almost immediate effect on reducing the cardiovascular risk by about 50%. Ex-smokers still have a higher risk than lifelong non-smokers. In one study, the survival rate of patients who stopped smoking after an acute myocardial infarction at 8 years of follow-up was about 75% compared with 60% for patients who continued to smoke. Similarly reinfarction is about twice as common in smokers than in those who stop smoking after a first infarction. At 8 years of follow-up, reinfarction was about 38% in smokers compared with 22% in quitters. Overall smoking increases mortality by about 2.5 times and reduces absolute survival by, on average, 10 years.

Hyperlipidaemia

High blood cholesterol is associated with an increased cardiovascular risk. However, as a single risk factor it is relatively weak – it becomes more important when associated with smoking, hypertension and diabetes. There is also an important interaction with age. In men, there is a doubling of risk from serum cholesterol in the lowest population quintile (<200 mg/dl; 5.2 mmol/l) to the highest (>260mg/dl; >6.7mmol/l).

Hypertension

Both diastolic and systolic hypertension have been shown to be risk factors for myocardial infarction and cardiovascular death. The relative risk of persistently elevated blood pressure of > 160 mmHg systolic is 4 times the risk compared with systolic blood pressure of < 120 mmHg.

The relative risk of persistently elevated diastolic blood pressure > 100 mmHg is 3 times higher when compared with a diastolic pressure of <80mmHg. Research data have

shown that reduction in diastolic pressure of 5–6 mmHg and systolic pressure of 10–14 mmHg over 5 years with drug therapy does reduce cardiac mortality and non-fatal myocardial infarction in elderly people by about 20%, and in younger people by about 14%. Data from the longitudinal epidemiological study in Framingham showed that left ventricular hypertrophy diagnosed by echocardiography is associated with a twofold increased risk in death in women and a 1.5-fold increased risk in men over a 4-year period.

Diabetes mellitus

This is a major risk factor for premature vascular disease, stroke, myocardial infarction and death. Diabetes increases the risk of developing coronary heart disease by 1.5 times at age 40–49 and by 1.7 times at age 50–59 in men and by 3.7 times at age 40–49, and 2.4 times at age 50–59 in women. There are data that show that diabetic control is important for cardiovascular risk, with correlations between cardiovascular events, ischaemic heart disease and death rate and glycosylated haemoglobin. Much more effective risk reduction is associated with aggressive treatment of the commonly associated hypertension, lipid abnormalities and obesity in the diabetic patient.

Obesity

Obesity has been increasing in epidemic proportions and confers a prognostic disadvantage. Those with body mass index (weight/ht^2) of 25–29 kg/m^2 are considered to be overweight and those >32 are classified as obese. The latter have a twofold relative increase in mortality from all causes and a threefold increase in cardiovascular death. One study showed that a high body mass index was associated with an increase risk of death per se, especially when it was present in young people aged 30–44 years. More recent evidence

suggests that waist circumference is an important independent risk factor as truncal or visceral obesity appears to be more atherogenic. An expanded waist circumference is a necessary criterion for the diagnosis of the metabolic syndrome, in addition to at least two of the other four criteria (Table 1.2).

Table 1.2 International Diabetes Federation definition of metabolic syndrome – focus on waist circumference.

Abdominal obesity plus at least two of the following:	>94 cm male, >80 cm female
Elevated triglycerides	≥1.7 mmol/l
Reduced HDL-cholesterol	<1.0 mmol/l male, 1.3 mmol/l female
Raised blood pressure	>130/80 mmHg
Raised fasting plasma glucose	≥5.6 mmol/l

HDL, High-density lipoprotein.

Despite the presence of the *obesity paradox* – overweight and obese patients with established cardiovascular disease seem to have a more favourable prognosis than leaner patients – there is data to support purposeful weight reduction in the prevention and treatment of cardiovascular diseases. Furthermore, interventional trials involving bariatric surgery for severe obesity have shown that significant weight reduction resulted in significantly reduced mortality.

Physical activity and fitness

There is a close inverse relationship between cardiorespiratory fitness and cardiac outcomes such as coronary disease and death. This can be readily assessed by exercise tolerance testing. Patients with a low level of cardiorespiratory fitness have a 70% higher risk for all-cause mortality and a 56% higher risk for coronary or cardiovascular events compared with those with a high level

of fitness. Those with intermediate levels of fitness have a 40% higher mortality risk and a 47% higher coronary or cardiovascular event rate than those with higher fitness. Following acute myocardial infarction or coronary artery bypass graft (CABG), cardiac rehabilitation programmes that promote exercise and weight loss can improve cardiometabolic risk profiles of patients.

Gender

Men have twice the cardiovascular mortality as women at all ages and in all parts of the world. This was thought to be related to the beneficial effect of female sexhormones, especially oestrogens, as the cardiovascular risk in women increases after the menopause. However, two large randomised controlled trials showed that hormone replacement therapy (HRT) did not reduce the cardiovascular risk in women; rather, the thrombotic effects of oestrogens precipitated fatal and non-fatal cardiovascular events, especially in the early years of treatment. Women appear to possess differently weighted risk factors than men for reasons that are unclear.

More recent data have shown strong associations of accelerated atherosclerosis with low levels of testosterone in men followed up for 4–8 years. Low testosterone level in men has been shown to be linked with increased mortality. Male HRT has not yet been shown to reduce cardiovascular risk, although results from animal studies are encouraging.

Psychosocial factors

Some psychosocial factors double the risk of developing cardiovascular disease. Social class has an important effect on mortality from heart disease with people in low-income groups having an excess mortality compared with high-income earners. This is not simply related to deprivation.

Within the same working cohort (e.g. Whitehall civil servants), cardiovascular events and mortality were found to be 2–3 times higher in those workers with low socioeconomic status compared with those with high socioeconomic status. In fact, there is little relationship between actual average income and life expectancy. It is not just a matter of money. Mortality is 2–3 times higher in people with poor social links than in those with good social support networks. The reasons are unclear but they are not explained by differences in other known risk factors such as smoking.

Depression

Depression carries an adverse prognosis, especially in association with coronary artery disease and is associated with an eightfold increase in cardiovascular death. Patients with depression have a fivefold increased mortality after acute myocardial infarction. There are no data to suggest that treatment of depression with any specific therapy reverses the excess mortality. Depression also influences the outcome after coronary artery bypass surgery. After controlling for age, sex, number of grafts, diabetes, smoking, left ventricular ejection fraction and previous myocardial infarction, moderate or severe depression at the time of surgery increased the risk of death by 2.4 times, and mild to moderate depression that persisted for 6 months conferred a 2.2 times increased risk of death, during a 5-year follow-up period.

How to assess cardiovascular risk

Cardiovascular risk stratification is carried out through clinical history, physical examination and serum biomarkers.