Essential Cardiology

Essential Cardiology

Principles and Practice

SECOND EDITION

Edited by

Clive Rosendorff, MD, PhD, FRCP

Professor of Medicine, Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, and Veterans Affairs Medical Center, Bronx, NY

Humana Press
Totowa, New Jersey

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

www.humanapress.com

Cover design by Patricia F. Cleary
Cover illustration by Colin Richards. Used with permission of the artist.

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341; E-mail: orders@humanapr.com; or visit our Website: www.humanapress.com

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN 1-59259-918-4

Library of Congress Cataloging-in-Publication Data
Essential cardiology : principles and practice / edited by Clive Rosendorff.-- 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-58829-370-X (alk. paper)
1. Heart--Diseases. 2. Cardiology.
[DNLM: 1. Cardiovascular Diseases--Outlines. 2. Cardiovascular Physiology--Outlines. WG 18.2 E78 2005] I. Rosendorff, Clive.
RC681.E85 2005
616.1'2--dc22

2005006266

PREFACE

This second edition reflects the very rapid advances that have been made in our understanding and management of cardiovascular disease since the first edition was published in 2001. All of the chapters have been extensively reviewed and rewritten. There are now two chapters on acute coronary syndromes, reflecting the modern classification: one on unstable angina pectoris and non-ST-segment elevation myocardial infarction, and the other on ST-segment elevation myocardial infarction. Otherwise the format of the first edition has been retained, to include sections on epidemiology, cardiovascular function, examination and investigation of the patient, disorders of rhythm and conduction, heart failure, congenital heart disease, coronary artery disease, valvular heart disease, hypertension, and other conditions affecting the heart. I am also very happy to welcome Drs. Arnold M. Katz, Martin M. Goldman, David Benditt, Edward K. Kasper, and Roger J. Hajjar as new senior authors.

I wish also to thank Pedro Perez for his superb contributions to the artwork, my assistants, Maria Anthony and Anitra Collins, and Paul Dolgert, John Morgan, Patricia Cleary, and Donna Niethe, and the editorial, production, and composition departments of Humana Press for their encouragement and hard work.

Clive Rosendorff, ***MD, PhD, FRCP***

Preface to the First Edition

"A big book," said Callimachus, the Alexandrian poet, "is a big evil!" Not always. There are some excellent, very big encyclopedias of cardiology, wonderful as works of reference. There are also many small books of cardiology, "handbooks" or "manuals," which serve a different purpose, to summarize, list, or simplify. This book is designed to fill a large gap between these extremes, to provide a textbook that is both substantial and readable, compact and reasonably comprehensive, and to provide an intelligent blend of molecular, cellular, and physiologic concepts with current clinical practice.

A word about the title. "Essential" is used here not in the sense of indispensable or absolutely required in all circumstances, for there is much more here than the generalist needs in order to practice good medicine, especially if there is easy access to a cardiology consultant. Rather, the word as used here denotes the essence or distillation or fundamentals of the mechanisms and practice of cardiology. The "Principles and Practice" subtitle affirms the idea that theory without a practical context may be academically satisfying but lacks usefulness, and practice without theory is plumbing. Good doctors understand the basic science foundation of what they do with patients, and great doctors are those who, as researchers or as teachers, see new connections between the basic sciences and clinical medicine.

I have been very fortunate to be able to assemble a team of great doctors who are outstanding physicians and scientists, most of them internationally recognized for their leadership position in their areas of specialization. They represent a careful blend of brilliance and experience, and, most of all, they all write with the authority of undoubted experts in their fields. They have all been asked to write up-to-date reviews of their respective areas of expertise, at a level that will be intelligible to noncardiologists as well as cardiologists, to medical students, internal medicine residents, general internists, and cardiology fellows. I believe that they have succeeded brilliantly, and I know that they are all very proud to have participated as authors in this project, the first textbook of cardiology of the new millennium. I am deeply grateful to all of them for the care and enthusiasm with which they carried out this task.

The organization of the book reflects pretty much the key issues that concern cardiologists and other internists at present; I have no doubt that the field will develop and change in time so that many of the modes of diagnosis and therapy described here will become much more prominent (such as gene therapy), while others may diminish or even disappear. This is what second or later editions of textbooks are for.

***Clive Rosendorff,** MD, PhD, FRCP*

CONTENTS

Preface ..... *v*

Preface to First Edition ..... *vii*

Contributors ..... *xiii*

Color Plates ..... *xix*

Part I. EPIDEMIOLOGY

1 Multivariable Evaluation of Candidates for Cardiovascular Disease
William B. Kannel *3*

Part II. CIRCULATORY FUNCTION

2 Molecular and Cellular Basis of Myocardial Contractility
Arnold M. Katz *21*

3 Ventricular Function
Lionel H. Opie *37*

4 Vascular Function
Clive Rosendorff *55*

5 Thrombosis
Yale Nemerson and Mark B. Taubman *77*

Part III. EXAMINATION AND INVESTIGATION OF THE PATIENT

6 The Medical History and Symptoms of Heart Disease
H. J. C. Swan *87*

7 Physical Examination of the Heart and Circulation
Jonathan Abrams *99*

8 Electrocardiography
Tara L. DiMino, Alexander Ivanov, James F. Burke, and Peter R. Kowey *117*

9 Echocardiography
Daniel G. Blanchard and Anthony N. DeMaria *139*

10 Exercise Testing
Gregory Engel and Victor Froelicher *169*

11 Radiology of the Heart
Gautham P. Reddy and Robert M. Steiner *185*

12 Cardiac Catheterization and Coronary Angiography
Mark J. Ricciardi, Nirat Beohar, and Charles J. Davidson *197*

13 Nuclear Imaging in Cardiovascular Medicine
Diwakar Jain and Barry L. Zaret *221*

14 Cardiovascular Magnetic Resonance and X-Ray Computed Tomography
Gerald M. Pohost, Radha J. Sarma, Patrick M. Colletti, Mark Doyle, and Robert W. W. Biederman *245*

15 Choosing Appropriate Imaging Techniques
Jonathan E. E. Fisher and Martin E. Goldman *269*

Part IV. DISORDERS OF RHYTHM AND CONDUCTION

16 Electrophysiology of Cardiac Arrhythmias
Sei Iwai, Steven M. Markowitz, Suneet Mittal, Kenneth M. Stein, and Bruce B. Lerman *285*

17 Treatment of Cardiac Arrhythmias
Davendra Mehta *305*

18 Syncope
Fei Lü, Scott Sakaguchi, and David G. Benditt *329*

Part V. HEART FAILURE

19 Pathophysiology of Heart Failure
Mark Scoote, Ian F. Purcell, and Philip A. Poole-Wilson *347*

20 Treatment of Congestive Heart Failure
Stephen S. Gottlieb *371*

Part VI. CONGENITAL HEART DISEASE

21 Congenital Heart Disease
Julien I. E. Hoffman *393*

Part VII. CORONARY ARTERY DISEASE

22 Pathogenesis of Atherosclerosis
Prediman K. Shah *409*

23 Risk Factors and Prevention, Including Hyperlipidemias
Antonio M. Gotto, Jr. and John Farmer *419*

24 Coronary Blood Flow and Myocardial Ischemia
Robert J. Henning and Ray A. Olsson *439*

25 Stable Angina
Satya Reddy Atmakuri, Michael H. Gollob, and Neal S. Kleiman *451*

26 Unstable Angina and Non-ST Segment Elevation Myocardial Infarction (Acute Coronary Syndromes)
Satya Reddy Atmakuri and Neal S. Kleiman *471*

27 ST Segment Elevation Myocardial Infarction
Rajat Deo, Christopher P. Cannon, and James A. de Lemos ***489***
28 Cardiopulmonary Resuscitation
Joseph P. Ornato ***521***
29 Rehabilitation After Acute MI
Fredric J. Pashkow ***531***

Part VIII. VALVULAR HEART DISEASE

30 Rheumatic Fever and Valvular Heart Disease
Edmund A. W. Brice and Patrick J. Commerford ***545***
31 Infective Endocarditis
Adolf W. Karchmer ***565***

Part IX. HYPERTENSION

32 Hypertension: *Mechanisms and Diagnosis*
Clive Rosendorff ***595***
33 Hypertension Therapy
Norman M. Kaplan ***615***

Part X. OTHER CONDITIONS AFFECTING THE HEART

34 Cardiomyopathies and Myocarditis
Edward K. Kasper ***641***
35 Pericardial Disease
David H. Spodick ***653***
36 Pulmonary Vascular Disease
Dermot O'Callaghan and Sean P. Gaine ***661***
37 Diseases of the Aorta
Eric M. Isselbacher ***681***

Part XI. ADDITIONAL TOPICS

38 Pregnancy and Cardiovascular Disease
Samuel C. B. Siu and Jack M. Colman ***693***
39 Heart Disease in the Elderly
Michael W. Rich ***705***
40 Cardiovascular Complications in Patients With Renal Disease
Richard A. Preston, Simon Chakko, and Murray Epstein ***729***
41 Assessment of Patients With Heart Disease for Fitness for Noncardiac Surgery
Joseph Savino and Lee A. Fleisher ***747***

42 Cardiovascular Gene and Cell Therapy
Eddy Kizana, Federica del Monte, Sian E. Harding, and Roger J. Hajjar *763*

43 Preventive Cardiology
Michael Miller *789*

44 Peripheral Arterial Disease
James J. Jang and Jonathan L. Halperin *807*

Index *829*

Contributors

Jonathan Abrams, MD • *Interim Section Chief of Cardiology, Professor of Medicine, University of New Mexico, School of Medicine, Albuquerque, NM*

Satya Reddy Atmakuri, MD • *Cardiology Fellow, The Methodist DeBakey Heart Center, Baylor College of Medicine, Houston, TX*

David G. Benditt, MD • *Professor of Medicine, Cardiovascular Division, University of Minnesota Medical School, Minneapolis, MN*

Nirat Beohar, MD • *Assistant Professor of Medicine, Northwestern Cardiovascular Institute, Northwestern Memorial Hospital, Northwestern University, Chicago, IL*

Robert W. W. Biederman, MD, FACC • *Director Cardiac MRI, Allegheny General Hospital; Assistant Professor of Medicine, Drexel College of Medicine, Pittsburgh, PA*

Daniel G. Blanchard, MD, FACC • *Professor of Medicine, University of California, San Diego, School of Medicine, and UCSD Medical Center; Director, Cardiology Fellowship Program and Chief of Clinical Cardiology, UCSD Thornton Hospital, San Diego, CA*

Edmund A. W. Brice, MB ChB, PhD, FCP (SA) • *Senior Lecturer, Department of Medicine, University of Stellenbosch; Cardiologist, Tygerberg Academic Hospital, Cape Town, South Africa*

James F. Burke, MD, FACC • *Clinical Assistant Professor of Medicine, Jefferson Medical College, Philadelphia; Director, Cardiovascular Disease Fellowship Program, The Lankenau Hospital, Wynnewood, PA*

Christopher P. Cannon, MD • *Associate Professor of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Simon Chakko, MD, FACP, FACC • *Chief, Cardiology Section, Miami Veterans Affairs Medical Center; Professor of Medicine, Department of Medicine, University of Miami School of Medicine, Miami, FL*

Patrick M. Colletti, MD • *Professor of Radiology, University of Southern California, Keck School of Medicine; Chief of MRI, USC Imaging Science Center, Los Angeles, CA*

Jack M. Colman, MD, FRCPC, FACC • *Staff Cardiologist, University Health Network and Mount Sinai Hospitals; Staff Cardiologist, Toronto Congenital Cardiac Centre for Adults; Associate Professor (Medicine), University of Toronto, Toronto, Canada*

Patrick J. Commerford, MB ChB, FCP (SA) • *Professor and Head of the Division of Cardiology, University of Cape Town; New Groote Schuur Hospital, Cape Town, South Africa*

Charles J. Davidson, MD • *Professor of Medicine, Northwestern Cardiovascular Institute, Northwestern Memorial Hospital, Northwestern University, Chicago, IL*

Federica del Monte, MD, PhD • *Cardiology Division, Harvard Medical School; Cardiology Laboratory of Integrative Physiology and Imaging, Massachusetts General Hospital; Cardiovascular Research Center, Charlestown, MA*

Anthony N. DeMaria, MD • *Professor of Medicine, Judith and Jack White Chair in Cardiology, Division of Cardiovascular Medicine, University of California, San Diego, School of Medicine; Director, Cardiovascular Center, UCSD Medical Center, San Diego, CA*

Rajat Deo, md • *Cardiology Fellow, University of Texas Southwestern Medical Center, Dallas, TX*

Tara L. DiMino, md • *Cardiology Fellow, The Lankenau Hospital and Institute for Medical Research, Wynnewood, PA*

Mark Doyle, phd • *Cardiac MRI Physicist, Allegheny General Hospital, Pittsburgh, PA*

Gregory Engel, md • *Cardiology Fellow, Cardiac Electrophysiology, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA*

Murray Epstein, md • *Professor of Medicine, Department of Medicine, University of Miami School of Medicine, Miami, FL*

John Farmer, md • *Associate Professor of Medicine, Baylor College of Medicine; Chief, Section of Cardiology, Ben Taub Hospital, Houston, TX*

Jonathan E. E. Fisher, md • *Department of Medicine (Cardiology), Mount Sinai School of Medicine, New York, NY*

Lee A. Fleisher, md, facc • *Robert D. Dripps Professor and Chair, Department of Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, PA*

Victor Froelicher, md • *Professor of Medicine, Stanford University School of Medicine; Cardiology Division, VA Palo Alto Health Care Systems, Palo Alto, CA*

Sean P. Gaine, md, phd, frcpi • *Consultant Respiratory Physician, National Pulmonary Hypertension Unit, Mater Misericordiae Hospital, University College Dublin, Dublin, Ireland*

Michael H. Gollob, md, frcpc • *Assistant Professor, Department of Medicine, University of Ottawa, Ottawa, Canada*

Martin E. Goldman, md • *Dr. Arthur and Hilda Master Professor of Medicine (Cardiology); Director, Echocardiography Laboratory, Zena and Michael A. Wiener Cardiovascular Institute, Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, NY*

Stephen S. Gottlieb, md • *Professor of Medicine, University of Maryland School of Medicine; Director, Heart Failure and Transplantation, University of Maryland Hospital, Baltimore, MD*

Antonio M. Gotto, Jr., md, dphil • *The Stephen and Suzanne Weiss Dean, Professor of Medicine, Weill Medical College of Cornell University, New York, NY*

Roger J. Hajjar, md, facc • *Associate Professor of Medicine, Harvard Medical School; Director, Cardiology Laboratory of Integrative Physiology and Imaging, Massachusetts General Hospital, Cardiovascular Research Center, Charlestown, MA*

Jonathan L. Halperin, md • *Robert and Harriet Heilbrunn Professor of Medicine (Cardiology), Mount Sinai School of Medicine; Director, Clinical Cardiology Services, The Zena and Michael A. Weiner, Cardiovascular Institute, The Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, New York, New York*

Sian E. Harding, phd • *Professor, National Heart Lung Institute, Imperial College, London, United Kingdom*

Robert J. Henning, md, facp, fccp, facc • *Professor of Medicine, Division of Cardiology, Department of Medicine, University of South Florida College of Medicine; James A. Haley Hospital, Moffitt Hospital, and Tampa General Hospital, Tampa, FL*

Julien I. E. Hoffman, md • *Professor Emeritus, University of California, San Francisco, CA*

Eric M. Isselbacher, md • *Medical Director, Thoracic Aortic Center, Massachusetts General Hospital; Assistant Professor of Medicine, Harvard Medical School, Boston, MA*

ALEXANDER IVANOV, MD • *Attending, Somerset Medical Center, Somerville; and Robert Wood Johnson University Hospital, New Brunswick, NJ*

SEI IWAI, MD • *Assistant Professor of Medicine, Weill Medical College of Cornell University, New York, NY*

DIWAKAR JAIN, MD • *Professor of Medicine, Director, Nuclear Cardiology Laboratory, Section of Cardiovascular Medicine, Drexel University College of Medicine, Philadelphia, PA*

JAMES J. JANG, MD • *Cardiology Fellow, Mount Sinai Medical Center, New York, NY*

WILLIAM B. KANNEL, MD, MPH, FACC • *Professor of Medicine and Public Health, Framingham Study/Boston University School of Medicine, Framingham, MA*

NORMAN M. KAPLAN, MD • *Clinical Professor of Medicine, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX*

ADOLF W. KARCHMER, MD • *Professor of Medicine, Harvard Medical School;Chief, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, MA*

EDWARD K. KASPER, MD, FACC • *Associate Professor of Medicine, Chief, Cardiology Division, Johns Hopkins Bayview Medical Center, Baltimore, MD*

ARNOLD M. KATZ, MD, DMed (Hon), FACP, FACC • *Professor of Medicine Emeritus, University of Connecticut School of Medicine, Farmington, CT; Visiting Professor of Medicine and Physiology, Dartmouth Medical School, Hanover, NH*

EDDY KIZANA, MB BS, FRACP • *Department of Cardiology and Gene Therapy Research Unit, Westmead Hospital, Westmead, New South Wales, Australia*

NEAL S. KLEIMAN, MD • *Associate Professor of Medicine, Director, Cardiac Catheterization Laboratories, The Methodist DeBakey Heart Center, Baylor College of Medicine, Houston, TX*

PETER R. KOWEY, MD, FACC • *Professor of Medicine, Jefferson Medical College, Philadelphia; Chief, Division of Cardiovascular Disease, Main Line Health Heart Center, Lankenau, Bryn Mawr; and Paoli Hospitals, Wynnewood, PA*

JAMES A. DE LEMOS, MD • *Coronary Care Unit Director, Parkland Memorial Hospital; Associate Professor of Medicine, University of Texas Southwestern Medical Center, Dallas, TX*

BRUCE B. LERMAN, MD • *Hilda Altschul Master Professor of Medicine; Chief, the Maurice and Corinne Greenberg Division of Cardiology; Director, Cardiac Electrophysiology Laboratory, Weill Medical College of Cornell University, New York, NY*

FEI LÜ, MD, PhD • *Assistant Professor of Medicine, Cardiovascular Division, Department of Medicine, University of Minnesota Medical School; Director, Cardiac Electrophysiology Laboratory, Fairview-University Medical Center, Minneapolis, MN*

STEVEN M. MARKOWITZ, MD • *Associate Professor of Medicine, Assistant Director, Cardiac Electrophysiology Laboratory, Weill Medical College of Cornell University, New York, NY*

DAVENDRA MEHTA, MD, PhD, FRCP, FACC • *Director, Cardiac Electrophysiology Section, Cardiovascular Institute; Associate Professor of Medicine, Mount Sinai School of Medicine, New York, NY*

MICHAEL MILLER, MD, FACC, FAHA • *Associate Professor of Medicine, Epidemiology, and Preventive Medicine; Director, Center for Preventive Cardiology, University of Maryland Medical Center, Baltimore, MD*

SUNEET MITTAL, MD • *Associate Professor of Medicine, Weill Medical College of Cornell University, New York, NY*

YALE NEMERSON, MD • *Phillip J. and Harriet L. Goodhart Professor of Medicine, Professor of Biochemistry, Mount Sinai School of Medicine, New York, NY*

DERMOT O'CALLAGHAN, MD • *Specialist Registrar in Respiratory Medicine, National Pulmonary Hypertension Unit, Mater Misericordiae University Hospital, University College Dublin, Dublin, Ireland*

RAY A. OLSSON, MD, FACP, FACC, Ch Chem, FRSC • *Professor of Medicine, Ed C. Wright Professor of Cardiovascular Research, Department of Internal Medicine, University of South Florida College of Medicine, Tampa, FL*

LIONEL H. OPIE, MD, DPhil, FRCP • *Professor of Medicine, Department of Medicine, University of Cape Town Medical School; Director, Hatter Institute, Cape Heart Center, Cape Town, South Africa*

JOSEPH P. ORNATO • MD, FACP, FACC, FACEP • *Professor and Chairman, Department of Emergency Medicine, Virginia Commonwealth University Medical Center, Richmond, VA*

FREDRIC J. PASHKOW, MD • *Clinical Professor of Medicine, Department of Medicine, John A. Burns School of Medicine, University of Hawaii; Senior Medical Director, Cardiovascular Thrombosis Medical Affairs, Sanofi-Aventis, Honolulu, HI*

GERALD M. POHOST, MD • *Chief of Cardiovascular Medicine, University of Southern California, Division of Cardiovascular Medicine, Los Angeles, CA*

PHILIP A. POOLE-WILSON, MD, FRCP, FESC, FACC • *Professor of Cardiology, Department of Cardiac Medicine, National Heart and Lung Institute, Imperial College, London, London, United Kingdom*

RICHARD A. PRESTON, MD, MBA • *Director, Division of Clinical Pharmacology, Department of Medicine, University of Miami School of Medicine, Miami, FL*

IAN F. PURCELL, MD, MRCP • *Consultant Cardiologist, Freeman Hospital, Newcastle upon Tyne, United Kingdom*

GAUTHAM P. REDDY, MD, MPH • *Assistant Professor of Radiology, University of California, San Francisco, San Francisco, CA*

MARK J. RICCIARDI, MD • *Assistant Professor of Medicine, Northwestern Cardiovascular Institute, Northwestern Memorial Hospital, Northwestern University, Chicago, IL,*

MICHAEL W. RICH, MD • *Associate Professor of Medicine, Cardiovascular Division, Department of Medicine, Washington University School of Medicine; Director, Cardiac Rapid Evaluation Unit, Barnes-Jewish Hospital, St. Louis, MO*

CLIVE ROSENDORFF, MD, PhD, FRCP, FACP, FACC • *Professor of Medicine, Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York; VA Medical Center, Bronx, NY*

SCOTT SAKAGUCHI, MD • *Associate Professor of Medicine, Cardiovascular Division, Department of Medicine; Director, Cardiac Electrophysiology Fellowship Program, University of Minnesota Medical School, Minneapolis, MN*

RADHA J. SARMA, MD, FACC, FAHA, FACP • *Associate Professor of Clinical Medicine, University of Southern California, Keck School of Medicine; Director, Exercise Lab, and Associate Director of Echocardiography Lab, LAC and USC Medical Center, Los Angeles, CA*

JOSEPH SAVINO, MD • *Associate Professor, Department of Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, PA*

MARK SCOOTE, MB BS, BSc, MRCP • *British Heart Foundation Clinical Research Fellow, Department of Cardiac Medicine, National Heart and Lung Institute, Imperial College London, London, United Kingdom*

PREDIMAN K. SHAH, MD • *Shapell and Webb Chair and Director, Division of Cardiology and Atherosclerosis Research Center, Cedars Sinai Medical Center; Professor of Medicine, David Geffen School of Medicine, UCLA, Los Angeles, CA*

SAMUEL C. B. SIU, MD, SM, FRCPC, FACC • *Staff Cardiologist, Toronto Congenital Cardiac Centre for Adults; Director of Echocardiography, University Health Network and Mount Sinai Hospitals; Associate Professor (Medicine), University of Toronto, Toronto, Ontario*

DAVID H. SPODICK, MD, DSc, FACC, FAHA, MACP • *Professor of Medicine, Cardiovascular Division, University of Massachusetts Medical School, Worcester, MA*

KENNETH M. STEIN, MD • *Associate Professor of Medicine, Associate Director, Cardiac Electrophysiology Laboratory, Weill Medical College of Cornell University, New York, NY*

ROBERT M. STEINER, MD • *Professor of Radiology, Temple University School of Medicine; Attending Radiologist Temple University Hospital, Philadelphia, PA*

H. J. C. SWAN, MD, PhD • *Professor of Medicine (Emeritus), UCLA School of Medicine; Director (Emeritus) Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA (Deceased)*

MARK B. TAUBMAN, MD • *Professor of Medicine and Chief of Cardiology; Director, Center for Cellular and Molecular Cardiology, University of Rochester School of Medicine and Dentistry, Rochester, NY*

BARRY L. ZARET, MD • *Robert W. Berliner Professor of Medicine, Professor of Diagnostic Radiology; Chief, Section of Cardiovascular Medicine; Associate Chairman for Clinical Affairs, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT*

Color Plates

Color Plates follow p. 268.

Color Plate 1 Apical four-chamber images with color-flow Doppler during diastole and systole. Red flow indicates movement toward the transducer (diastolic filling); blue flow indicates movement away from the transducer (systolic ejection). RA, right atrium; RV, right ventricle; LV, left ventricle. (Chapter 9, Fig. 5; *see* full caption discussion on pp. 143–144. From ref. *1*, with permission.)

Color Plate 2 Parasternal long-axis image showing a multicolored jet (indicating turbulent flow) of aortic regurgitation in the left ventricular outflow tract. The jet is narrow in width, suggesting mild regurgitation. AO, aorta; LA, left atrium; LV, left ventricle. (Chapter 9, Fig. 11A; *see* complete figure and caption on p. 151 and discussion on pp. 150–151. From ref. *1*, with permission.)

Color Plate 3 Parasternal long-axis view in a case of severe mitral regurgitation. The color Doppler jet is directed posteriorly and is eccentric (black arrows). The jet "hugs" the wall of the left atrium (LA) and wraps around all the way to the aortic root (white arrows). LV, left ventricle. (Chapter 9, Fig. 13; *see* full caption on p. 154 and discussion on p. 152. From ref. *1*, with permission.)

Color Plate 4 Apical four-chamber view of an ostium secundum atrial septal defect. On the left, a defect in the mid-atrial septum is present (arrows). On the right, there is color flow through the shunt. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. (Chapter 9, Fig. 22A; *see* complete figure and caption on p. 164 and discussion on pp. 162–163. From ref. *1*, with permission.)

Color Plate 5 Exercise (Ex) and rest (R) ^{99m}Tc- sestamibi and exercise ^{18}FDG (Isch) images of a 67-yr-old man with angina and no prior myocardial infarction. There is a large area of partially reversible perfusion abnormality involving the septum, anterior wall, and apex (small arrows). Intense ^{18}FDG uptake is present in these areas (solid arrowheads). Coronary angiography showed 90% stenosis of the left anterior descending coronary artery and a 60% stenosis of the left circumflex artery. (Chapter 13, Fig. 10; *see* full caption on p. 239 and discussion on 238. Reproduced with permission from ref. *71*.)

Color Plate 6 Right atrial electroanatomical mapping of automatic atrial tachycardia. Timing of atrial electrograms is color-coded. Red areas represent sites of early activation. Application of radiofrequency current (blue dots) at the earliest site lead to termination of tachycardia. (Chapter 17, Fig. 2; *see* full caption on p. 311 and discussion on p. 310.)

Color Plate 7 Color-flow Doppler echocardiography demonstrates the high-velocity jet entering the left ventricle (arrow). (Chapter 30, Fig. 4; *see* full caption on p. 551 and discussion on p. 550.)

I EPIDEMIOLOGY

1 Multivariable Evaluation of Candidates for Cardiovascular Disease

William B. Kannel, MD, MPH

INTRODUCTION

A preventive approach to management of atherosclerotic cardiovascular disease (CVD) is needed because once CVD becomes manifest, it is often immediately lethal and those fortunate enough to survive seldom can be restored to full function. Prevention of the major atherosclerotic CVD events is now feasible because several modifiable predisposing risk factors have been ascertained that when corrected, can reduce the likelihood of such events occurring *(1,2)*. Multivariate risk formulations for estimating the probability of cardiovascular events conditional on the burden of a number of specified risk factors have been produced to facilitate evaluation of candidates for CVD in need of preventive management *(3–6)*.

The risk factor concept has become an integral feature of clinical assessment of candidates for initial or recurrent cardiovascular events. These risk factors represent associations that may or may not be causal. Most factors associated with an initial cardiovascular event are also predictive of recurrent episodes. The risk of a recurrent event is usually dominated by indicators of the severity of the first event, such as the number of arteries occluded or the amount of ventricular dysfunction, but other predisposing risk factors continue to play an important role. Risk factors enabling assessment of risk may be modifiable or nonmodifiable. The presence of nonmodifiable risk factors may nevertheless assist in risk assessment, and also may affect the degree of urgency for correction of modifiable risk factors (e.g., a strong family history of CVD).

Absent evidence from clinical trials, observational studies can provide evidence supporting a causal link between risk factors and CVD. Strong associations are less likely to be due to confounding and a causal relationship is more likely if exposure to the risk factor precedes the onset of the disease. Likewise, a causal relationship is likely if the association is dose-dependent and consistently demonstrated under diverse circumstances. Finally, the association should be biologically plausible.

Risk of CVD events is usually reported as a relative risk or as an odds ratio. Risk can also be expressed as an attributable risk by subtracting the rate in those without the risk factor from the rate in those who have it. For coronary disease risk factors, the absolute attributable risk increases with age, whereas the relative risk tends to decrease. The population-attributable fraction takes into account the prevalence of the risk factor as well as the risk ratio, assessing the impact of the risk factor on the incidence of disease in the population and the benefit of removing it from the population. An unimpressive risk-factor risk ratio can have a major public health impact because of its high prevalence in the general population.

Four decades of epidemiological research have identified a number of modifiable CVD risk factors that have a strong dose-dependent and independent relationship to the rate of development of atherosclerotic CVD *(2)*. Importantly, these risk factors can be readily ascertained from ordinary

From: *Essential Cardiology: Principles and Practice, 2nd Ed.*
Edited by: C. Rosendorff © Humana Press Inc., Totowa, NJ

Table 1
Risk of CVD Events According to Standard Risk Factors Framingham Study 36-Yr Follow-Up

	Age 35–64 yr				*Age 65–94 yr*			
	Rate/1000		*Rel. risk*		*Rate/1000*		*Rel. risk*	
CHD Risk Factors	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
High chol.	34	15	1.9[c]	1.8[b]	59	39	1.2[a]	2.0[c]
Hypertension	45	21	2.0[c]	2.2[c]	73	44	1.6[c]	1.9[c]
Diabetes	39	42	1.5[c]	3.7[c]	79	62	1.6[b]	2.1[c]
Smoking	33	13	1.5[b]	1.1[d]	53	38	1.0[d]	1.2[d]
ECG-LVH	79	55	3.0[c]	4.6[c]	134	94	2.7[c]	3.0[c]
ABI								
High chol.	3	2	1.0[d]	1.1[d]	10	12	1.0[d]	1.0[d]
Hypertension	7	4	5.7[c]	4.0[c]	20	17	2.0[c]	2.6[c]
Diabetes	7	4	3.0[c]	2.4[a]	20	28	1.6[d]	2.9[c]
Smoking	4	1	2.5[b]	1.0[d]	17	20	1.4[d]	1.9[c]
ECG-LVH	13	13	5.1[c]	8.1[c]	44	51	3.6[c]	5.0[c]
PAD								
High chol.	8	4	2.0[b]	1.9[d]	18	8	1.4[d]	1.0[d]
Hypertension	10	7	2.0[c]	3.7[c]	17	10	1.6[a]	2.0[b]
Diabetes	18	18	3.4[c]	6.4[c]	21	16	9.7[a]	2.6[b]
Smoking	9	5	2.5[c]	2.0[b]	18	11	8.5[b]	1.8[a]
ECG-LVH	16	17	2.7[b]	5.3[c]	36	14	23.7[b]	2.2[a]
CHF								
High chol.	7	4	1.2[d]	1.1[d]	21	18	1.0[d]	1.0[d]
Hypertension	14	6	4.0[c]	3.0[c]	33	24	1.9[c]	1.9[c]
Diabetes	23	21	4.4[c]	8.0[c]	40	51	2.0[c]	3.6[c]
Smoking	7	3	1.5[c]	1.1[d]	23	22	1.0[d]	1.3[a]
ECG-LVH	71	36	15.0[c]	13.0[c]	99	84	4.9[c]	5.4[c]

CHD, coronary heart disease; ABI, atherothrombotic brain infarction; PAD, peripheral artery disease; CHF, heart failure.

Rates are biennial per 1000 and age-adjusted. Risk ratios are age-adjusted.

Risk ratio, relative risk for persons with a risk factor versus those without it. For cholesterol >240 compared to <200 mg/dL. Hypertension >140/90 mmHg.

[a] $p < 0.05$.

[b] $p < 0.01$.

[c] $p < 0.001$.

[d] NS.

Source: ref. *41*. Copyright 1996; with permission from Elsevier.

office procedures. Framingham Study epidemiological research has documented several classes of risk factors such as atherogenic personal traits, lifestyles that promote them, signs of organ damage, and innate susceptibility. Most of the relevant risk factors are easy to assess during an office visit and include systolic blood pressure, blood lipids, glucose tolerance, cigarette smoking, and left ventricular hypertrophy on the electrocardiogram (ECG) *(2,7)*.

DISEASE-SPECIFIC EFFECTS

The impact of the standard established risk factors on atherosclerotic CVD events is displayed in Table 1. All the standard CVD risk factors contribute powerfully and independently to the rate of subsequent coronary disease in all its clinical manifestations. For atherothrombotic brain infarction, hypertension and ECG-left ventricular hypertrophy predominate and lipids appear to play a lesser role. For peripheral artery disease, glucose intolerance, left ventricular hypertrophy, and cigarette smoking are paramount, whereas cholesterol is less important. For heart failure, hyper-

Table 2
Development of Coronary Heart Disease
by Total/HDL Cholesterol Ratio Versus Total Cholesterol
According to Age 16 Yr Follow-up Framingham Study

	Total/HDL-C ratio (Quintile 5/Quintile 1)			*Total cholesterol (>240/<200 mg/dL)*	
AGE	*49–59*	*60–69*	*70–81*	*35–64*	*65–94*
Men	3.4[a]	2.9[a]	2.3[a]	1.9[c]	1.2[d]
Women	3.7[a]	6.7[a]	3.3[a]	1.8[b]	2.0[c]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
[d] NS.
Source: ref. *41*. Copyright 1996; with permission from Elsevier.

Table 3
Efficiency of Blood Lipids
and Ratios in Predicting Coronary Disease
Framingham Study Subjects Ages 50–80 Yr

	Age-adjusted Q_5/Q_1 risk ratios	
	Men	*Women*
Total cholesterol	1.9	2.5
LDL cholesterol	1.9	2.5
HDL cholesterol	0.4	0.5
Total/HDL cholesterol	2.5	3.1
LDL/HDL cholesterol	2.5	2.8

Q, quintiles of blood lipid distribution.
Source: ref. *42*. Copyright 1992; with permission from Elsevier.

tension, diabetes, and ECG-left ventricular hypertrophy (LVH) are all important, whereas total cholesterol appears to be unrelated (unless expressed as a total/HDL-cholesterol ratio). The standard risk factors also influence CVD rates with different strengths in men and women *(1,8,9)*. Some of the standard risk factors tend to have lower risk ratios in advanced age, but this reduced relative risk is offset by a high absolute incidence of disease in advanced age, making the standard risk factors highly relevant in the elderly.

REFINEMENTS IN STANDARD RISK FACTORS

The atherogenic potential of the serum total cholesterol derives from its LDL-cholesterol fraction, whereas its HDL component is protective and inversely related to the development of coronary disease *(10,11)*. The strength of the relation of total cholesterol to coronary disease declines after age 60 yr in men but the total/HDL-cholesterol ratio continues to predict events reliably in the elderly of both sexes (Table 2). It also predicts equally well at total cholesterol values above and below 240 mg/dL. This ratio has been found to be one of the most efficient lipid profiles for predicting cardiovascular events *(12,13)*. Comparing age-adjusted fifth to first quintile lipid CVD risk ratios for the individual lipids and their ratios it is evident that the total/HDL and LDL/HDL cholesterol ratios are much more powerful predictors of CHD than the individual lipids that comprise them (Table 3).

Table 4
Increment in Risk of CVD Events Per Standard Deviation Increase in Blood Pressure Components Framingham Study 30-Yr Follow-Up

	Standardized increment in risk			
	Men		*Women*	
Pressure component	*35–64 Yr*	*65–94 Yr*	*35–64 Yr*	*65–94 Yr*
Systolic	41%[a]	51%[a]	43%[a]	23%[a]
Diastolic	35%[a]	30%[a]	33%[a]	9%[b]
Pulse Pressure	29%[a]	42%[a]	36%[a]	22%[a]
Mean Arterial	41%[a]	44%[a]	42%[a]	18%[a]

[a] $p < 0.001$.
[b] p = NS.
Source: ref. *43*. Copyright 2000; with permission from Elsevier.

Table 5
Risk of CVD Events According to Pulse Pressure
30-Yr Follow-Up Framingham StudyAge-Adjusted Rate Per 1000

	Age 35–64		*Age 65–94*	
Pulse pressure (mmHg)	*Men*	*Women*	*Men*	*Women*
<40	9	4	2	17
40–49	13	6	16	19
50–59	16	7	32	22
60–69	22	10	39	25
>70	33	16	58	32
Increment per 10 mmHg	19.7%	20.9%	23.4%	10.5%

Source: ref. *43*. Copyright 2000; with permission from Elsevier.

Evaluation of hypertension now places more emphasis on the systolic blood pressure component and recognizes isolated systolic hypertension as a hazard for development of CVD. At all ages in either sex, for all the atherosclerotic CVD outcomes, systolic blood pressure has been shown to have a greater impact than the diastolic pressure (Table 4) *(14)*. Isolated systolic hypertension by definition denotes increased pulse pressure and risk of CVD increases stepwise with the pulse pressure at all ages in each sex (Table 5). Framingham Study data suggest an important role of the pulse pressure at any level of systolic blood pressure *(15)*. Reliance on the diastolic blood pressure to evaluate the risk of CVD in the elderly with an elevated systolic blood pressure can be misleading because counter to expectations of those who do, risk *increases* the *lower* the accompanying diastolic pressure *(15)*.

Diabetes and obesity are now conceptualized as components of an "insulin resistance or metabolic syndrome" consisting of abdominal obesity, elevated blood pressure, dyslipidemia, hyperinsulinemia, glucose intolerance, and abnormal lipoprotein lipase levels *(16)*. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) guidelines identify the metabolic syndrome as a target for therapy in the management of dyslipidemia *(17)*. The diagnosis of metabolic syndrome is designated when three or more of the following risk factors are present: waist circumference exceeding 88 cm in women or 102 cm in men, triglycerides of 150 mg/dL or greater, HDL-C under 40 mg/dL (men) or under 50 mg/dL (women), blood pressure of 130/85 mmHg or greater, and fasting plasma glucose of 110 mg/dL or greater. Using this definition of the metabolic syndrome, analysis of National Health and Nutrition Examintion Survey (NHANES) II data suggest a 23.7% age-adjusted prevalence of this syndrome in the US *(18)*.

Table 6
Impact of Diabetes on CVD Events in Men and Women 36-Yr Follow-Up Framingham Study Subjects Ages 35–64 Yr

	Age-adjusted biennial rate per 1000		*Age-adjusted risk ratio*		*Excess risk per 1000*	
CVD Events	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
CHD	39	21	1.5[a]	2.2[b]	12	12
PAD	18	18	3.4[b]	6.4[b]	13	15
CHF	23	21	4.4[b]	7.8[b]	18	18
STROKE	15	6	2.9[b]	2.6[b]	10	4
Total CVD	76	65	2.2[b]	3.7[b]	42	47

CHD, coronary heart disease; PAD, peripheral artery disease; CHF, heart failure.
[a]$p < 0.01$.
[b]$p < 0.001$.
Source: ref. *41*. Copyright 1996; with permission from Elsevier.

RISK FACTORS IN WOMEN

CVD risk factors are highly prevalent in middle-aged and elderly women. Two thirds of such women have at least one major risk factor. The national burden of atherosclerotic CVD is projected to increase substantially as elderly women constitute a progressively greater proportion of the US population. Women and men share the same CVD risk factors but some are more prevalent or exert a greater impact in women than in men. There are also some that are unique to women, such as early menopause and multiple pregnancies. With the exception of diabetes and ECG-LVH, the absolute risk for most risk factors is lower in women than men.

Because of the lower incidence of CVD in women than men, the most cost-effective preventive approach requires global risk assessment for targeting of high-risk women for preventive measures. Intensive risk factor screening is particularly needed for elderly women, African American women, and those of lower socioeconomic status. High total/HDL-cholesterol ratios, ECG-LVH, and diabetes markedly reduce the female coronary disease advantage *(9)*. Diabetes is clearly a greater CVD hazard for women than men virtually eliminating their advantage over men for coronary disease, heart failure, and peripheral artery disease (Table 6). Women with diabetes require comprehensive screening to detect the usually accompanying elevated triglyceride, reduced HDL cholesterol, hypertension, and abdominal obesity. Minority women and those with gestational diabetes, who are prone to develop an adverse coronary risk profile, deserve particular attention.

Reduced HDL cholesterol predicts coronary disease even better in women than in men. Women on average, have HDL-cholesterol levels that are 10 mg/dL higher than those in men throughout life so that it seems more appropriate to characterize "low" HDL cholesterol as under 50 mg/dL rather than 35 mg/dL, as was recommended in ATP II guidelines. Despite controversy about hypertriglyceridemia as an independent risk factor, it is an important marker for increased vulnerability to CVD for women as well as for men, and the combination of low HDL and high triglyceride, reflecting insulin resistance and presence of small-dense LDL, imparts an increased CVD risk. The majority of elderly women have hypertension, and isolated systolic hypertension is more prevalent in elderly women than in men. Its concordance with risk-enhancing high pulse pressure, obesity, dyslipidemia, and insulin resistance should be noted.

Risk factors unique to women include early menopause and bilateral oophorectomy. Estrogen replacement therapy has failed to eliminate the more than twofold increase in risk of coronary disease in this subgroup of women. Women who undergo early menopause require close surveillance for development of an adverse cardiovascular risk profile.

THE ELDERLY

The major modifiable risk factors remain relevant in the elderly. The strength of risk factors associated with CVD diminishes with advancing age, but this lower risk ratio is offset by a higher absolute risk. This makes risk factor control in the elderly at least as cost-effective as in the middle-aged. Epidemiologic research has quantified the impact of the standard CVD risk factors in the elderly *(19)*. Dyslipidemia, hypertension, glucose intolerance, and cigarette smoking all have smaller hazard ratios in advanced age, but this is offset by higher absolute and attributable risks. Diabetes operates more strongly in elderly women than men, further attenuating their waning advantage over men in advanced age (Table 1). Insulin resistance promoted by abdominal obesity in advanced age is an important feature of the CVD hazard of diabetes in the elderly. Hypertension, particularly the isolated systolic variety, is highly prevalent in the elderly, and is a safely modifiable hazard. Dyslipidemia, particularly the total/HDL cholesterol ratio, remains a major risk factor in the elderly that, in contrast to the total cholesterol, continues to be highly predictive in advanced age (Table 2). Left ventricular hypertrophy remains an ominous harbinger of CVD in the elderly, indicating an urgent need for attention to its promoters including hypertension, diabetes, obesity, and myocardial ischemia or valve disease. High-normal fibrinogen, C-reactive protein (CRP), and leukocyte counts in the elderly may indicate the presence of unstable atherosclerotic lesions. As in the middle-aged, all the major risk factors in the elderly tend to cluster so that the hazard of each one is powerfully influenced by the associated burden of the others. Multivariate risk assessment can quantify the joint effect of the burden of risk factors making it possible to more efficiently target elderly candidates for CVD for preventive measures *(3–6)*.

ATHEROSCLEROTIC COMORBIDITY

Atherosclerotic CVD is usually a diffuse process involving the heart, brain, and peripheral arteries. The presence of one clinical manifestation substantially increases the likelihood of having or developing others *(20)*. The major risk factors tend to affect all arterial territories and clinical atherosclerosis affecting the heart may also directly predispose to strokes and heart failure. Measures taken to prevent coronary disease should have an additional benefit in preventing atherosclerotic peripheral artery and stroke events as well as heart failure.

Coronary artery disease places a patient at considerable risk not only for a myocardial infarction, angina, sudden death, or heart failure, but also for transient ischemic attacks, strokes, and intermittent claudication because of concomitant atherosclerotic disease in the other vascular territories *(20)*. The incidence of other cardiovascular disease accompanying coronary disease is substantial *(21)*. The Framingham Study found that in men and women, respectively, an initial myocardial infarction is accompanied by intermittent claudication 9% and 10% of the time, by strokes or TIAs 5% and 8% of the time, and by heart failure 3% and 10% of the time *(21)*. Persons in the Framingham Study with intermittent claudication had a two- to threefold increased risk of developing coronary disease. Over 10 yr, 45% developed coronary heart disease. After an initial myocardial infarction, strokes and heart failure occurred at three to six times the rate of the general population. The 10-yr probability of a stroke or TIA was 16% in men and 24% in women, a rate three to four times that of the general population. Heart failure occurred in about 30% of patients who had experienced an MI, which represents a four- to sixfold increase in risk. After sustaining an atherothrombotic stroke, 25% to 45% developed coronary disease, a twofold increase in risk.

After an MI coexistence of intermittent claudication increased age-adjusted coronary mortality 1.7-fold in men and 1.5-fold in women, and of recurrent MI increased twofold in men and 1.6-fold in women *(21)*.

NOVEL RISK FACTORS

Because CVD often occurs in persons with what is considered acceptable or average standard risk factor values, novel risk factors are being sought. Among these are lipoprotein (a) (Lp[a]), homo-

cysteine, fibrinogen, small-dense LDL, insulin resistance, fibrinolytic function assessed by tPA and PAI-1 antigens, platelet function, and inflammatory parameters such as CRP *(22–24)*. The novel risk factors under consideration are characterized as emerging because information about their relevance is incomplete. There is no consensus about sensitive and specific diagnostic tests for many of these risk factors so that it is difficult to make recommendations for screening to detect high-risk persons. For some there is lack of consistent prospective epidemiologic evidence indicating that the novel marker can be detected in healthy persons prior to the onset of an initial cardiovascular event. Fibrinogen, Lp (a), CRP, and homocysteine may increase after a myocardial infarction, making interpretation of retrospective data speculative. To date, consistent prospective data are available for fibrinogen, CRP, tPA, and PAI-1. Prospective studies for Lp (a) and homocysteine have been both positive and negative. It is also not clear whether these novel risk factors add to our ability to predict events over and above that already achievable using the established cardiovascular risk factors. To date, data demonstrating the additive value of Lp (a) and homocysteine are inconsistent, whereas the inflammatory parameters such as fibrinogen and CRP have been shown to improve prediction. An additional uncertainty relates to whether the novel risk factor is modifiable and whether such modification reduces the likelihood of a cardiovascular event. Randomized trials are needed to determine whether specific therapies to modify these novel markers actually reduce the risk of CVD events. Enthusiasm for screening for these emerging risk factors must be tempered and should not supersede the need to deal more effectively with the established risk factors where there is a widely available methodology of measurement, a high population prevalence of the risk factors, a consistent prospective connection with the rate of development of CVD, and demonstrated benefit of correction in terms of reduced morbidity and mortality.

MULTIVARIATE RISK STRATIFICATION

Atherosclerotic CVD events can be efficiently predicted from risk factors that are readily ascertained through routine office procedures and laboratory tests *(3–6)*. Optimal risk predictions require quantitative synthesis of the various independently contributing risk factors into a composite estimate. For this purpose, multivariable risk formulations are employed to quantify the combined effect of these interrelated risk factors. This concept takes into account the multifactorial elements of CVD risk and the continuous gradient of response. This allows identification of high-risk persons with multiple mild to moderate risk factor aberrations, from whom most of the coronary events emerge. Categorical assessment of risk by assignment of arbitrary values to designate the point at which a continuous risk variable is to be considered a "risk factor" has some pragmatic utility, but this approach is inefficient because it overlooks the substantial high-risk segment of the population with multiple marginal abnormalities. Global risk assessment is also essential because the major risk factors tend to cluster together at four to five times the rate expected by chance so that when confronted with any particular risk factor one is obliged to seek out the others. Isolated occurrence of the standard risk factors is uncommon, ranging from 11% to 38% (Table 7).

Multivariable risk formulations can quantify the global risk based on the actual risk factor values over a wide range. For office use, scoring systems have been devised based on Framingham Study multivariable risk formulations that provide estimates of global risk for any combination of risk factors. The standard risk factors to be ascertained are total and HDL cholesterol, systolic blood pressure, cigarette smoking, diabetic status, and age for each sex. From the estimated rate of disease, based on the risk-factor makeup of the patient, compared to the average rate for persons of the same age, the urgency for treatment can be estimated without needlessly alarming patients with only one "risk factor" in isolation or falsely reassuring patients at high risk because of multiple marginal abnormalities. These risk formulations have been shown to accurately predict disease in a variety of population samples *(25–27)*.

Other risk factor information, important in implementing therapy, includes triglycerides, weight, physical activity, and family history, but does not greatly enhance risk estimation. Weight gain and abdominal obesity are particularly important because they are major determinants of risk factor

Table 7
Risk Factor Clustering in the Framingham Study
Offspring Cohort Subjects Ages 18–74 Yr

Index quintile variable (sex-specific)		*Percent with specified no. of additional risk factors*	
	Sex	*None*	*Two or more*
High cholesterol	Men	29%	43%
	Women	26%	57%
Low HDL-cholesterol	Men	27%	45%
	Women	38%	36%
High BMI	Men	23%	48%
	Women	15%	54%
High systolic BP	Men	25%	46%
	Women	19%	53%
High triglyceride	Men	11%	61%
	Women	20%	50%
High glucose	Men	23%	45%
	Women	29%	44%

Risk factors: upper quintile of distribution of all variables except HDL-C (lowest quintile).
Source: ref. *44*.

Table 8
Risk Factor Clustering According to Body Mass Index in the Framingham Study
Offspring Cohort With Elevated Blood Pressure Subjects Ages 18–74 Yr

Men		*Women*	
BMI (kg/m$^{2)}$	*Avg. no. risk factors*	*BMI (kg/m$^{2)}$*	*Avg. no. risk factors*
<23.7	1.68	<20.8	1.80
23.7–25.5	1.85	20.8–22.3	2.00
25.6–27.2	2.06	22.4–23.9	2.22
27.3–29.5	2.28	24.0–26.8	2.20
>29.5	2.35	>26.8	2.66

Risk factors are top quintiles of systolic blood pressure, total cholesterol, triglycerides, and glucose; and bottom quintile of HDL-cholesterol.
Source: ref. *43*. Copyright 2000; with permission from Elsevier.

clustering by promoting insulin resistance. The average number of standard risk factors acquired increases with body mass index in both sexes (Table 8).

Coronary Risk Profile

Coronary heart disease is the most common outcome of the standard risk factors, equaling in incidence all the other atherosclerotic CVD outcomes combined (Fig. 1). Because it is the most common and most lethal of the atherosclerotic sequelae of the standard risk factors, prevention of coronary disease deserves the highest priority. Multivariable coronary risk formulations have been developed based on continuous variable relationships to coronary disease outcome, and more recently integrating categorical approaches that have become part of the framework of blood pressure (JNC-VII) and cholesterol (NCEP) programs in the US *(28)*. This enables physicians to pull together all the relevant risk factor information into a composite estimate of the risk of having a coronary event and compare this to the average or optimal risk for persons of the same age and sex (Tables 9 and 10). The risk of developing coronary disease for any particular risk factor can be seen to vary widely depending on the burden of other associated risk factors in Fig. 2.

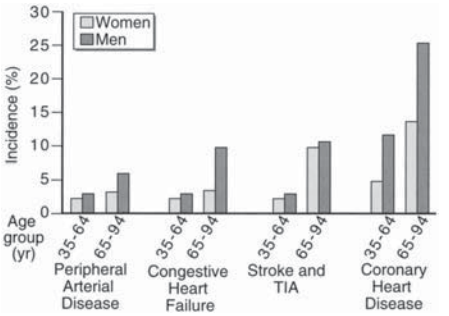


Fig. 1. Incidence of cardiovascular events by age and sex: Framingham Heart Study 36-yr follow-up. TIA, transient ischemic attack. (From ref. *41*. Copyright 1996; with permission from Elsevier.)

Stroke Risk Profile

A stroke, the most feared of the atherosclerotic diseases of the elderly, can also be risk-stratified in relation to the standard risk factors plus knowledge of the presence of coronary disease, heart failure, or atrial fibrillation (Table 11) *(4)*. The chief risk factor for a stroke is hypertension, but the risk associated with an elevated blood pressure varies over a 10-fold range depending on the degree of its coexistence with other risk factors that commonly accompany it (Fig. 3). Using the stroke risk profile table, it is possible to estimate the joint effect of any combination of the major predisposing factors in terms of the absolute and relative risk.

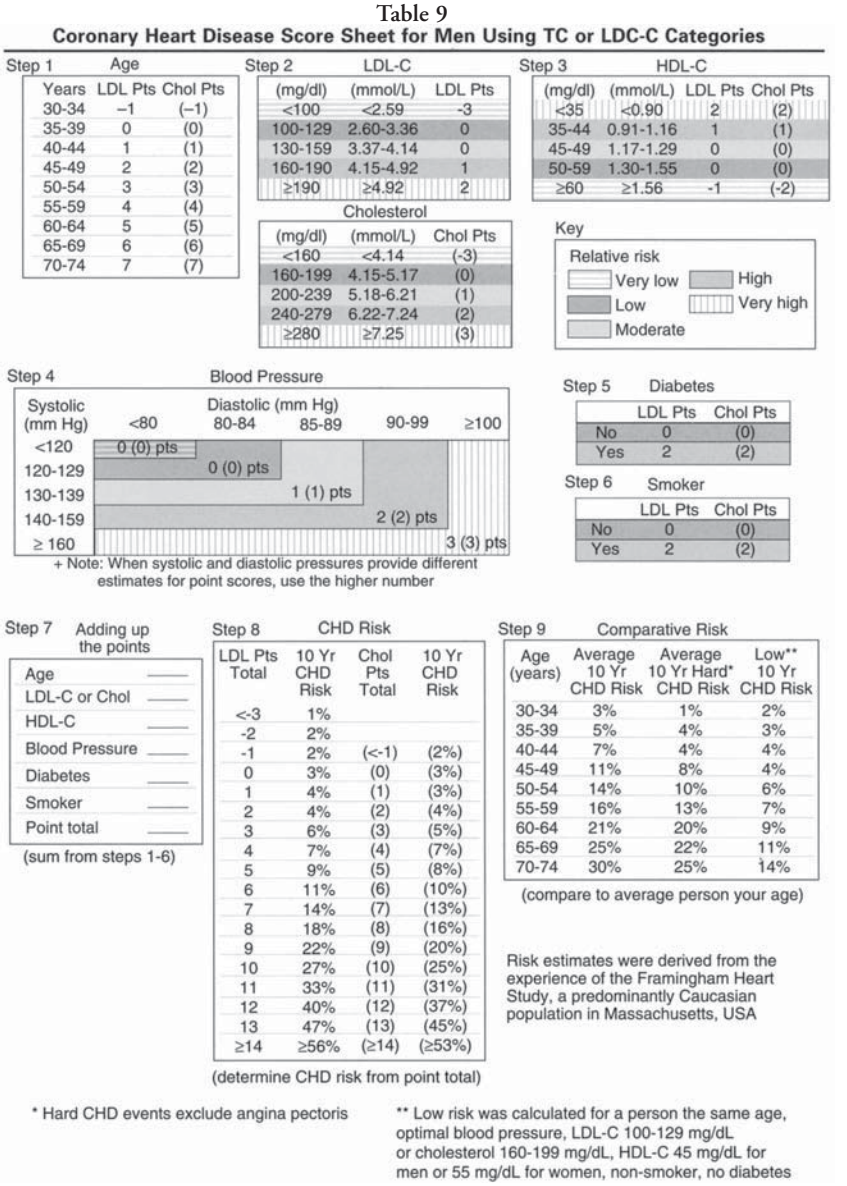
Heart Failure Profile

Heart failure is a lethal terminal stage of cardiac disease, with a survival experience resembling that of cancer *(29)*. A substantial reduction in the incidence and mortality from heart failure can be achieved only by the early detection and treatment of persons prone to left ventricular dysfunction so that it can be corrected before overt failure ensues. High-risk candidates for heart failure must be cost-effectively targeted for echocardiographic evaluation to detect the presence of left ventricular dysfunction. The Framingham Study has identified and quantified major contributing risk factors for the development of heart failure *(30)*. Using these, multivariable risk profiles have been developed that efficiently predict failure, providing risk estimates in those with the major predisposing conditions such as hypertension, coronary disease and valvular heart disease *(6)*. The ingredients of the profile consist of ECG-LVH, cardiomegaly on chest film, reduced vital capacity, heart rate, presence of heart murmurs, systolic blood pressure, and diabetes (Fig. 4). Using this risk assessment it is possible to identify high-risk candidates for heart failure who constitute good candidates for echocardiographic examination with a high likelihood of positive findings. Such persons stand to benefit from vigorous preventive measures such as therapy with angiotensin-converting enzyme (ACE)-inhibitors, cardiac revascularization, or valve surgery.

Profile for Peripheral Artery Disease

Using 38-yr follow-up data from the Framingham Study a risk profile for intermittent claudication was developed *(5)*. The variables needed are age, sex, serum cholesterol, blood pressure, cigarette smoking, diabetes, and coronary disease status (Table 12). Computation of multivariable risk using this risk profile allows physicians to identify high-risk candidates for development of peripheral artery disease and to educate such patients about modification of the cardiovascular risk factors. Identification of persons at risk of intermittent claudication is important not only because it limits mobility, and can lead to limb loss in those who develop it, but also because it is associated with a two- to fourfold excess of mortality, predominantly from CVD. The standard risk factors predict intermittent claudication even better than they predict coronary disease. Physicians can readily determine the probability of developing peripheral artery disease for each patient using a point score based on these risk factor data *(5)*.

Table 9
Coronary Heart Disease Score Sheet for Men Using TC or LDC-C Categories



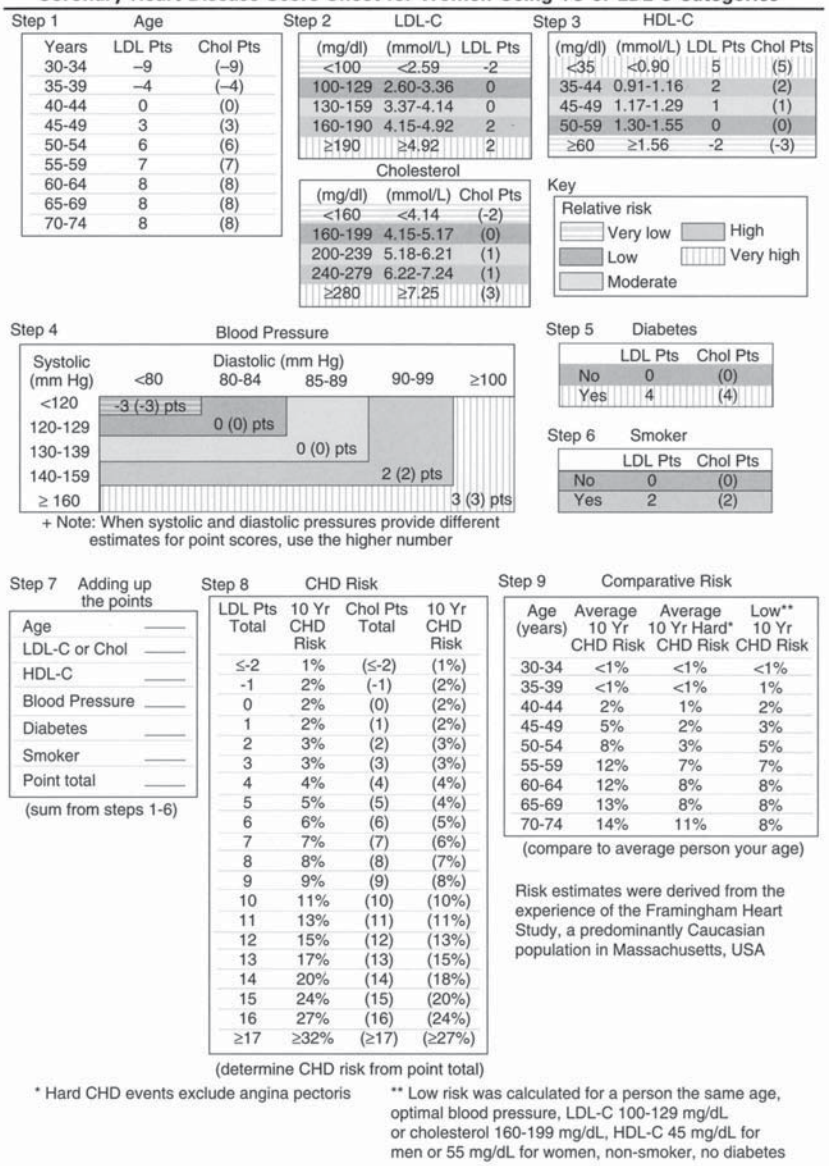
The scoring uses age, TC (or LDL-C), HDL-C, blood pressure, diabetes, and smoking and estimates risk for CHD over a period of 10 yr based on Framingham experience in men 30 to 74 yr old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC 160 to 199 mg/dL (or LDL 100 to 129 mg/dL), HDL-C of 45 mg/dL in men, no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurements are available. Pts indicates points. (TCA, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease.)

Source: ref. *45*. With permission from Lippincott Williams & Wilkins.

Risk Stratification of Existing Coronary Disease

Based on Framingham Study data, risk formulations have also been developed for predicting another coronary event, a stroke, or a death from cerebrovascular disease in persons who have already sustained a coronary event *(31)*. Risk of these adverse outcomes can be estimated from the

Table 10
Coronary Heart Disease Score Sheet for Women Using TC or LDL-C Categories



Scoring uses age, TC, HDL-C, blood pressure, diabetes, and smoking and estimates risk for CHD over a period of 10 yr based on Framingham experience in women 30 to 74 yr old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC 160 to 199 mg/dL (or LDL 100 to 129 mg/dL), HDL-C of 55 mg/dL in women, no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurements are available. Pts indicates points. (TCA, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease.)

Source: ref. *45*. With permission from Lippincott Williams & Wilkins.

joint effect of age, diabetic status, total and HDL cholesterol, and systolic blood pressure. The 2-yr probability of these events conditional on the risk factor burden in survivors of coronary events can be estimated over a wide range and compared to the average risk.

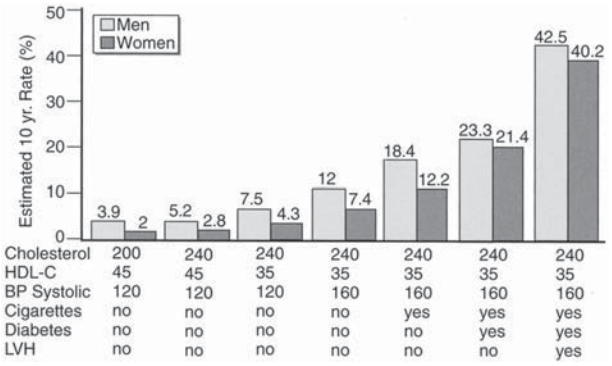


Fig. 2. Incidence of coronary heart disease: Framingham Heart Study 1972–1984, 42-yr-old adults. Reprinted from ref. *44*.

Table 11
Probability of a Stroke Within 10 Yr for Persons Age 55–85
Without a Previous Stroke Framingham Heart Study—Women

Points	*0*	*+1*	*+2*	*+3*	*+4*	*+5*	*+6*	*+7*	*+8*	*+9*	*+10*
Age	55	58	61	64	67	70	73	76	79	82	85
SBP	100	110	120	130	145	155	165	175	185	195	205
HypRx	No		M	F							
Diabetes	No		M	F							
Cigs	No			Yes							
CVD	No		F	M							
A.Fib.	No				M		F				
LVH	No				F		M				

Points	*10-yr. prob*	*Age (yr)*	*Av. 10-yr prob*
23	57%	60–64	5%
24	64%	65–69	7%
25	71%	70–74	11%
26	78%	75–79	16%
27	84%	80–84	24%

Source: ref. *4*; with permission from Lippincott Williams & Wilkins.

PREVENTIVE IMPLICATIONS

Comparison of the profiles for each of the various atherosclerotic CVD outcomes strongly suggests that correction of any particular set of risk factors imparts a bonus in reducing the risk of all outcomes. Reliance on single-risk-factor detection and treatment may be justified on a population basis, but is shortsighted on an individual basis. The goal in treating hypertension, diabetes, or dyslipidemia is not to simply correct these abnormalities but rather to prevent their CVD sequelae. They should be targeted for treatment from a multivariable risk profile and the goal of treatment should be to improve the global risk. Because of the tendency of all the established risk factors to cluster, it is imperative that physicians, when confronted with any particular risk factor, seek out the others likely to be present and take these into account in evaluating the risk and formulating the treatment regimen required.

A substantial proportion of the elderly warrant preventive measures because they are free of overt disease and active in their retirement years. Also, because of the aging of the general population it will be necessary to keep more of the elderly in the workforce, necessitating primary prevention of CVD. Because of the high average risk of CVD events in the elderly there is actually a great poten-

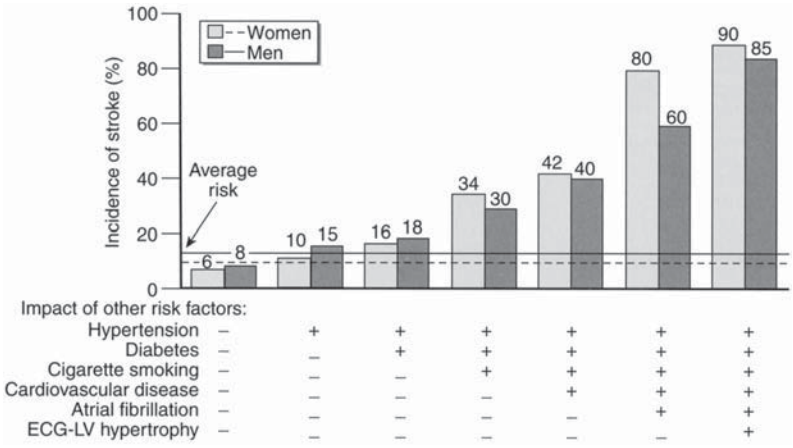


Fig. 3. The Framingham Heart Study: 10-yr probability of stroke, subjects aged 70 yr, systemic blood pressure 160 mmHg. ECG-LV, electrocardiographic left ventricular. (From ref. *4*; with permission from Lippincott Williams & Wilkins.)

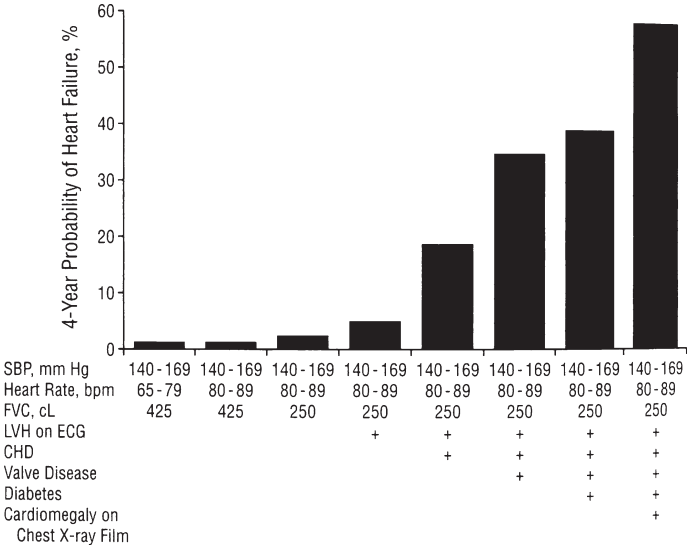


Fig. 4. Risk of heart failure in hypertensive men aged 60 to 64 yr by burden of associated risk factors after 38-yr follow-up in the Framingham Study. SBP indicates systolic blood pressure; FVC, forced vital capacity; LVH on ECG, left ventricular hypertrophy on electrocardiogram; and CHD, coronary heart disease. Plus sign indicates that patients in this category had this condition. (From ref. *6*. Copyright 1999 American Medical Association.)

tial benefit of preventive measures, but to avoid overtreatment it is important to assess multivariable risk and to take into account general heath status. There is little justification for pessimism about the efficacy of preventive measures in the elderly. The major risk factors can be safely modified without inducing intolerable side effects or adversely affecting the quality of the last years of life. The major risk factors remain highly relevant in the elderly not only for primary prevention but for secondary prevention as well.

Controlled trials have provided consistent evidence of the benefit of reducing elevated blood pressure and correcting dyslipidemia *(32,33)*. Lowering LDL and raising HDL cholesterol have been shown to slow progression of atherosclerosis. Primary prevention trials have shown consistent benefit for coronary disease by reducing LDL and raising HDL cholesterol even in persons with only average lipid values *(34,35)*.

Table 12
Regression Coefficients for Computation of Multivariable Risk of Intermittent Claudication

Variable	*β-coefficient*	*Standard error*
Intercept	–8.9152	0.5241
Male sex	0.5033	0.1134
Age	0.0372	0.0063
Blood pressure		
Normal	Referent	
High normal	0.2621	0.1769
Stage 1 HBP	0.4067	0.1559
Stage 2+ HBP	0.7977	0.1519
Diabetes	0.9503	0.1360
Cigarettes per day	0.0314	0.0039
Cholesterol (mg/dL)	0.0048	0.0010
CHD	0.9939	0.1160

Source: ref. *5*. With permission from Lippincott Williams & Wilkins.

Meta-analysis of hypertension trials indicates benefits of treatment of hypertension for overall vascular mortality, stroke morbidity and mortality, and fatal and nonfatal coronary events. Recent trials have also demonstrated the benefits of treating isolated systolic hypertension in the elderly for stroke, coronary disease, and heart failure *(36,37)*. Antiatherogenic recommendations for diabetes now focus on correction of the metabolically linked dyslipidemia and hypertension that usually accompany it. Weight control appears to be an important preventive measure for avoiding atherosclerotic CVD (Table 8). Because of difficulty in achieving sustained weight reduction, there is as yet no direct evidence that weight reduction reduces the risk of clinical cardiovascular events despite convincing evidence that slimming improves the entire cardiovascular risk profile. Persons who maintain optimal weight have a 35–60% lower risk of developing CVD than those who become obese.

Meta-analysis of the benefits of physical activity for coronary disease estimates a 50% reduction in risk that is attributable to exercise. Even moderate exercise appears to improve both the predisposing risk factors and risk of developing coronary disease. Although controlled trial data are lacking, observational data indicate that after cessation of smoking coronary disease risk declines to half that of those who continue to smoke. This benefit is observed in a matter of months without regard to the amount smoked or the duration of smoking. Quitting smoking deserves a high priority in prevention of CVD because it is ranked as a leading preventable cause of the disease.

Meta-analysis of randomized trials conducted in persons with clinical vascular disease has shown that low-dose aspirin can reduce the incidence of subsequent myocardial infarction, stroke, or cardiovascular mortality by about 25%. In primary prevention trials initial myocardial infarctions were reduced 33%. As a result, aspirin has been recommended for primary prevention in men who are at high risk of coronary disease.

Two recent trials of the efficacy of hormone replacement therapy have challenged our understanding of the influence of the menopause and the alleged protective role of estrogen against atherosclerotic CVD *(38,39)*. This confirmed the 1985 epidemiological prediction of the Framingham Study reported by Wilson et al. *(40)* who reported that despite control for the major CVD risk factors and a more favorable risk profile to begin with, women reporting estrogen use had a more than 50% excess of CVD morbidity and a two-fold increased risk of stroke. Increased myocardial infarction rates were also observed, particularly in those who smoked. Among nonsmokers, estrogen use was associated with a significant excess incidence of stroke. Importantly, the Framingham Study data did not show any CVD benefit of estrogen replacement therapy and concluded