Clive Rosendorff
Editor

Essential Cardiology

Principles and Practice

Third Edition

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Editor
Clive Rosendorff, MD, PhD, DScMed, FRCP,
FACC, FAHA
Department of Medicine
The Mount Sinai School of Medicine
The James J. Peters VA Medical Center
Bronx, NY, USA

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Preface to the Third Edition

This third edition reflects the very rapid advances that have been made in our understanding and management of cardiovascular disease since the first (2001) and second (2005) editions. All of the chapters from the second edition have been extensively reviewed and rewritten. There are new chapters on Cardiovascular Disease in Women, Diabetes and the Cardiovascular System, and Cardiovascular Disease in Cancer Patients, reflecting an increasing awareness of the special features and needs of these populations. With the very rapid developments in the molecular and cell biology of cardiovascular disease, the previous chapter on Cardiovascular Gene and Cell Therapy has been split into separate chapters on Cardiovascular Gene Therapy and Cardiovascular Cell Therapy. Otherwise, the general format of the second 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, other conditions affecting the heart (cardiomyopathies and myocarditis, pericardial disease, pulmonary vascular disease, diseases of the aorta), and special populations (women, pregnancy, elderly, renal disease, diabetes, cancer) and miscellaneous (preventive cardiology, peripheral vascular disease, preoperative assessment, gene therapy, cell therapy).

I am very happy to welcome Drs. Ralph B. D'Agostino, Rhian M. Touyz, Mark Crowther, Patrick T. O'Gara, Bruce B. Lerman, Francis E. Marchlinski, Martin R. Cowie, Michael A. Gatzoulis, John M. Canty, Jr., Arthur S. Leon, Ronald Victor, Bernhard Maisch, Nanette K. Wenger, Jolien W. Roos-Hesselink, Jorge Plutzky, Edward T. H. Yeh, and Piero Anversa as new senior authors. My thanks to all contributors for their part in producing an outstanding learning resource.

I also wish to acknowledge my assistant Indrawattie Naipal, the production editor Michael D. Sova, and the editorial, production, and composition departments of Springer, for their encouragement and hard work.

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 and 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, 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. 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 later editions of textbooks are for.

Clive Rosendorff, MD, PhD, DScMed, FRCP, FACC, FAHA

Contents

Contributors

Temilolu O. Aje, MD, MPH Division of Cardiology, Department of Medicine, University of Maryland, Baltimore, MD, USA

Piero Anversa, MD Division of Cardiovascular Medicine, Departments of Anesthesia and Medicine, Brigham and Women's Hospital, Boston, MA, USA

Farzana R. Bacchus, MD Department of Medicine, University of Toronto, Toronto, ON, Canada

David G. Benditt, MD Department of Medicine, Cardiac Arrhythmia Center, University of Minnesota Medical School, Minneapolis, MN, USA

Nirat Beohar, MD, FACC, FSCAI Division of Cardiology at Mount Sinai Medical Center, Department of Cardiology, Columbia University, Miami Beach, FL, USA

Daniel G. Blanchard, MD Division of Cardiovascular Medicine, UCSD Sulpizio Cardiovascular Center, San Diego Medical Center, University of California, La Jolla, CA, USA

Giovina Lara Bomba, MD Department of Cardiology, The Mount Sinai Hospital, New York, NY, USA

James F. Burke, MD, FACC Division of Cardiovascular Disease, Lankenau Medical Center, Wynnewood, PA, USA

John M. Canty Jr., MD Department of Medicine/Cardiovascular Medicine, University at Buffalo, Buffalo, NY, USA

Paul Cohen, MD, PhD Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Patrick J. Commerford, MB, ChB, FCP (SA), FACC Cardiac Clinic, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, Western Cape, South Africa

Odelia Cooper, MD Division of Endocrinology, Diabetes, and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Martin R. Cowie, MD, MSc, FRCP, FRCP (Ed), FESC Clinical Cardiology, National Heart and Lung Institute, Imperial College London (Royal Brompton Hospital), London, UK

Mark Crowther, MD Faculty of Health Sciences, St Joseph's Hospital, McMaster University, Hamilton, ON, Canada

Blanche J. Cupido, MB, ChB, FCP (SA) Cardiac Clinic, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, Western Cape, South Africa

Ralph B. D'Agostino Sr., PhD Department of Mathematics and Statistics, Boston University, Boston, MA, USA

Charles J. Davidson, MD Department of Medicine, Northwestern Memorial Hospital, Chicago, IL, USA

James A. de Lemos, MD Department of Cardiology, UT Southwestern Medical Center, Dallas, TX, USA

Anthony N. DeMaria, MD Division of Cardiovascular Medicine, UCSD Sulpizio Cardiovascular Center, San Diego Medical Center, University of California, San Diego, CA, USA

Oana Dickinson, MD Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Tara L. DiMino, MD, FACC Safety Evaluation and Risk Management, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Collegeville, PA, USA

Mark Doyle, PhD Department of Medicine, Allegheny General Hospital, Pittsburgh, PA, USA

David M. Dudzinski, MD, JD Departments of Cardiology and Medicine, Massachusetts General Hospital, Boston, MA, USA

Jonathan R. Enriquez, MD Department of Cardiology, University of Missouri-Kansas City, Kansas City, MO, USA

Murray Epstein, MD, FACP, FASH Division of Nephrology and Hypertension, University of Miami, School of Medicine, Miami, FL, USA

John A. Farmer, MD Department of Medicine (Cardiology), Baylor College of Medicine, Houston, TX, USA

Lee A. Fleisher, MD Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Victor Froelicher, MD Department of Cardiovascular Medicine, Stanford University Hospital and Clinics, Stanford, CA, USA

Sean P. Gaine, MD, PhD Department of Respiratory Medicine, Mater Misericordiae University Hospital, Dublin, Ireland

Michael A. Gatzoulis, MD, PhD Adult Congenital Heart Disease, Royal Brompton Hospital, London, UK

Martin E. Goldman, MD Department of Cardiology, Mount Sinai Medical Center, New York, NY, USA

Stephen S. Gottlieb, MD Department of Medicine, University of Maryland, Baltimore, MD, USA

Antonio M. Gotto Jr., MD, DPhil Department of Medicine, Weill Cornell Medical College, New York, NY, USA

Rajat Gupta, MD Department of Cardiovascular Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA

Roger J. Hajjar, MD Cardiovascular Research Center, Mount Sinai School of Medicine, New York, NY, USA

Jonathan L. Halperin, MD Department of Medicine (Cardiology), Mount Sinai School of Medicine, New York, NY, USA

Clinical Cardiology Services, The Zena and Michael A. Weiner Cardiovascular Institute, The Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, New York, NY, USA

Colleen M. Harrington, MD Department of Cardiology, Johns Hopkins Hospital, Baltimore, MD, USA

Eric M. Isselbacher, MD Cardiology Division, Massachusetts General Hospital, Boston, MA, USA

Alexander Ivanov, MD, FACC Department of Cardiology, Somerset Medical Center/ Robert Wood Johnson University Hospital, Somerville, NJ, USA

Sei Iwai, MD Division of Cardiology, Department of Medicine, Stony Brook University Medical Center, Stony Brook, NY, USA

Diwakar Jain, MD, FACC, FRCP, FASNC Section of Cardiology, New York Medical College, Westchester Medical Center, Valhalla, NY, USA

Mark R. Johnson, MBBS, PhD, MRCOG, MRCP Department of Obstetrics and Gynecology, Chelsea and Westminster Hospital, Imperial College School of Medicine, London, UK

Eoin P. Judge, MD Department of Respiratory Medicine, Mater Misericordiae University Hospital, Dublin, Ireland

Jan Kajstura, PhD Division of Cardiovascular Medicine, Departments of Anesthesia and Medicine, Brigham and Women's Hospital, Boston, MA, USA

William B. Kannel, MD, MPH, FACC (Deceased) Department of Medicine and Public Health, Framingham Study/Boston University School of Medicine, Framingham, MA, USA

Suraj Kapa, MD Department of Cardiac Electrophysiology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Norman M. Kaplan, MD Department of Cardiology, UT Southwestern Medical School, Dallas, TX, USA

Adolf W. Karchmer, MD Medicine/Infectious Disease Division, Beth Israel Deaconess Medical Center, Boston, MA, USA

Edward K. Kasper, MD, FACC, FAHA Department of Medicine/Cardiology, Johns Hopkins Medical Institutions, Baltimore, MD, USA

Arnold M. Katz, MD, DMed (Hon) University of Connecticut School of Medicine, Dartmouth Medical School, Harvard Medical School, Norwich, VT, USA

Hee-Won Kim, PhD Department of Radiology, University of Southern California, Los Angeles, CA, USA

Peter Kim, MD Department of Cardiology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Neal Kleiman, MD, FACC Cardiac Catheterization Laboratories, The Methodist Debakey Heart and Vascular Center, Houston, TX, USA

Department of Medicine, Weill Cornell Medical College, New York, NY, USA

Peter R. Kowey, MD, FACC, FAHA, FHRS Division of Cardiovascular Disease, Lankenau Medical Center, Wynnewood, PA, USA

Dimitra Krexi, MD Adult Congenital Heart Disease, Royal Brompton Hospital, London, UK

Thomas J. LaRocca, MD, PhD Department of Pediatrics, University of California, San Francisco, CA, USA

Arthur S. Leon, MS, MD Laboratory of Physiological Hygiene and Exercise Science, School of Kinesiology, University of Minnesota, Minneapolis, MN, USA

Norman Elliot Lepor, MD Cedars-Sinai Heart Institute, Beverly Hills, CA, USA

Annarosa Leri, MD Division of Cardiovascular Medicine, Departments of Anesthesia and Medicine, Brigham and Women's Hospital, Boston, MA, USA

Bruce B. Lerman, MD Division of Cardiology, Department of Medicine, Cornell University Medical Center, New York Presbyterian Hospital, New York, NY, USA

Benjamin D. Mackie, MD Department of Medicine (Cardiology), Emory University School of Medicine, Atlanta, GA, USA

Bernhard Maisch, MD, PhD Department of Internal Medicine and Cardiology, University Hospital Marburg (UKGM GmbH), Marburg, Hessia, Germany

Francis E. Marchlinski, MD Division of Cardiovascular Medicine, EPS Division, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Steven M. Markowitz, MD Division of Cardiology, Department of Medicine, Cornell University Medical Center, New York Presbyterian Hospital, New York, NY, USA

Sachin Mehta, MD Department of Cardiology, Baylor College of Medicine, Houston, TX, USA

Michael Miller, MD Division of Cardiology, Department of Medicine, University of Maryland, Baltimore, MD, USA

Augusto C. Montezano, PhD Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

Dermot O'Callaghan, MD Department of Respiratory Medicine, Mater Misericordiae University Hospital, Dublin, Ireland

Patrick O'Gara, MD Cardiovascular Department, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA

Lionel H. Opie, MD, DPhil, DSc Department of Medicine, Hatter Institute for Cardiovascular Research in Africa, University of Cape Town, Cape Town, South Africa

Joseph P. Ornato, MD, FACP, FACC, FACEP Department of Emergency Medicine, Virginia Commonwealth University, Richmond, VA, USA

Jorge Plutzky, MD Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Gerald M. Pohost, MD, FAHA, FACC Department of Radiology, Keck School of Medicine, University of Southern California, Beverly Hills, CA, USA

Department of Medicine, School of Medicine, Loma Linda University, Beverly Hills, CA, USA

Philip A. Poole-Wilson, MD, FRCP, FESC, FACC (Deceased) Department of Cardiac Medicine, National Heart and Lung Institute, Imperial College London, London, UK

Matina Prapa, MD Adult Congenital Heart Disease, Royal Brompton Hospital, London, UK

Venkata Krishna Puppala, MD, MPH Department of Medicine, Healtheast Care System, Minneapolis, MN, USA

Gautham P. Reddy, MD, MPH Department of Radiology, University of Washington Medical Center, Seattle, WA, USA

Mark J. Ricciardi, MD Department of Internal Medicine, University of New Mexico Hospital, Albuquerque, NM, USA

Michael W. Rich, MD Cardiovascular Division, Washington University School of Medicine, St. Louis, MO, USA

J.W. Roos-Hesselink, MD, PhD Department of Cardiology, Erasmus MC, Rotterdam, The Netherlands

Clive Rosendorff, MD, PhD, DScMed, FRCP, FACC, FAHA Department of Medicine, The Mount Sinai School of Medicine, The James J. Peters VA Medical Center, Bronx, NY, USA

Marcello Rota, PhD Division of Cardiovascular Medicine, Departments of Anesthesia and Medicine, Brigham and Women's Hospital, Boston, MA, USA

T.P.E. Ruys, MD Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands

Scott Sakaguchi, MD Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Joseph S. Savino, MD Department of Anesthesia and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Prediman K. Shah, MD Division of Cardiology, Cedars Sinai Heart Institute, Los Angeles, CA, USA

Robert M. Steiner, MD Department of Radiology, Temple University Health System, Philadelphia, PA, USA

Haowei (Linda) Sun, MD Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Sheldon W. Tobe, MD, MScCH (HPTE), FRCP (C), FACP, FASH Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Rhian M. Touyz, BSc (Hons), MSc (Med), PhD, MBBCh Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

Abhimanyu (Manu) Uberoi, MD, MS Department of Cardiovascular Medicine, Stanford University Hospital and Clinics, Stanford, CA, USA

Anselm Uebing, MD, PhD Adult Congenital Heart Disease, Royal Brompton Hospital, London, UK

Pimprapa Vejpongsa, MD Department of Cardiology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Ronald G. Victor, MD Department of Medicine, The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Gabriel Vorobiof, MD, FACC Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Christopher M. Walker, MD Department of Radiology, University of Washington, Kent, WA, USA

Brian R. Weil, PhD Department of Medicine/Cardiovascular Medicine, University at Buffalo, Buffalo, NY, USA

Nanette Kass Wenger, MD, MACC, MACP, FAHA Department of Medicine (Cardiology), Emory University School of Medicine, Atlanta, GA, USA

Edward T.H. Yeh, MD Department of Cardiology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Anthony F. Yu, MD Department of Cardiology, Mount Sinai Medical Center, New York, NY, USA

Shirin Zarafshar, MD Department of Internal Medicine, Stanford University Hospital and Clinics, Stanford, CA, USA

Barry L. Zaret, MD, FACC Section of Cardiology, Yale University School of Medicine, New Haven, CT, USA

Multivariable Evaluation of Candidates for Cardiovascular Disease

1

Ralph B. D'Agostino Sr. and William B. Kannel†

Introduction

A preventive approach to the management of atherosclerotic cardiovascular disease (CVD) is needed. Once CVD becomes manifest, it is often immediately fatal. It is the leading cause of death in the USA and across most of the world [1, 2]. Further, those fortunate enough to survive can seldom be restored to full function. Extensive epidemiologic research and controlled randomized clinical trials have identified modifiable predisposing risk factors which, when corrected, can reduce the likelihood of the occurrence of CVD [3–5]. Further, because it is a multifactorial disease with the risk factors interacting multiplicatively over time to promote CVD [6–8], the risk factors need to be assessed jointly. To accomplish this, multivariate risk prediction functions (algorithms) which estimate the probability of cardiovascular events conditional on the burden of specified risk factors have been produced to facilitate evaluation of candidates for CVD in need of preventive management [9–16].

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 risk factors associated with an initial cardiovascular event are also predictive of recurrent episodes [17]. While 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, other predisposing risk factors continue to play an important role [18]. Risk factors enabling assessment of risk may be modifiable or non-modifiable. The presence of non-modifiable risk factors may 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).

Much of the information on CVD risk factors come from prospective observational studies such as the Framingham Heart Study. 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 causality is further supported if the association is also 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 CVD 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. Physicians and patients often have difficulty interpreting relative risks and the other measures listed above [19–22]. For example, a relative risk of 20 sounds high, but if the incidence rate in the referent group is close to zero, the incidence rate will also be close to zero in the group with relative risk of 20. In contrast to this, a relative risk of 1.2 may sound small but could be very important when the incidence rate in the referent group is high. Responding to this difficulty,

R.B. D'Agostino Sr., FAHA (✉)
Department of Mathematics and Statistics, Boston University,
111 Cummington Street, Boston, MA 02215, USA
e-mail: ralph@bu.edu

W.B. Kannel†, MD, MPH, FACC
Department of Medicine and Public Health,
Framingham Study/Boston University School of Medicine,
Framingham, MA, USA

†deceased

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researchers and policy makers have shifted to absolute risks, that is, the absolute probabilities of developing CVD within a given time interval, when using risk prediction functions. These are easier to interpret and can be used for recommendations for interventions when individuals exceed unacceptable risk thresholds [14, 19–22].

Over six 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 [5, 9–17]. Importantly, these risk factors can be readily ascertained from ordinary office procedures. Framingham Study epidemiological research has documented classes of risk factors such as atherogenic personal traits, lifestyles that promote them, and innate susceptibility. Most of the relevant risk factors are easy to assess during an office visit and include systolic blood pressure, blood lipids (total and HDL cholesterol) diabetes status, and current smoking [5, 23]. These above listed risk factors in addition to age and sex are the standard CVD risk factors that are basic components in most risk prediction functions.

In the following, we summarize the data that established the standard risk factors. We then present the justification and need for multivariate evaluation and prediction functions along with some of its history. We illustrate them using examples of existing functions. Then we discuss the evaluation of the performance of the functions and the validity and transportability of existing functions. Then we end with the discussion of adding new variables (novel biomarkers) to risk prediction.

Establishing and Evaluating the Standard CVD Risk Factors

Disease-Specific Effects

CVD in this chapter is defined as coronary heart disease (CHD, consisting of myocardial infarction (MI), angina, coronary insufficiency, and angina), cerebrovascular disease (including stroke and transient ischemic attack (TIA)), peripheral artery disease (PAD), and congestive heart failure (CHF). Epidemiological cohort studies including the Framingham Study, which started in 1948, deliberately set out to identify the variables that relate to the development of CVD [6, 7]. The search was fruitful, and in 1961, William Kannel coined the term risk factors for what was identified [24]. These risk factors first were focused on CHD and then extended to the other components of CVD. Table 1.1 displays the event rates and age-adjusted relative risks of the dichotomized versions of the standard major risk factors (high cholesterol, hypertension, diabetes, and smoking) on various CVD events. Most relative risks are statistically significant. For CHD, all CVD risk factors contribute powerfully and independently to all its clinical manifestations. For atherothrombotic brain infarction (ABI), hypertension and diabetes predominate and lipids play a lesser role. For PAD, diabetes and cigarette smoking are paramount, with cholesterol being less important. For CHF, hypertension and diabetes are important, whereas total cholesterol appears to be unrelated. The standard risk factors also influence CVD rates with different strengths in men and women [4, 26, 27]. 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. Data such as these provided convincing evidence of the importance of these risk factors.

Refinements in Standard Risk Factors

The atherogenic potential of serum total cholesterol was determined to be derived from its LDL cholesterol fraction, and its HDL component proved to be protective and inversely related to the development of coronary disease [28, 29]. The strength of the relation of total cholesterol to coronary disease declines after age 60 years in men, but the total/HDL cholesterol ratio continues to predict events reliably in the elderly of both sexes (Table 1.2). 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 [30, 31]. 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 more powerful predictors of CHD than the individual lipids that comprise them (Table 1.3). However, knowledge of the individual (total and HDL-C) components is important, and in risk assessment and treatment recommendations, both are examined as two separate, but related, risk factors [14–16]. Also the joint consideration of HDL-C and non-HDL-C cholesterol is now common.

Evaluation of hypertension shifted from emphasis on diastolic blood pressure to 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 1.4) [34]. 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 1.5). Framingham Study data suggest an important role of the pulse pressure at any level of systolic blood pressure [35]. Reliance on the diastolic blood pressure to evaluate the risk of CVD in the

Table 1.1 Risk of CVD events according to standard risk factors Framingham Study 36-year follow-up

	Age 35–64 year				Age 65–94 year			
	Rate/1,000		Rel. risk		Rate/1,000		Rel. risk	
CHD/risk factors	Men	Women	Men	Women	Men	Women	Men	Women
High cholesterol	34	15	1.9***	1.8**	59	39	1.2*	2.0***
Hypertension	45	21	2.0***	2.2***	73	44	1.6***	1.9***
Diabetes	39	42	1.5***	3.7***	79	62	1.6**	2.1***
Smoking	33	13	1.5**	1.1[a]	53	38	1.0[a]	1.2[a]
ABI								
High cholesterol	3	2	1.0[a]	1.1[a]	10	12	1.0[a]	1.0[a]
Hypertension	7	4	5.7***	4.0***	20	17	2.0***	2.6***
Diabetes	7	4	3.0***	2.4*	20	28	1.6[a]	2.9***
Smoking	4	1	2.5**	1.0[a]	17	20	1.4[a]	1.9***
PAD								
High chol.	8	4	2.0**	1.9[a]	18	8	1.4[a]	1.0[a]
Hypertension	10	7	2.0***	3.7***	17	10	1.6*	2.0**
Diabetes	18	18	3.4***	6.4***	21	16	9.7*	2.6**
Smoking	9	5	2.5***	2.0**	18	11	8.5**	1.8*
CHF								
High chol.	7	4	1.2[a]	1.1[a]	21	18	1.0[a]	1.0[a]
Hypertension	14	6	4.0***	3.0***	33	24	1.9***	1.9***
Diabetes	23	21	4.4***	8.0***	40	51	2.0***	3.6***
Smoking	7	3	1.5***	1.1[a]	23	22	1.0[a]	1.3*

Based on data from Kannel and Wilson [25]
Rates are biennial per 1,000 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
CHD coronary heart disease, *ABI* atherothrombotic brain infarction, *PAD* peripheral artery disease, *CHF* heart failure
*$p<0.05$
**$p<0.01$
***$p<0.001$
[a]NS

Table 1.2 Development of coronary heart disease by Total/HDL cholesterol ratio versus total cholesterol according to age:16-year 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*	2.9*	2.3*	1.9***	1.2[a]
Women	3.7*	6.7*	3.3*	1.8**	2.0***

Based on data from Kannel and Wilson [25]
Quintile 5/quintile 1: ratio fifth risk quintile to first for total/HDL-C
*$p<0.05$
**$p<0.01$
***$p<0.001$
[a]NS

Table 1.3 Efficiency of blood lipids and ratios in predicting coronary disease Framingham Study subjects ages 50–80 year

	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

Reprinted from Kannel and Wilson [32]. With permission from Elsevier
Q quintiles of blood lipid distribution

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 [35].

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

Table 1.4 Increment in risk of CVD events per standard deviation increase in blood pressure components Framingham Study 30-year follow-up

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

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*$p < 0.001$
[a]NS

Table 1.5 Risk of CVD events according to pulse pressure 30-yr follow-up Framingham Study age-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

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abnormal lipoprotein lipase levels [36]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) guidelines identified the metabolic syndrome as a target for therapy in the management of dyslipidemia [14]. 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 Examination Survey (NHANES) II data suggests a 23.7 % age-adjusted prevalence of this syndrome in the USA [37].

Need for Multivariable Evaluation

As the above demonstrates the relations of the standard modifiable risk factors to CVD are striking and important. Also as the above shows the relations are not uniform across sexes and ages. A closer look at risk factors in the individual sexes and across ages demonstrates the need to consider the risk factors jointly. This is increased further in the presence of comorbidity (i.e., already having a CVD condition). Below we illustrate this by looking at risk factors in women, in the elderly, and in those with comorbid CVD events. These and the clustering of risk factors in individuals as is also presented below supply ample evidence of the need to consider the risk factors jointly. Along the way is also the indication that maybe more than the standard risk factors would be helpful in risk prediction.

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, 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 and diabetes markedly reduce the female coronary disease advantage [27]. 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 1.6). Women with diabetes require comprehensive screening to detect the usually accompanying elevated triglyceride, reduced HDL cholesterol, hypertension, and abdominal obesity. Minority

Table 1.6 Impact of diabetes on CVD events in men and women 36-year follow-up Framingham Study subjects ages 35–64 year

	Age-adjusted biennial rate per 1,000		Age-adjusted risk ratio		Excess risk per 1,000	
CVD events	Men	Women	Men	Women	Men	Women
CHD	39	21	1.5*	2.2**	12	12
PAD	18	18	3.4**	6.4**	13	15
CHF	23	21	4.4**	7.8**	18	18
Stroke	15	6	2.9**	2.6**	10	4
Total CVD	76	65	2.2**	3.7**	42	47

Based on data from Kannel and Wilson [25]
CHD coronary heart disease, *PAD* peripheral artery disease, *CHF* heart failure
*$p<0.01$
**$p<0.001$

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, and it is appropriate to characterize "low" HDL cholesterol as under 50 mg/dL. 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.

Risk Factors in the Elderly

The major modifiable risk factors do remain relevant in the elderly. The strength of risk factors associated with CVD, however, diminishes with advancing age, but this lower risk ratio is offset by a higher absolute risk [14, 15]. 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 well over 20 years ago [38]. 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 1.1). 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 1.2). As stated earlier, the joint evaluation of total cholesterol and HDL-C is important. Left ventricular hypertrophy is also 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 [9–16].

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 [39]. 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 [39]. The incidence of other cardiovascular disease accompanying coronary disease is substantial [40]. 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 [40]. Persons in the Framingham Study with intermittent claudication had a two- to threefold increased risk of developing coronary disease. Over 10 years, 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-year 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, 25–45 % 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 [40].

The Clustering of the Standard Risk Factors

While the first two sections above focused on woman and the elderly, the clustering of the standard risk factors is not limited to these. The standard risk factors tend to cluster together in men and women four to five times the rate expected by chance so that when one confronted with any risk factor, one is obliged to seek out the others. Isolated occurrence of the standard risk factor is uncommon ranging from 11 to 38 % (Table 1.7).

Multivariate Risk Stratification

Risk Scores/Risk Profiles

The standard CVD risk factors have strong relations to the development of CVD, they cluster together, and, while the effects vary, they are valid for both sexes and across age groups. The Framingham Heart Study recognized these facts and addressed the question of whether the individual risk factors could be combined into multivariate functions to give an assessment (i.e., the probability or risk) of developing CVD events over specific time periods (e.g., 10 years). In particular, attention was focused on the development of primary events (e.g., a first CVD event in a person who had no history of CVD at the time of evaluation). The study did produce these functions and continues to do [9–16, 42, 43]. These multivariable risk functions (also called Framingham risk functions, Framingham Risk Scores, or Framingham risk profiles) are for estimating the probability of a particular CVD event conditional on the burden of a number of specific risk factors and can be used for the evaluation of candidates for CVD in need of preventive management.

Major Framingham risk functions exist and have had widespread use for global CVD [16], CHD [9, 12], hard CHD events (MI and coronary deaths) [42], stroke [10, 43], CHF [13], and PAI [11]. The cholesterol treatment guideline for the Adult Treatment Panel III is based on a Framingham risk function for hard CHD events [14, 15, 44].

Table 1.7 Risk-factor clustering in the Framingham Study offspring cohort subjects ages 18–74 year

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

Based on data from Kannel [41]
Risk factors: upper quintile of distribution of all variables except HDL-C (lowest quintile)