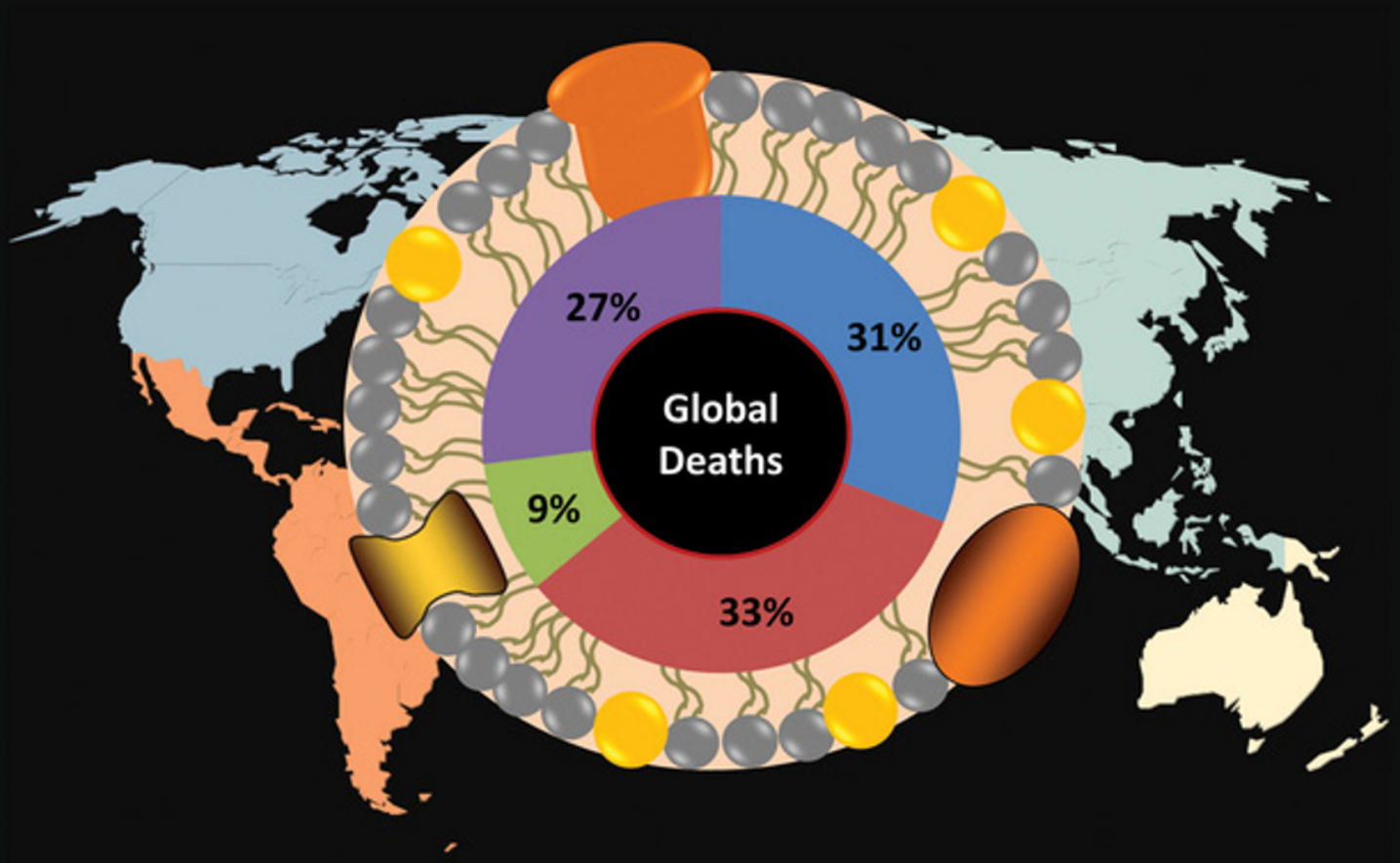
Cardiovascular Diseases

From Molecular Pharmacology to Evidence-Based Therapeutics



Y. Robert Li

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From Molecular Pharmacology to Evidence-Based Therapeutics

Y. ROBERT LI
Professor of Pharmacology
Chair of Department of Pharmacology
Campbell University SOM
Buies Creek, North Carolina, USA

Adjunct Professor of Biomedical Engineering and Sciences
Virginia Tech-Wake Forest University
School of Biomedical Engineering and Sciences
Blacksburg, Virginia, USA

Adjunct Professor of Biomedical Sciences and Pathobiology
Department of Biomedical Sciences and Pathobiology
Virginia-Maryland Regional College of Veterinary Medicine
Virginia Polytechnic Institute and State University
Blacksburg, Virginia, USA

Adjunct Professor of Biology
Department of Biology
University of North Carolina College of Arts and Sciences
Greensboro, North Carolina, USA

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CONTENTS

PREFACE

Cardiovascular diseases remain the leading cause of death globally, though the mortality associated with these diseases in developed countries has been significantly reduced over the past decades owing to the availability of effective treatment approaches. Among the available therapeutic strategies, drug therapy continues to be an important modality in the management of various forms of cardiovascular diseases. In this context, cardiovascular pharmacology serves as the foundation for pharmacotherapeutics of cardiovascular diseases and has become an increasingly important subject in cardiovascular medicine.

While there are multiple excellent pharmacology books with chapters being devoted to cardiovascular drugs, a book that systematically integrates essentials, advancements, and clinical correlations for cardiovascular drugs would facilitate the learning of knowledge on using these pharmacological agents to prevent and treat cardiovascular diseases. The aim of this book is to provide a comprehensive coverage of molecular pharmacology of various classes of cardiovascular drugs and evidence-based pharmacotherapeutics in the management of common cardiovascular diseases and conditions, including dyslipidemias, hypertension, ischemic heart disease, heart failure, cardiac arrhythmias, and ischemic stroke. As outlined in the following text, the book contains eight units with a total of 28 chapters.

Unit I (Chapters 1 and 2):	General Introduction
Unit II (Chapters 3–5):	Dyslipidemias
Unit III (Chapters 6–12):	Hypertension and Multitasking Cardiovascular Drugs
Unit IV (Chapters 13–15):	Ischemic Heart Disease: Stable Ischemic Heart Disease
Unit V (Chapters 16–19):	Ischemic Heart Disease: Acute Coronary Syndromes
Unit VI (Chapters 20–22):	Heart Failure
Unit VII (Chapters 23–25):	Cardiac Arrhythmias
Unit VIII (Chapters 26–28):	Ischemic Stroke

To set the stage for subsequently discussing the diverse topics of cardiovascular pharmacology and therapeutics, Unit I provides two introductory chapters. Chapter 1 introduces general aspects of cardiovascular diseases, including definition, classification, and epidemiology, as well as the overall strategies for prevention and control. Chapter 2 briefly surveys the general principles of pharmacology and provides an overview of the key and emerging concepts in cardiovascular pharmacology and therapeutics.

Unit II consists of three chapters (Chapters 3–5) devoted to the discussion of pharmacology and therapeutics of dyslipidemias. Chapter 3 reviews lipoprotein metabolism and lipoprotein disorders to lay a basis for understanding how drugs impact diverse lipoprotein metabolic pathways to treat various dyslipidemias. Chapter 4 examines molecular pharmacology of various classes of drugs for treating dyslipidemias, including statins, bile acid sequestrants, cholesterol absorption inhibitors, fibrates, niacin, as well as newly approved drugs for homozygous familial hypercholesterolemia. The chapter also considers phytosterols, phytostanols, omega-3 fatty acids, and emerging drugs for dyslipidemias. The principles and current evidence-based guidelines for management of dyslipidemias in clinical practice are covered in Chapter 5.

Unit III consisting of seven chapters (Chapters 6–12) discusses pharmacology and therapeutics of hypertension, as well as various classes of cardiovascular drugs. Chapter 6 provides an overview of hypertension, including definition, epidemiology, and pathophysiology and drug targeting. Because the different drug classes used for treating

hypertension are also commonly employed in the management of other cardiovascular diseases, molecular pharmacology of these multitasking cardiovascular drug classes is considered in separate chapters (Chapters 7–11). These drug classes include diuretics (Chapter 7), sympatholytics (Chapter 8), inhibitors of the renin–angiotensin–aldosterone system (Chapter 9), calcium channel blockers (Chapter 10), and nitrates and other vasodialtors (Chapter 11). Following discussion of these multitasking drug classes, the principles and current evidence-based guidelines for hypertension management in clinical practice are given in Chapter 12, the last chapter of Unit III.

Unit IV contains three chapters (Chapters 13–15) devoted to discussing pharmacology and therapeutics of stable ischemic heart disease. Chapter 13 gives an overview on ischemic heart disease and discusses pathophysiology of stable ischemic heart disease and mechanistically based drug targeting of stable angina. Chapter 14 reviews anti-anginal drugs that have already been discussed in previous chapters and also considers some newly approved and emerging anti-anginal drugs that are not covered elsewhere in the book. The principles and current evidence-based guidelines for management of stable ischemic heart disease/stable angina in clinical practice are given in Chapter 15.

Unit V consisting of four chapters (Chapters 16–19) considers pharmacology and therapeutics of acute coronary syndromes (ACS), including unstable angina (UA), acute non-ST elevation myocardial infarction (NSTEMI), and acute ST elevation myocardial infarction (STEMI). Chapter 16 provides an overview of definition and epidemiology of ACS and discusses current understanding of ACS pathophysiology and the mechanistically based drug targeting as well as related therapeutic modalities. Chapter 17 examines molecular pharmacology of drugs for treating ACS, including anticoagulants, platelet inhibitors, and thrombolytic agents. This lays a basis for understanding general principles and current evidence-based guidelines for the management of UA/NSTEMI and STEMI in clinical practice in Chapters 18 and 19, respectively.

Unit VI has three chapters (Chapters 20–22) that consider pharmacology and therapeutics of heart failure, a common clinical syndrome representing the end stage of a number of different cardiac diseases. Chapter 20 gives an overview of heart failure, including definition, classification, epidemiology, and pathophysiology and drug targeting. The major drug classes for treating heart failure include diuretics (Chapter 7), β-blockers (Chapter 8), inhibitors of the renin–angiotensin–aldosterone system (Chapter 9), vasodilators (Chapter 11), and positive inotropic agents. Chapter 21 discusses pharmacological basis of using the above drug classes in treating heart failure. Since inotropic drugs have not been covered elsewhere in the book, Chapter 21 focuses on molecular pharmacology of this drug class in heart failure treatment. The chapter also introduces emerging therapeutic modalities for heart failure. The principles and current evidence-based guidelines for management of heart failure in clinical practice are provided in Chapter 22.

Unit VII consisting of three chapters (Chapters 23–25) discusses pharmacology and therapeutics of cardiac arrhythmias. Chapter 23 provides an overview of cardiac arrhythmias, including classification, epidemiology, and pathophysiology and drug targeting. Chapter 24 discusses molecular pharmacology of classical antiarrhythmic drugs (Vaughan–Williams class I–IV drugs) with a focus on those whose efficacy is supported by recent clinical research. The chapter also considers antiarrhythmic agents that do not fall into the Vaughan–Williams classification, as well as emerging drugs with promising results from randomized clinical trials. Chapter 25 describes the general principles and current evidence-based guidelines for management of arrhythmias in clinical practice with an emphasis on pharmacological therapy. Since arrhythmias are a large group of disorders, the chapter focuses on those that have the most significant clinical and public health impact, including atrial fibrillation and certain forms of ventricular tachyarrhythmias.

Unit VIII, the last unit of the book, contains three chapters (Chapters 26–28) devoted to discussing pharmacology and therapeutics of ischemic stroke. Chapter 26 gives an overview of ischemic stroke, including definition, classification, epidemiology, risk factors, and pathophysiology and drug targeting. The preventive and therapeutic intervention of ischemic stroke involves five areas of management: primary prevention, early treatment of acute ischemic stroke, neuroprotection, secondary prevention, and neurorepair. Although neuroprotection and neurorepair are promising strategies, presently, they are primarily experimental approaches. Drug therapy remains as a major component of the effective intervention of ischemic stroke. Chapter 27 discusses the major classes of drugs that are used in each of the above areas. Since most of the drugs discussed in the chapter have been covered in preceding chapters, Chapter 27 only summarizes current evidence-based consensus statements on their clinical efficacy in preventive and therapeutic intervention of ischemic stroke. The principles and current evidence-based guidelines for management of ischemic stroke in clinical practice are provided in Chapter 28, the last chapter of the book.

It is hoped that this book by integrating the most recent advancements in molecular pharmacology and most current evidence-based, guideline-directed therapeutics of cardiovascular diseases will provide the readers a unique approach to understanding the rapidly evolving field of cardiovascular medicine and therapeutics. Because of the rapidly evolving nature of cardiovascular medicine, and medicine as a whole, the information contained in this book is subject to change based on new scientific knowledge and clinical experience. Although the author of the book has checked with sources believed to be reliable and accurate at the time of

publication, information included in the book may not be accurate in every respect due to the possibility of human errors and rapid changes in medical sciences. As such, the author of the book does not warrant that the information contained in the work is in every respect accurate and complete. The author disclaims all responsibility for any errors or omissions or for the results obtained from the use of the information contained in this book. The readers are advised to seek independent verification for any data, advice, or recommendations contained in the work.

This book would not have been possible without the assistance of my son Jason Z. Li who drew all of the chemical structures for the whole book, and my wife Hong Zhu, MD, MPH, who critically reviewed the entire book manuscript. I am grateful to those (over 100 scientists worldwide) who provided me reprints of their publications and/or comments on part of the book manuscript. I am thankful for the time and effort made by Mr. Jonathan Rose, Senior Editor, and other editorial personnel, especially Ms. Shiji Sreejish, at Wiley, which made the work possible and of high quality.

Apex, North Carolina
September 23, 2014

Y. ROBERT LI, MD, MPH, PhD

LIST OF ABBREVIATIONS

ABC	ATP-binding cassette
ABCA1	ATP-binding cassette protein A1
ABCG2	ATP-binding cassette protein G2
ABCG5	ATP-binding cassette protein G5
ABCG8	ATP-binding cassette protein G8
ACAT	acyl-CoA:cholesterol acyltransferase
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
Ach	acetylcholine
ACLS	advanced cardiovascular life support
ACS	acute coronary syndromes
ADE	adverse drug event
ADHF	acute decompensated heart failure
ADP	adenosine diphosphate
ADR	adverse drug reaction
AF	atrial fibrillation
AFL	atrial flutter
AHA	American Heart Association
AHF	acute heart failure
AHFS	acute heart failure syndromes
AHRQ	Agency for Healthcare Research and Quality
ALA	alpha-linolenic acid
ALDH2	mitochondrial aldehyde dehydrogenase-2
ALK1	activin receptor-like kinase type 1
ALT	alanine aminotransferase
AMA	American Medical Association
AMI	acute myocardial infarction
ANP	atrial natriuretic peptide
APC	atrial premature complex
APD	action potential duration
aPTT	activated partial thromboplastin time
AR	aldosterone receptor
ARB	angiotensin receptor blocker
ARVC	arrhythmogenic right ventricular cardiomyopathy
ASA	American Stroke Association
ASCVD	atherosclerotic cardiovascular disease
ASH	American Society of Hypertension
AST	aspartate aminotransferase
AT	atrial tachycardia
AT_1	angiotensin receptor type 1
AT_2	angiotensin receptor type 2
AT_4	angiotensin receptor type 4
ATP	adenosine triphosphate
ATP	Adult Treatment Panel
ATP III	Adult Treatment Panel III
AV	atrioventricular
AVNRT	Atrioventricular nodal reciprocating tachycardia
AVRT	atrioventricular reentrant tachycardia
b.i.d.	twice a day
BHS	British Hypertension Society
BMPR2	bone morphogenetic protein receptor type 2
BP	blood pressure
BRMAC	Biological Response Modifiers Advisory Committee
CABG	coronary artery bypass grafting
CAD	coronary artery disease
cAMP	3′-5′-cyclic adenosine monophosphate

CCB calcium channel blocker
CCS Canadian Cardiovascular Society
cCTA coronary computed tomography angiogram
CDC Centers for Disease Control and Prevention
CETP cholesterol ester transfer protein
cGMP cyclic guanosine monophosphate
cGMP cyclic-3′,5′-guanosine monophosphate
CHD coronary heart disease
CHEP Canadian Hypertension Education Program
CKD chronic kidney disease
CM chylomicron
CMR chylomicron remnant
CNS central nervous system
COPD chronic obstructive pulmonary disease
COR class of recommendation
COX cyclooxygenase
CPR cardiopulmonary resuscitation
CPVT catecholaminergic polymorphic ventricular tachycardia
CQI continuous quality improvement
CrCl creatinine clearance
CRT cardiac-resynchronization therapy
CTEPH chronic thromboembolic pulmonary hypertension
CYP cytochrome P450
DAPT dual antiplatelet therapy
DASH Dietary Approaches to Stop Hypertension
DBP diastolic blood pressure
DC direct current
DES drug-eluting stent
DGAT-2 acyl-CoA:diacylglycerol acyltransferase-2
DHA docosahexaenoic acid
DHHS Department of Health and Human Services
DTI direct thrombin inhibitor
DVT deep vein thrombosis
EAS European Atherosclerosis Society
ECG electrocardiogram
ECG electrocardiography
EF ejection fraction
eGFR estimated glomerular filtration rate
EMA European Medicines Agency
EMS emergency medical services
EPA eicosapentaenoic acid
EPAD established peripheral arterial disease
Epi epinephrine
ERP effective refractory period
ESC European Society of Cardiology
ESCs embryonic stem cells
ESH European Society of Hypertension
ESO European Stroke Organisation
ET-1 endothelin-1
ET-2 endothelin-2
ET-3 endothelin-3
ET_A endothelin receptor type A
ET_B endothelin receptor type B
FAT focal atrial tachycardia
FDA Food and Drug Administration
FFA free fatty acid
FMC first medical contact
FXR farnesoid X receptor
GAS genome-wide association study
GBD global burden of disease
GDMT guideline-directed medical therapy
GFR glomerular filtration rate
GP IIb/IIIa glycoprotein IIb/IIIa
GTP guanosine triphosphate
GWTG Get With the Guidelines
HbA1c glycosylated hemoglobin
HCM hypertrophic cardiomyopathy
HDL high-density lipoprotein
HDL-C high-density lipoprotein cholesterol
HF heart failure
HF-PEF heart failure with preserved ejection fraction
HF-REF heart failure with reduced ejection fraction
HFSA Heart Failure Society of America
HIT heparin-induced thrombocytopenia
HITTS heparin-induced thrombocytopenia and thrombosis syndrome
HIV human immunodeficiency virus
HL hepatic lipase
HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A
HoFH homozygous familial hypercholesterolemia
HRE hormone response element
HRS Heart Rhythm Society
ICD implantable cardioverter defibrillator
ICD International Classification of Diseases and Related Health Problems
ICD-10 International Statistical Classification of Diseases and Related Health Problems—10th Revision
ICH intracranial hemorrhage
IDL intermediate-density lipoprotein
IHD ischemic heart disease
IND investigational new drug application

INR international normalized ratio
IOM Institute of Medicine
iPSCs induced pluripotent stem cells
ISA intrinsic sympathomimetic activity
ISH International Society of Hypertension
IST inappropriate sinus tachycardia
Iv intravenous
JBS Joint British Societies
JNC Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JNC7 the Seventh Report of the Joint National Committee on the Prevention Detection, Evaluation, and Treatment of High Blood Pressure
JPC junctional premature complex
LBBB left bundle-branch block
LCAT lecithin–cholesterol acyltransferase
LDL low-density lipoprotein
LDL-C low-density lipoprotein cholesterol
LDLR low-density lipoprotein receptor
LDLRAP LDL receptor adaptor protein
LGL Lown–Ganong–Levine
LM lifestyle modifications
LMWH low-molecular-weight heparin
LOE level of evidence
Lp(a) lipoprotein(a)
LPL lipoprotein lipase
LQTS long QT syndrome
LV left ventricular
LVD left ventricular dysfunction
LVEF left ventricular ejection fraction
LXR liver X receptor
MAO monoamine oxidase
MAT multifocal atrial tachycardia
MCA middle cerebral artery
MCS mechanical circulatory support
METs metabolic equivalents
MI myocardial infarction
MMP matrix metalloproteinase
MTP microsomal triglyceride transfer protein
NAD nicotinamide adenine dinucleotide
NADP nicotinamide adenine dinucleotide phosphate
NCDs noncommunicable diseases
NCEP National Cholesterol Education program
NCHS National Center for Health Statistics
NDA new drug application
NE norepinephrine
NHANES National Health and Nutrition Examination Survey
NHLBI National Heart, Lung, and Blood Institute
NICE National Institute for Health and Care Excellence
NICE National Institute for Health and Clinical Excellence
NIHSS National Institutes of Health Stroke Scale
NO nitric oxide
NPC1L1 Niemann–Pick C1-Like 1
NPR-A natriuretic peptide receptor-A
Nrf2 nuclear factor E2-related factor 2
NSAID nonsteroidal anti-inflammatory drugs
NSTEMI non-ST-elevation myocardial infarction
NSTEMI non-ST-segment elevation myocardial infarction
NYHA New York Heart Association
OTC ornithine transcarboxylase
PAF platelet-activating factor
PAH pulmonary arterial hypertension
PAR protease-activated receptor
PCI percutaneous coronary intervention
PCSK9 proprotein convertase subtilisin/kexin type 9
PDE phosphodiesterase
PDE3 phosphodiesterase 3
PDE5 phosphodiesterase 5
PE pulmonary embolism
PGD_2 prostaglandin D_2
PGs prostaglandins
PGx pharmacogenetics/pharmacogenomics
PIAs positive inotropic agents
PLA_2 phospholipase A_2
PLTP phospholipid transfer protein
PON1 paraoxonase 1
PPAR-α peroxisome proliferator-activated receptor-α
PPARγ peroxisome proliferator-activated receptor-gamma
PSVT paroxysmal supraventricular tachycardia
PTCA percutaneous transluminal coronary angioplasty
PVC premature ventricular complex
q.i.d. 4 times a day
QTc corrected QT
RAAS renin–angiotensin–aldosterone system
ROS reactive oxygen species
ROS/RNS reactive oxygen/nitrogen species
ROSC return of spontaneous circulation
SA sinoatrial
SBP systolic blood pressure

SCA	sudden cardiac arrest
SCAD	stable coronary artery disease
SCD	sudden cardiac death
SFXa	selective factor Xa
sGC	soluble guanylate cyclase
SIHD	stable ischemic heart disease
siRNA	RNA interference
SMC	smooth muscle cell
SND	SA node dysfunction
SNP	single nucleotide polymorphism
SNS	sympathetic nervous system
SOE	strength of evidence
$sPLA_2$	secretory PLA_2
SR-B1	scavenger receptor B1
SREBP	sterol regulatory element-binding protein
SREBP1c	sterol regulatory element-binding protein 1c
STEMI	ST-elevation myocardial infarction
t.i.d.	3 times a day
TdP	torsades de pointes
TIA	transient ischemic attack
TLC	therapeutic lifestyle changes
TOS	The Obesity Society
tPA	tissue plasminogen activator
TR	thyroid hormone receptor
TxA_2	thromboxane A_2
UA	unstable angina
UFH	unfractionated heparin
USDA	United States Department of Agriculture
VF	ventricular fibrillation
VKOR	vitamin K epoxide reductase
VKORC1	the C1 subunit of VKOR
VLDL	very low-density lipoprotein
VT	ventricular tachycardia
WHO	World Health Organization
WPW	Wolff–Parkinson–White
X-SCID	X-linked severe combined immunodeficiency disease

UNIT I

GENERAL INTRODUCTION

1

INTRODUCTION TO CARDIOVASCULAR DISEASES

1.1 OVERVIEW

The heart has always held a special fascination for humans: it has been the seat of the soul, the home of emotions, and the pump that when beating symbolizes life and when silent signifies death [1]. Perhaps no other organ in the human body has been so closely scrutinized. Hence, the management of cardiovascular diseases, including the use of medications, has always been a focus of medicine. To set a stage for the subsequent discussion of the diverse topics of cardiovascular pharmacology and therapeutics, this chapter provides a brief introduction to various general aspects of cardiovascular diseases. These include definition, classification, and epidemiology of cardiovascular diseases, as well as the overall strategies for their prevention and control. An introduction to the principles of pharmacology in general and cardiovascular pharmacology in particular is given in Chapter 2.

1.2 DEFINITION OF CARDIOVASCULAR DISEASES

In order to define the term cardiovascular diseases, it is imperative to first provide an overview of the cardiovascular system. Briefly, cardiovascular system refers to an integrated organ system consisting of the heart and blood vessels. Blood flows through a network of blood vessels that extend between the heart and the peripheral tissues. These blood vessels are subdivided into a pulmonary circuit, which carries blood to and from the gas exchange surface of the lungs, and a systemic circuit, which transports blood to and from the rest of the body. Each circuit begins and ends at the heart, and the blood vessels and the heart collectively constitute the cardiovascular system. As noted, blood is a central player in the cardiovascular system, and hence, study of the cardiovascular system inevitably involves examination of the blood, including its components and functionality. It should be noted that cardiovascular system and circulatory system are frequently used interchangeably; however, strictly, the circulatory system is composed of the cardiovascular system, which distributes blood, and the lymphatic system, which distributes lymph.

Cardiovascular diseases refer to a group of diseases involving the heart, blood vessels, or the sequelae of poor blood supply due to a decreased vascular supply and include (i) diseases of the heart, (ii) vascular diseases of the brain (also known as cerebrovascular diseases), and (iii) diseases of other blood vessels (Fig. 1.1). Hence, cardiovascular diseases affect the heart, the brain, and other organs or systems of the human body.

1.3 CLASSIFICATION OF CARDIOVASCULAR DISEASES

1.3.1 Classification Based on Anatomical Location

Cardiovascular diseases are classified in various ways. One scheme is based primarily on the anatomical location of the disease pathogenesis and broadly classifies cardiovascular diseases into two categories: (i) diseases of the heart and (ii) vascular diseases (Fig. 1.2).

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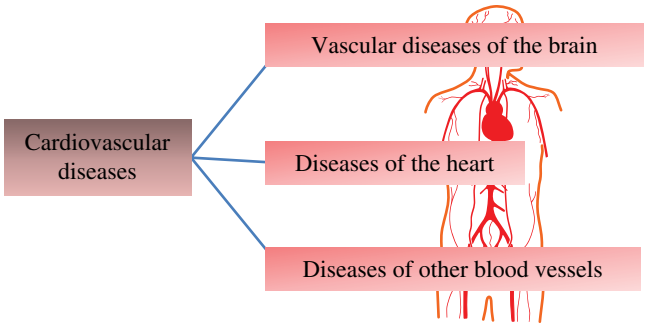


FIGURE 1.1 Definition of cardiovascular diseases. The term cardiovascular diseases refers to a group of diseases, including the diseases of the heart, vascular diseases of the brain, and the diseases of other blood vessels.

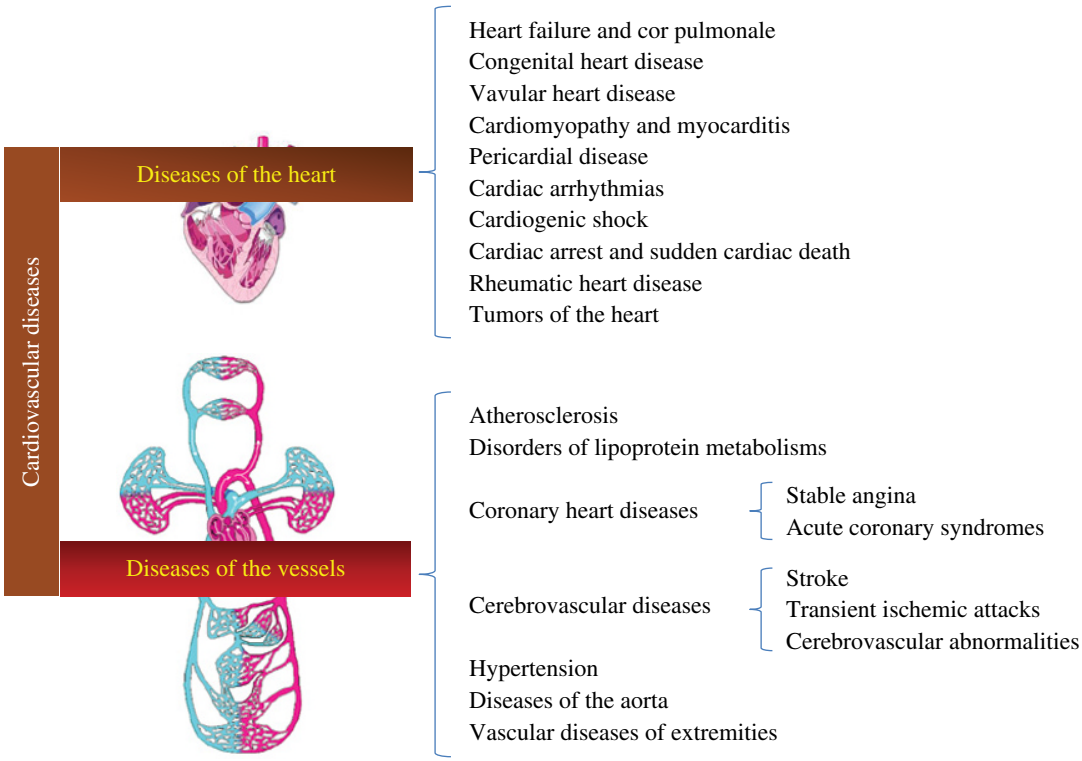


FIGURE 1.2 Classification of cardiovascular diseases. Primarily based on anatomical location, cardiovascular diseases are classified into diseases of the hearts and diseases of the vessels. As illustrated, coronary heart disease and stroke belong to the category of diseases of the vessels.

1.3.2 Classification Based on the Involvement of Atherosclerosis

Another classification scheme emphasizes the primary involvement of atherosclerosis and classifies cardiovascular diseases into (i) cardiovascular diseases due to atherosclerosis (also known as atherosclerotic cardiovascular diseases) and (ii) other cardiovascular diseases (Table 1.1). In this context, atherosclerosis is responsible for ~75% of all deaths due to cardiovascular diseases.

1.3.3 Total Cardiovascular Diseases and ICD-10 Classification

In addition to the aforementioned classification schemes, the American Heart Association (AHA) has recently introduced the concept of total cardiovascular diseases. This category (ICD-10 codes I00–I99, Q20–Q28; see next paragraph for the description of ICD-10) includes rheumatic fever/rheumatic heart disease (I00–I09); hypertensive diseases (I10–I15); ischemic (coronary) heart disease (I20–I25); pulmonary heart

TABLE 1.1 Classification of cardiovascular diseases based on the involvement of atherosclerosis

Classification basis	Disease
Cardiovascular diseases due to atherosclerosis (also known as atherosclerotic cardiovascular diseases)	Coronary heart diseases Cerebrovascular diseases Diseases of the aorta and arteries including hypertension and peripheral vascular diseases
Other cardiovascular diseases	Congenital heart diseases Rheumatic heart diseases Cardiac arrhythmias

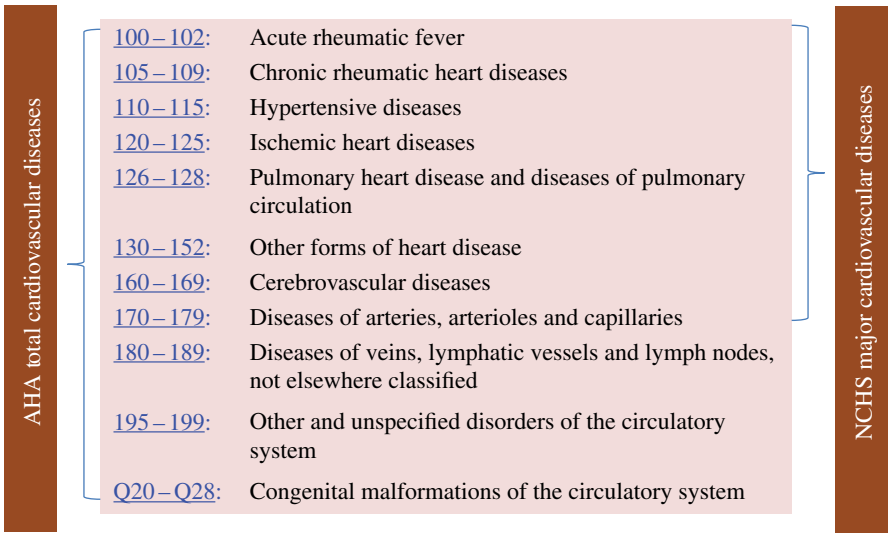


FIGURE 1.3 The ICD-10 disease codes included in the American Heart Association (AHA) total cardiovascular diseases and the US National Center for Health Statistics (NCHS) major cardiovascular diseases. As shown, the AHA total cardiovascular diseases are more comprehensive than the NCHS major cardiovascular diseases.

disease and diseases of pulmonary circulation (I26–I28); other forms of heart disease (I30–I52); cerebrovascular disease (stroke) (I60–I69); atherosclerosis (I70); other diseases of arteries, arterioles, and capillaries (I71–I79); diseases of veins, lymphatics, and lymph nodes not classified elsewhere (I80–I89); and other and unspecified disorders of the circulatory system (I95–I99), as well as congenital cardiovascular defects (Q20–Q28) [2].

ICD denotes International Classification of Diseases. It is the international standard diagnostic classification for all general epidemiological, many health management purposes, and clinical use. The current 10th revision, that is, ICD-10, was endorsed by the Forty-Third World Health Assembly in May 1990 and came into use in the World Health Organization (WHO) member states as from 1994. According to the ICD-10, diseases of the circulatory system are included in I00–I99, whereas the congenital malformations of the circulatory system (Q20–Q28) are included in the disease category of congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99). Hence, the AHA category of total cardiovascular diseases covers all diseases of the circulatory system, including both cardiovascular and lymphatic systems. On the other hand, the National Center for Health Statistics (NCHS) of the United States employs the term major cardiovascular diseases for reporting mortality data. The NCHS category of major cardiovascular diseases represents ICD codes I00–I78 and hence is less comprehensive than that of the AHA's total cardiovascular diseases (Fig. 1.3).

1.4 PREVALENCE, INCIDENCE, AND TREND OF CARDIOVASCULAR DISEASES

This section provides an overview of some of the major statistical and epidemiological data on cardiovascular diseases in the context of noncommunicable diseases (NCDs) in the globe as well as in selected countries, including the United States and China. The key data are also summarized in tables. Some pertinent terms are provided in Box 1.1.

BOX 1.1 GLOSSARY

- **Disease prevalence:** It is an estimate of how many people have a disease at a given point or period in time. Prevalence is sometimes expressed as a percentage of population.
- **Disease incidence:** An incidence rate refers to the number of new cases of a disease that develop in a population per unit of time. The unit of time for incidence is not necessarily 1 year although we often discuss incidence in terms of 1 year.
- **Mortality:** It refers to the total number of deaths attributable to a given disease in a population during a specific interval of time, usually a year.
- **Death rate or mortality rate:** It refers to the relative frequency with which death occurs within some specified interval of time in a population. Mortality rate is typically expressed as number of deaths per 100,000 individuals per year.
- **The World Health Organization (WHO):** The WHO is the directing and coordinating authority for health within the United Nations system. WHO was established in 1948 with headquarters in Geneva of Switzerland. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends.
- **Epidemiology:** Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control of health problems. The objectives of epidemiology include (i) identification of the etiology or cause of a disease and the relevant risk factors; (ii) determination of the extent of disease found in the community; (iii) study of the natural history and prognosis of disease; (iv) evaluation of both existing and newly developed preventive and therapeutic measures and modes of healthcare delivery; and (v) providing the foundation for developing public policy relating to environmental problems, genetic issues, and other considerations regarding disease prevention and health promotion.
- **Global burden of disease:** Global burden of disease analysis provides a comprehensive and comparable assessment of mortality and loss of health due to diseases, injuries, and risk factors for all regions of the world. The overall burden of disease is assessed using the disability-adjusted life year (DALY), a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health. The original Global Burden of Disease Study (GBD 1990 Study) was commissioned by the World Bank in 1991 to provide a comprehensive assessment of the burden of 107 diseases and injuries and 10 selected risk factors for the world and 8 major regions in 1990. The methods of the GBD 1990 Study created a common metric to estimate the health loss associated with morbidity and mortality. It generated widely published findings and comparable information on disease and injury incidence and prevalence for all world regions. It also stimulated numerous national studies of burden of disease. These results have been used by governments and nongovernmental agencies to inform priorities for research, development, policies, and funding. The new Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2010 Study) commenced in the spring of 2007 and is the first major effort since the original GBD 1990 Study to carry out a complete systematic assessment of global data on all diseases and injuries. The GBD 2010 Study constitutes an unprecedented collaboration of 488 scientists from 303 institutions in 50 countries, focusing on describing the state of health around the world using a uniform method. The GBD 2010 Study results for the world and 21 regions have recently been reported for 291 diseases and injuries, 1160 sequelae of these causes, and 67 risk factors or clusters of risk factors [3]. This project is funded by the Bill and Melinda Gates Foundation.
- **Statistics:** Statistics is the study of the collection, organization, analysis, and interpretation of data.

BOX 1.2 THE WHO DEFINITION OF NONCOMMUNICABLE DISEASES

Noncommunicable diseases are identified by the WHO as "group II diseases," a category that aggregates (based on ICD-10 code; see Section 1.3.3 for ICD-10) the following conditions/causes of death: malignant neoplasms, other neoplasms, diabetes mellitus, endocrine disorders, neuropsychiatric conditions, sense organ diseases, cardiovascular diseases, respiratory diseases (e.g., chronic obstructive pulmonary disease, asthma, others), digestive diseases, genitourinary diseases, skin diseases, musculoskeletal diseases (e.g., rheumatoid arthritis), congenital anomalies (e.g., cleft palate, Down syndrome), and oral conditions (e.g., dental caries). These are distinguished from group I diseases (communicable, maternal, perinatal, and nutritional conditions) and group III diseases (unintentional and intentional injuries).

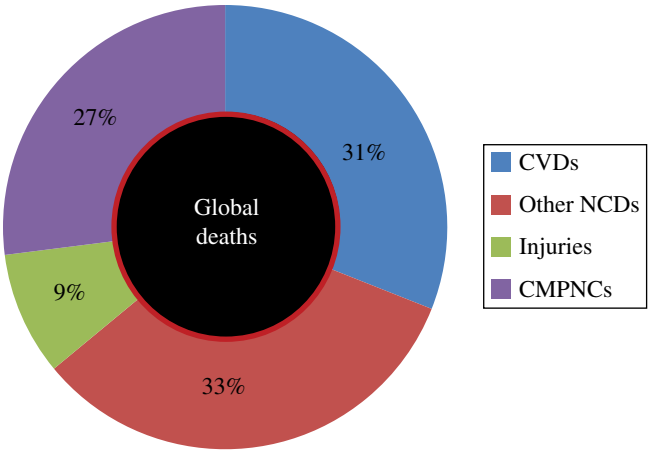


FIGURE 1.4 Global deaths caused by cardiovascular diseases (CVDs). As illustrated, CVDs are responsible for ~30% of all global deaths. NCDs denote noncommunicable diseases; CMPNCs denote communicable, maternal, perinatal, and nutritional conditions.

1.4.1 NCDs and Cardiovascular Diseases: The Global Status

According to the WHO, NCDs, including chiefly cardiovascular diseases (heart disease and stroke), cancer, chronic respiratory diseases, and diabetes, are the leading cause of mortality in the world, responsible for 36 million (or 63%) of the 57 million of the global deaths in 2008. The WHO definition for NCDs is given in Box 1.2. The burden of these diseases is rising disproportionately among lower-income countries and populations. In 2008, nearly 80% of NCD deaths (i.e., 29 million) occurred in low- and middle-income countries with about 29% of deaths occurring before the age of 60 years in these countries, dispelling the myth that such conditions are mainly a problem of affluent societies. Without action, the NCD epidemic is projected to kill 52 million people annually by 2030. A report by the World Economic Forum and the Harvard School of Public Health in September 2011 showed that the estimated cumulative output loss due to NCDs over the next 20 years represents ~4% of annual global gross domestic product (GDP) and will be $47 trillion by 2030. The increasing global crisis in NCDs is a barrier to development goals including poverty reduction, health equity, economic stability, and human security. The above staggering numbers and issues convinced the United Nations (UN) to convene its second-ever high-level general assembly meeting on health in September 2011 in New York, United States. This UN high-level meeting on NCDs along with its political declaration is an unprecedented opportunity to create a sustained global movement against premature death and preventable morbidity and disability from NCDs [4–6].

Among the 36 million NCD deaths in 2008, cardiovascular diseases caused 17.3 million deaths (or 48% of all NCD deaths) followed by cancers (7.6 million or 21% of all NCD deaths), respiratory diseases (4.2 million or 11.7% of all NCD deaths), and diabetes (1.3 million or 3.6% of all NCD deaths). These four groups of diseases account for around 80% of all NCD deaths. Globally, NCD deaths are projected to increase by 15% between 2010 and 2020.

As shown in Figure 1.4, cardiovascular diseases remain the number one global killer of the human population, accounting for about 30% of all deaths (including communicable, noncommunicable, and other disease deaths) in the world. Notably, based on the WHO 2011 Global Atlas on Cardiovascular Disease Prevention and Control, out of the 17.3 million cardiovascular deaths in 2008, ischemic heart diseases (myocardial infarction) were responsible for 7.3 million deaths, and strokes were responsible for 6.2 million deaths. This figure remained largely unchanged in 2010 based on a report from the Global Burden of Disease 2010 Study [7]. Together, ischemic heart diseases and strokes account for nearly 80% of all cardiovascular deaths in the world and are the top two killers of the human population (Table 1.2), making them globally the two most pressing cardiovascular diseases for prevention and control.

1.4.2 The Status of Cardiovascular Diseases in the United States

1.4.2.1 Statistics In the United States, currently, more than 82 million adults (more than one in three) have one or more types of cardiovascular diseases. Mortality data show that cardiovascular diseases, as the underlying causes of death, accounted for 31.9% (787,650) of all 2,468,435 deaths in 2010, or approximately one of every 3 deaths in the United States. The 2010 overall death rate from cardiovascular diseases in the United States was 235.5 per 100,000. On the

TABLE 1.2 Top 10 causes of the death in the world in 2011

Rank	Disease	Deaths in millions	% deaths
1	Ischemic heart disease	7.0	11.2
2	Stroke	6.2	10.6
3	Lower respiratory infections	3.2	6.7
4	Chronic obstructive pulmonary disease	3.0	5.8
5	Diarrheal diseases	1.9	4.7
6	HIV/AIDS[a]	1.6	3.0
7	Trachea, bronchus, lung cancers	1.5	2.7
8	Diabetes mellitus	1.4	2.6
9	Road injury	1.3	2.2
10	Prematurity	1.2	1.9

Source: The World Health Organization.
[a]HIV/AIDS denotes human immunodeficiency virus/acquired immunodeficiency syndrome.

TABLE 1.3 Ten leading causes of death in the United States in 2010

Rank	Disease	Deaths[a]	% total deaths
1	Diseases of heart	597,689	24.2
2	Malignant neoplasms	574,743	23.3
3	Chronic lower respiratory diseases	138,080	5.6
4	Cerebrovascular diseases	129,476	5.2
5	Accidents (unintentional injuries)	120,859	4.9
6	Alzheimer's disease	83,494	3.4
7	Diabetes mellitus	69,071	2.8
8	Nephritis, nephrotic syndrome, and nephrosis	50,476	2.0
9	Influenza and pneumonia	50,097	2.0
10	Intentional self-harm (suicide)	38,364	1.6

Source: The United States Centers for Disease Control and Prevention (CDC) National Vital Statistics Report 2013, 61(4).
[a]Total deaths in 2010: 2,468,435.

basis of 2010 mortality rate data, more than 2150 Americans die of cardiovascular diseases each day, an average of one death every 40 s. The total cost of cardiovascular diseases in the United States for 2010 is estimated to be $315.4 billion, accounting for 15% of total health expenditures in 2010, more than any other major diagnostic group [8].

Based on the 2014 update from the AHA [8], the prevalence (incidence) of various types of cardiovascular diseases in adults in the United States is as follows:

- Hypertension: 78,000,000
- Coronary heart disease: 15,400,000
  - Myocardial infarction (also known as heart attack): 7,600,000 (incidence: 720,000)
  - Angina pectoris: 7,800,000 (incidence: 565,000)
- Heart failure: 5,100,000 (incidence: 825,000)
- Stroke: 6,800,000 (incidence: 795,000)
- Congenital cardiovascular defects: 650,000–1,300,000

1.4.2.2 Trend According to the AHA 2014 Update [8], from 2000 to 2010, the overall cardiovascular disease death rates declined 31.0%. However, cardiovascular diseases are still the leading cause of death in the United States. Declines in stroke death rate (a 35.8% decrease in annual stoke death rate from 2000 to 2010) now rank stroke as the fourth leading cause of death in the nation (as of 2008; Table 1.3). Although the cardiovascular mortality has decreased substantially over the past decades (Fig. 1.5) possibly due to effective prevention and better treatments for heart attacks, congestive heart failure, stroke, and other conditions, the cardiovascular disease prevalence and costs have been growing steadily and are projected to increase substantially in the future. For example, by 2030, 40.5% of the US population is projected to have some form of cardiovascular diseases. Between 2010 and 2030, real total direct medical costs of cardiovascular diseases are projected to triple, from $273 billion to $818 billion. Real indirect costs (due to lost productivity) for all cardiovascular diseases are estimated to increase from $172 billion in 2010 to $276 billion in 2030, an increase of 61% [9].

1.4.3 The Status of Cardiovascular Diseases in China

According to the official data available through the WHO (http://www.who.int), in China, about 230 million people currently have cardiovascular diseases. This translates into

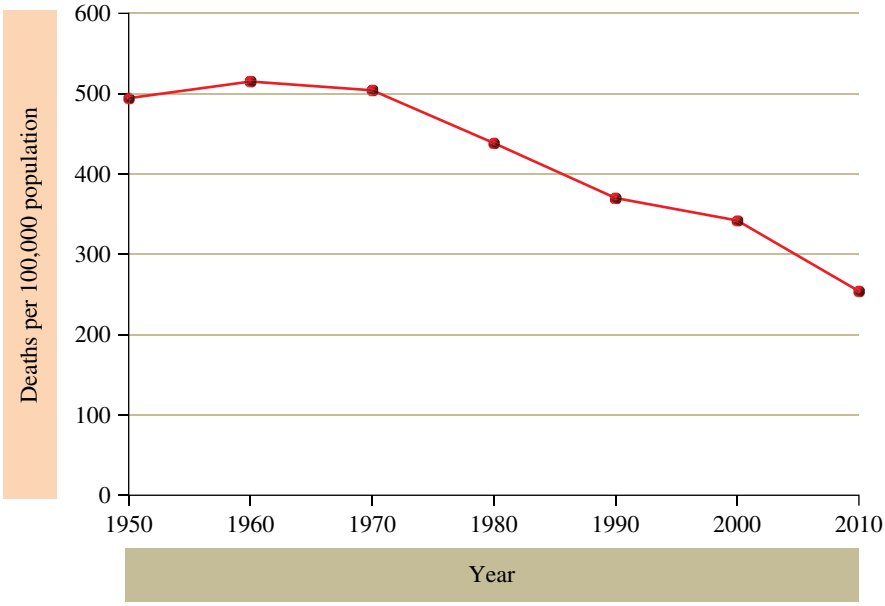


FIGURE 1.5 Cardiovascular disease mortality rates in the United States over the past seven decades. As shown, the past three to four decades have witnessed remarkable decreases in cardiovascular mortality rates. This achievement most likely results from implementation of effective health promotion initiatives and the availability of new effective treatments, including drug therapies.

one in five adults in China having a cardiovascular disease. In 2010, 154.8 per 100,000 deaths per year were estimated to be associated with cardiovascular diseases in urban areas and 163.1 per 100,000 in rural areas. This number accounts for 20.9%/17.9% (urban/rural) of China's total number of deaths per year.

Annual cardiovascular events are predicted to increase by 50% between 2010 and 2030 based on population aging and growth alone in China. Projected trends in blood pressure, total cholesterol, diabetes mellitus (increases), and active smoking (decline) would increase annual cardiovascular disease events by an additional 23%, an increase of ~21.3 million cardiovascular events and 7.7 million cardiovascular deaths.

1.5 RISK FACTORS OF CARDIOVASCULAR DISEASES

1.5.1 Classification of Cardiovascular Disease Risk Factors

It is known that the development of cardiovascular diseases results from the complicated interactions between genes and environmental and dietary factors. The major risk factors for developing cardiovascular diseases are classified by the WHO into (i) behavioral risk factors, (ii) metabolic risk factors, and (iii) other risk factors (Table 1.4). On the other hand, the AHA classifies cardiovascular risk factors into (1) major risk factors and (ii) contributing risk factors. The major risk factors are further divided into modifiable and nonmodifiable major risk factors (Table 1.5).

TABLE 1.4 The WHO classification of cardiovascular disease risk factors

Risk factor category	Risk factor[a]
Behavioral risk factors	Tobacco use
	Physical inactivity
	Unhealthy diet (rich in salt, fat, and calories)
	Harmful use of alcohol
Metabolic risk factors	Hypertension
	Diabetes mellitus
	Dyslipidemia
	Overweight and obesity
	Other metabolic risk factors (e.g., excess homocysteine)
Other risk factors	Advancing age
	Genetic disposition
	Gender
	Psychological factors (e.g., stress, depression, anxiety)
	Poverty and low educational status

Source: The World Health Organization.

[a]The term risk factor is defined as an exposure, behavior, or attribute that, if present and active, clearly increases the probability of a particular disease in a group of people who have the risk factor compared with an otherwise similar group of people who do not.

1.5.2 Major Cardiovascular Disease Risk Factors and Their Impact

As noted earlier, there are many risk factors associated with the development of cardiovascular diseases. The major risk factors, including tobacco use, hypertension, high cholesterol,

TABLE 1.5 The AHA classification of cardiovascular disease risk factors

Risk factor category		Risk factor
Major risk factors (significantly increase the risk of cardiovascular diseases)	Nonmodifiable factors (cannot be changed)	Increasing age
		Male sex
		Heredity
	Modifiable factors (can be modified, treated, or controlled by changing your lifestyle or taking medicine)	Tobacco smoke
		Unhealthy diet[a]
		High blood cholesterol
		High blood pressure
		Physical inactivity
		Obesity and overweight
		Diabetes mellitus
		Chronic kidney disease[b]
Contributing risk factors (other factors are associated with increased risk of cardiovascular disease, but their significance and prevalence haven't yet been precisely determined)		Stress
		Alcohol

Source: The American Heart Association (http://www.heart.org).

[a] Note that diet and nutrition are classified as contributing factors according to the AHA website listed earlier. This might cause confusion as unhealthy diet represents a major risk factor for cardiovascular diseases. As such, "diet and nutrition" is removed from the contributing risk factors category, and instead, "unhealthy diet" is added to the major risk factors category under "modifiable factors."

[b] Recent evidence suggests that chronic kidney disease is also a major risk factor for cardiovascular diseases. This is a particularly important risk factor considering the high global prevalence (8–16%) of chronic kidney disease [10, 11].

obesity, physical inactivity, and unhealthy diet, have a high prevalence across the world. Of particular significance in developing countries is the fact that while they are grappling with increasing rates of cardiovascular diseases, they still face the scourges of poor nutrition and infectious diseases. Nevertheless, with the exception of sub-Saharan Africa, cardiovascular diseases are also the leading cause of death in the developing world.

You will not necessarily develop cardiovascular diseases if you have a risk factor. But the more risk factors you have, the greater is the likelihood that you will, unless you take actions to modify your risk factors and work to prevent them from compromising your heart health. Table 1.6 summarizes the impact of some of the major risk factors on the development of cardiovascular diseases.

1.6 PREVENTION AND CONTROL OF CARDIOVASCULAR DISEASES

The mortality and morbidity of cardiovascular diseases (with ischemic heart disease and stroke as the major contributors) in the United States have been significantly reduced over the past decades owing to implementation of various health promotion initiatives and the availability of effective surgical procedures and drugs. Regardless of the aforementioned accomplishments, cardiovascular diseases remain a major public health issue in the developed countries including the United States, as well as worldwide. As noted in Section 1.5.2, with the exception of sub-Saharan Africa, cardiovascular diseases are the leading cause of death in the developing world. Globally, cardiovascular diseases (mainly ischemic heart disease and stroke) account for ~30% of all deaths, and the figure will surely increase in both developing and developed countries as risk factors for the diseases (primarily dyslipidemia, hypertension, obesity, diabetes mellitus, physical inactivity, poor diet, and smoking) continue to increase. In this context, the leading causes of death in the world in 2030 are projected to be ischemic heart disease and stroke.

The globally increasing burden of cardiovascular diseases has prompted various international and national organizations including the WHO, the World Heart Federation, the AHA, as well as many government agencies to take measures to prevent and control these diseases. In this regard, the past several years have witnessed a number of international and national initiatives and activities toward cardiovascular health promotion. These include the UN 2011 High-Level General Assembly Meeting on NCDs, the World Heart Federation Call to Action to Prevent and Control Cardiovascular Diseases, the AHA 2020 Health Impact Goal, and the US Department of Health and Human Services (DHHS) *Million Hearts* initiative. A brief description of these initiatives helps understand the key issues and major measures in the prevention and control of cardiovascular diseases in the world. In essence, the key to prevention and control of the global cardiovascular pandemic is to take measures to control the major modifiable risk factors of cardiovascular diseases. However, enforcement and execution of the effective measures represent a great global challenge.

1.6.1 The UN High-Level Meeting and Tackling Cardiovascular Diseases at the Global Level

The UN high-level meeting (in September 2011) on NCDs and the declaration represents an unprecedented opportunity for those involved in the prevention and treatment of

TABLE 1.6 The impact of some of the major cardiovascular disease risk factors

Risk factor	Impact
Family history	Premature paternal history of a heart attack is associated with a 70% increase in the risk of a heart attack in women and a 100% increase in men [12, 13]. Sibling history of heart disease increases the odds of heart disease by ~50% [14]
Smoking/tobacco use	Cigarette smoking increases cardiovascular disease risk in a "dose"-dependent manner in both men and women. Women smokers have an additional 25% higher risk than men smokers [15]. Nonsmokers who are exposed to secondhand smoke at home or workplace increase their risk of developing cardiovascular diseases by 25–30%. Current smokers have a 2–4 times increased risk of stroke compared with nonsmokers or those who have quit for over 10 years [16]. Although smoking cessation is associated with weight gain, quitting smoking has a net cardiovascular benefit [17]. Hence, every smoker should be encouraged to quit smoking and given support to do so [18]
Physical inactivity	Insufficient physical activity can be defined as <5 times 30 min of moderate activity per week, or <3 times 20 min of vigorous activity per week, or equivalent. People who are insufficiently physically active have a 20–30% increased risk of all-cause mortality compared to those who engage in at least 30 min of moderate-intensity physical activity most days of the week. Physical inactivity is responsible for over 12% of the global burden of myocardial infarction after accounting for other cardiovascular disease risk factors, such as cigarette smoking, diabetes mellitus, hypertension, abdominal obesity, lipid profile, no alcohol intake[a], and psychosocial factors [19]
Unhealthy diet	Dietary habits affect multiple cardiovascular risk factors, including both established risk factors (hypertension, dyslipidemias, glucose levels, and obesity/weight gain) and novel risk factors (e.g., inflammation and endothelial cell function). An unhealthy dietary pattern characterized by higher intake of processed meat, red meat, refined grains, French fries, sweets/desserts, and salt increases cardiovascular mortality by more than 20%. On the other hand, a healthy dietary pattern characterized by higher intake of vegetables, fruits, fish, poultry, and whole grains and lower intake of sodium reduces cardiovascular mortality by >20% [20]
Overweight and obesity	Overweight and obesity increase the risk of developing cardiovascular diseases. Childhood obesity is also a predictor of an increased rate of death, owing primarily to an increased risk of cardiovascular disease. Overweight and obesity are associated with other cardiovascular risk factors, such as hypertension, dyslipidemias, and diabetes mellitus. Interestingly, a recent study reported that those who were overweight or obese as children but who became nonobese as adults had a cardiovascular risk profile that was similar to that of persons who were never obese [21]. This suggests that that childhood obesity does not permanently increase cardiovascular disease risk provided that childhood obesity is successfully treated. Given that atherosclerotic cardiovascular diseases are a major driver of healthcare expenditures in the United States as well as worldwide, the development of more effective strategies for treating and preventing childhood obesity is a cost-effective way of achieving a long-term reduction in global atherosclerotic cardiovascular diseases [22]
Dyslipidemias	Raised blood cholesterol increases the risk of heart disease and stroke. Globally, one third of ischemic heart disease is attributable to high blood cholesterol. For every 30 mg/dl change in low-density lipoprotein cholesterol (LDL-C), the relative risk for coronary artery disease is changed in proportion by about 30% [23]
Hypertension	Nearly 70% of people who have a first heart attack, 77% of those who have a first time stroke, and 74% of those who have congestive heart failure have hypertension [20]
Diabetes mellitus	At least 68% of people >65 years of age with diabetes mellitus die of some form of heart disease; 16% die of stroke. Heart disease death rates among adults with diabetes mellitus are two to four times higher than the rates for adults without diabetes mellitus [20]
Metabolic syndrome[b]	Metabolic syndrome increases the risk of developing cardiovascular diseases by 78–135% [24, 25]
Chronic kidney disease	Cardiovascular mortality is about twice as high in patients with stage 3 chronic kidney disease (estimated glomerular filtration rate 30–59 ml/min per 1.73 m^2) and three times higher at stage 4 (15–29 ml/min per 1.73 m^2) than that in individuals with normal kidney function. The adjusted risk of cardiovascular mortality is more than doubled at the upper end of the microalbuminuria category (30–299 mg/g), compared with the risk in individuals with normal albuminuria [11]

[a] Moderate consumption of alcohol is associated with a decreased risk of developing cardiovascular diseases due, at least partly, to its beneficial effects on high-density lipoprotein cholesterol (HDL-C). Moderation means an average of one to two drinks per day for men and one drink per day for women. A drink (15 ml pure ethanol) is one 12 oz. beer, 4 oz. of wine, 1.5 oz. of 80-proof spirits, or 1 oz. of 100-proof spirits. In contrast, overconsumption of alcohol increases the risk of developing cardiovascular and other diseases.

[b] The term metabolic syndrome (also known as syndrome X, insulin resistance syndrome) refers to a cluster of risk factors for cardiovascular diseases and type 2 diabetes mellitus. Several different definitions for metabolic syndrome are in use; in the United States, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition and its two subsequent revisions have been used most commonly. By this definition, metabolic syndrome is diagnosed when three or more of the following five risk factors are present:

1. Fasting plasma glucose ≥100 mg/dl or undergoing drug treatment for elevated glucose
2. HDL-C <40 mg/dl in men or <50 mg/dl in women or undergoing drug treatment for reduced HDL-C
3. Triglycerides ≥150 mg/dl or undergoing drug treatment for elevated triglycerides
4. Waist circumference ≥102 cm in men or >88 cm in women
5. Blood pressure ≥130 mm Hg systolic or ≥85 mm Hg diastolic or undergoing drug treatment for hypertension or antihypertensive drug treatment in a patient with a history of hypertension

TABLE 1.7 The nine challenges and priorities identified by the World Heart Federation

1	Secure an outcomes statement at the United Nations high-level summit on noncommunicable diseases, taking place in September 2011
2	Enhance benefits of smoking cessation and implement affordable smoking cessation programs at the community level
3	Increase access to affordable, quality essential medicines for cardiovascular diseases in low- and middle-income countries
4	Close disparities in cardiovascular disease health
5	Increase the prevalence of workplace-wellness initiatives
6	Integrate cardiovascular disease prevention, detection, and treatment into primary healthcare settings
7	Increase the cardiovascular disease health workforce
8	Strengthen global, regional, and national partnerships
9	Improve data collection and monitoring of care provided to coronary heart disease patients

Source: The World Heart Federation.

cardiovascular diseases and all other concerned parties, including the member nations of the UN and their health ministries, to act and initiate priority programs and interventions that can avert the evolving pandemic of cardiovascular diseases and address the devastating worldwide effects of NCDs [26, 27]. The Lancet NCD Action Group and the NCD Alliance Group have proposed five high-priority interventions that include tobacco control, salt reduction, improved diets and physical activity, reduction in harmful alcohol intake, and access to essential drugs and technologies [28]. It is estimated that the implementation of these interventions (cost/person/year) would be $1.72 in China and $1.52 in India and is generally affordable worldwide. Salt reduction and tobacco control are the two population-directed interventions with the highest health impact. Full implementation of the Framework on Tobacco Control strategies would avert 5.5 million deaths over 10 years in 23 low- and middle-income countries. Reduction of salt intake by only 15% through mass media campaigns and industry reformulation of food products would avert 8.5 million deaths in 23 high-burden countries over 10 years.

1.6.2 The World Heart Federation Call to Action to Prevent and Control Cardiovascular Diseases

The World Heart Federation (http://www.world-heart-federation.org), representing 198 societies of cardiology and heart foundations worldwide, is acting with strong support and involvement from its member societies in developed nations, such as the AHA, the American College of Cardiology, and the European Society of Cardiology, whose expertise and experience with the prevention and treatment of cardiovascular diseases are substantial, to advocate for and assist with the implementation of effective strategies and initiatives that will lessen the global burden of cardiovascular diseases.

In the State of the Heart: Cardiovascular Disease Report (2011), the World Heart Federation and partner organizations call for a sustained worldwide effort to prevent and control cardiovascular diseases and encourage immediate endeavors by international organizations, national governments, healthcare professionals, and, importantly, the general public. The report identifies nine cardiovascular challenges and priorities for the global community (Table 1.7) to act on to prevent and control the global pandemic of cardiovascular diseases.

1.6.3 The AHA 2010 Health Impact Goal, 2020 Health Impact Goal, and Ideal Cardiovascular Health

1.6.3.1 2010 Impact Goal The AHA stated mission is "to build healthier lives, free of cardiovascular diseases and stroke." Consistent with that mission, the AHA set a strategic direction in 1998 to provide information and offer solutions for the prevention and treatment of cardiovascular diseases (including stroke) in people of all ages, with special emphasis on those at high risk. The identified goal was to reduce coronary heart disease, stroke, and risk by 25% by 2010, as measured by three key indicators [29, 30] listed below:

- A reduction by 25% in deaths due to coronary heart disease and stroke
- A reduction by 25% in prevalence of smoking, hypercholesterolemia, physical inactivity, and uncontrolled hypertension
- A zero growth rate of obesity and diabetic individuals

Despite the ambitious nature of the 2010 Impact Goal, by 2008, the reduction in the death rate due to coronary artery disease eclipsed 30.7%, and the reduction in the death rate due to stroke reached 29.4% [29]. What is even more provocative, however, is that at least 50% of the reduction in deaths due to coronary artery disease and stroke is attributable to a greater representation of preventive efforts, especially control of blood pressure, treatment of dyslipidemias, and a reduction in smoking. Yet, and ironically, the metric of a 25% risk reduction for smoking and physical inactivity and a zero growth rate for obesity and diabetes were not consistently met and have proven to be more difficult to achieve and will represent major challenges to the even more ambitious 2020 Impact Goal.

1.6.3.2 2020 Impact Goal and Ideal Cardiovascular Health The strategic approaches and progress toward the 2010 Impact Goal pointed to innovations that are required to define and implement new strategies for cardiovascular risk prevention, improving cardiovascular health, and preventing disease events and deaths. Accordingly, the AHA established its 2020 Impact Goal: "By 2020, to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%" [29]. The 2020 Impact Goal for the first time set an objective improvement in cardiovascular health as a necessary component of the goal. This was driven by the need for greater efforts in risk prevention and subsequently a greater reduction in the burden of cardiovascular diseases (including stroke).

Several key elements were addressed in the 2020 Impact Goal, including (i) the definition of cardiovascular health; (ii) the various attributes to cardiovascular health grouped into two broad categories, that is, four health behaviors (related to status of smoking, body mass index, physical activity, and diet) and three health factors (related to status of total blood cholesterol, blood pressure, and blood glucose); and (iii) an algorithm that would not only define health status but also would promote meaningful changes in cardiovascular health status for both adults and children.

An aggregation of the above seven health behaviors and health factors, now referred to as "The Simple 7," was established and made available to the public on the AHA website (http://www.heart.org/mylifecheck). "The Simple 7" consists of the following: (i) stop smoking, (ii) lose weight, (iii) get active, (iv) eat better, (v) control cholesterol, (vi) manage blood pressure, and (vii) reduce blood sugar. The definition of ideal cardiovascular health is provided in Table 1.8. To meet the complete definition of ideal cardiovascular health, an individual would need to meet the ideal levels of all seven components.

TABLE 1.8 Definition of ideal cardiovascular health: "The Simple 7" [29]

Goal/metric	Ideal cardiovascular health definition
1. Current smoking	
Adults >20 years of age	Never or quit >12 months ago
Children 12–19 years of age	Never tried; never smoked whole cigarette
2. Body mass index	
Adults >20 years of age	<25 kg/m^2
Children 12–19 years of age	<85th percentile
3. Physical activity[a]	
Adults >20 years of age	≥150 min/week moderate intensity or ≥75 min/week vigorous intensity or combination
Children 12–19 years of age	≥60 min of moderate- or vigorous-intensity activity every day
4. Healthy diet components[b]	
Adults >20 years of age	4–5 components
Children 12–19 years of age	4–5 components
5. Total cholesterol	
Adults >20 years of age	<200 mg/dl (untreated value)
Children 12–19 years of age	<170 mg/dl (untreated value)
6. Blood pressure	
Adults >20 years of age	<120/<80 mm Hg (untreated values)
Children 12–19 years of age	<90th percentile (untreated value)
7. Fasting plasma glucose	
Adults >20 years of age	<100 mg/dl (untreated value)
Children 12–19 years of age	<100 mg/dl (untreated value)

[a] Intensity of physical activity or exercise intensity can be defined in absolute or relative terms [31]. Absolute intensity reflects the rate of energy expenditure during exercise and is usually expressed in metabolic equivalents (METs), where one MET equals the resting metabolic rate of 3.5 ml O_2/kg body weight/minute. Relative intensity refers to the percent of aerobic power utilized during exercise and is expressed as percent of maximal heart rate or percent of VO_2max. Moderate-intensity activities are those performed at a relative intensity of 40–60% of VO_2max (or absolute intensity of 4–6 METs). Vigorous-intensity activities are those performed at a relative intensity of >60% of VO_2max (or absolute intensity of >6 METs). Moderate activities include such activities as brisk walking at 4 mph (5 METs), stationary cycling at 50 W (3 METs), or bicycling at 8 mph (5 METs). Vigorous activities include jogging 5 mph (8 METs), running 6 mph (10 METs), bicycling 12–13 mph (8 METs), and aerobic stepping 6–8 in. (8.5 METs). Easy or light activities are defined as <3 METs. Examples of light activities are walking 2 mph (2.5 METs), golfing with a cart, or playing piano.

[b] Healthy diet components include the following:

1. Fruits and vegetables: ≥4.5 cups per day
2. Fish: ≥two 3.5-oz servings per week (preferably oily fish)
3. Fiber-rich whole grains (≥1.1 g of fiber per 10 g of carbohydrate): ≥three 1-oz-equivalent servings per day
4. Sodium: ≤1500 mg per day
5. Sugar-sweetened beverages: ≤450 kcal (36 oz) per week.

1.6.3.3 Extremely Low Prevalence of Ideal Cardiovascular Health in the Recent "Heart Strategies Concentrating on Risk Evaluation" Study As stated earlier, the AHA 2020 Impact Goal focuses on promotion of health and control of risk rather than solely on prevention and treatment of specific cardiovascular diseases. As described earlier, this goal includes a new construct of cardiovascular health composed of four health behaviors and three health factors. The prevalence of the new AHA metrics that define ideal cardiovascular health has been addressed in a recent cohort of volunteers participating in a community-based health-screening survey, the Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) [32]. The results of the Heart SCORE study are sobering and the penetration of poor health is alarming. Among the 1933 participants (mean age 59 years; 44% blacks; 66% women), only one person (0.1%) met all seven components of the AHA definition of ideal cardiovascular health. The indices of ideal health behaviors and ideal health factors were only met by 2 and 1.4% of participants, respectively. The large gap between the prevalence of ideal cardiovascular health and the AHA 2020 Impact Goal suggests that the attainment of the stated goals for the next decade may be much more challenging than originally conceived. Targeted efforts will be required at multiple levels (e.g., individual, social, environmental, policies and intervention, and access to quality healthcare) in order to ensure the achievement of this ambitious goal [32, 33].

1.6.4 US DHSS "Million Hearts" Initiative

1.6.4.1 What Is It? As indicated in Section 1.4.2, at present, more than 14 million Americans are inflicted with a myocardial infarction or stroke with over 1.5 million new cases diagnosed each year. Cardiovascular diseases (notably myocardial infarction and stroke) are the leading cause of death in the United States and the largest cause of lower life expectancy among blacks. Related medical costs and productivity losses approach $450 billion annually, and inflation-adjusted direct medical costs are projected to triple over the next two decades if present trends continue. To reduce this burden, the US DHHS; other federal, state, and local government agencies; and a broad range of private-sector partners including the AHA lunched a "Million Hearts" initiative (http://millionhearts.hhs.gov) on September 13, 2011, to prevent one million heart attacks and strokes over the next 5 years by implementing proven, effective, inexpensive interventions [34]. Building on work already underway thanks to the Affordable Care Act, "Million Hearts" will help improve Americans' health and increase productivity.

1.6.4.2 Two Major Goals "Million Hearts" is focused on two goals:

- Empowering Americans to make healthy choices such as preventing tobacco use and reducing sodium and trans-fat consumption. This can reduce the number of people who need medical treatment such as blood pressure or cholesterol medications to prevent heart attacks and strokes.
- Improving care for people who do need treatment by encouraging a targeted focus on **a**spirin for people at risk, **b**lood pressure control, **c**holesterol management, and **s**moking cessation ("ABCS")—which address the major risk factors for cardiovascular diseases and can help to prevent heart attacks and strokes.

1.6.4.3 Five Strategies "Million Hearts" aims to improve heart disease and stroke prevention by:

- Improving access to effective care
- Improving the quality of care
- Focusing more clinical attention on heart attack and stroke prevention
- Increasing public awareness of how to lead a heart-healthy lifestyle
- Increasing the consistent use of high blood pressure and cholesterol medications

1.6.4.4 Six 2017-Specific Goals By empowering Americans to make healthy choices and improving care, Million Hearts strives to achieve six specific goals by 2017, as listed in Table 1.9.

1.6.4.5 Perspectives "Million Hearts" makes preventing heart attacks and strokes a top priority for the DHHS, its component agencies, and the broader healthcare system. "Million Hearts" targets improvements in both clinical preventive practice (e.g., reducing uncontrolled blood pressure and cholesterol, increasing aspirin use to prevent and reduce the severity of heart attacks and strokes) and community prevention (e.g., eliminating smoking and exposure to secondhand smoke, decreasing sodium and *trans*-fat intake in the population).

The "Million Hearts" initiative is aligned with the heart disease and stroke targets of the Healthy People 2020 (http://www.healthypeople.gov), which have been set on the basis of achieving a 10–20% improvement in cardiovascular prevention over a 10-year period. By using the diverse platforms of health reform to launch a rigorous effort to achieve successful clinical and community preventive interventions, the campaign is expected to produce a 10% reduction in the rate of acute cardiovascular events each year. There are ~2 million heart attacks and strokes in the United States annually. A 10% reduction would equate to 200,000 prevented cardiovascular events per year. If this rate is achieved and sustained over the 5-year campaign, "Million Hearts" will reach the goal of preventing one million heart attacks and strokes.

"Million Hearts" has the potential to make a significant contribution to the AHA 2020 Impact Goal to prevent 20%

TABLE 1.9 The six 2017-specific goals of the "Million Hearts" initiative

Indicator	Baseline	2017 goal
Aspirin use for people at high risk	47%	65%
Blood pressure control	46%	65%
Effective treatment of high cholesterol (LDL cholesterol)	33%	65%
Smoking prevalence	19%	17%
Sodium intake (average)	3.5 g/day	20% reduction
Artificial trans-fat[a] consumption (average)	1% of calories/day	50% reduction

Source: United States DHHS.

[a]Artificial trans fats (also known as trans-fatty acids or partially hydrogenated oils) are manufactured fats created during an industrial process that adds hydrogen to liquid vegetable oils to stabilize polyunsaturated fatty acids to prevent them from becoming rancid and to keep them solid at room temperature. Natural trans fats are uncommon, and small amounts of trans fats occur naturally in some meat and dairy products, including beef, lamb, and butterfat. The health effects of the naturally occurring trans fats are currently unknown. Unless otherwise specified, the term "trans fats" refers primarily to artificial trans fats. Artificial trans fats impose significant adverse health effects and increase the risk of developing coronary heart disease, stroke, and diabetes mellitus, among others [35, 36]. Many food companies and restaurants have eliminated trans fats over the past decade, in part because of the US Food and Drug Administration (FDA) nutrition label changes enacted in 2006. And some local governments, including New York City, already prohibit the use of trans fats in foods [37]. According to the FDA, these restrictions have helped reduce trans-fat intake among Americans from 4.6 g daily in 2003 to about 1 g a day in 2012. To further reduce the adverse health impact of trans fats, in November 2013, the FDA announced a plan to ban artificial trans fats in foods. According to the FDA estimate, the proposed ban on the use of trans fats could prevent an additional 20,000 heart attacks and 7,000 deaths annually in the United States.

of cardiovascular disease (including stroke) deaths by 2020 by preventing 10% of deaths resulting from myocardial infarction and stroke (which account for one third of all cardiovascular disease deaths) over 5 years. It would be expected that preventing one million heart attacks and strokes would reduce cardiovascular disease deaths even further by also reducing deaths from other cardiovascular disease causes.

To reach the AHA 2020 Impact Goal for cardiovascular health (to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases including stroke by 20% by 2020), ~4 million cardiovascular events must be prevented in 10 years. The AHA 2020 Impact Goal may be more aggressive than the "Million Hearts" goal, but the data show that with concerted public/private and cross-organizational effort to achieve a range of clinical and community preventive interventions, these goals are achievable [38].

1.7 CARDIOVASCULAR RISK PREDICTION AND EVIDENCE-BASED TREATMENTS

The decrease in the cardiovascular mortality rate in the United States and some developed nations has been hailed as one of the great achievements in public health. The reduction in the cardiovascular mortality rate started before powerful modern medical treatments entered mainstream medical practice, signifying that improvements in risk factors (primarily smoking, total cholesterol, and blood pressure) were key milestones to initiate decline. Nevertheless, analyses suggest that, more recently, both propitious changes in risk factors and the introduction of effective treatments have contributed greatly to reducing cardiovascular mortality rates in the United States and some developed countries, although the balance of these two contributors varies among countries [39]. It has been suggested that further reductions in cardiovascular mortality can be realized if more aggressive targets for improving the distribution of risk factors in the population can be met and if compliance with evidence-based treatments can be increased [39, 40]. Hence, risk management based on cardiovascular risk prediction and evidence-based treatments, including drug therapies, are indispensible components of the armamentarium for combating cardiovascular diseases and reducing their global burden. This section introduces the cardiovascular risk prediction algorithms and briefly describes the status of evidence-based treatments, especially drug therapies, to serve as a prelude to the introduction to principles of cardiovascular pharmacology in Chapter 2.

1.7.1 Cardiovascular Risk Prediction

Primary prevention (Table 1.10) is paramount for the large number of individuals who are at high risk for developing cardiovascular diseases. Given limited resources, finding low-cost prevention strategies is a top priority in both developed and developing regions. Using prediction algorithms or risk scores to identify those at high risk to target specific behavioral or pharmacological interventions is a well-established primary prevention strategy and has proven to be cost-effective.

Various methods to predict cardiovascular risk use information on multiple risk factors, including age, gender, smoking, hypertension, diabetes mellitus, and blood lipids. Of these, perhaps the best known is the Framingham Risk Score [41], with simple online tools readily available to calculate 10-year risk of coronary artery disease-related adverse events (http://www.mecalc.com/framingham-cardiac-risk-score). The predicted risk has been used by certain clinical guidelines to make clinical decisions about treatments with drugs.

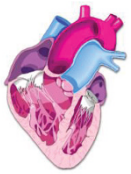
Although the original Framingham Risk Score estimates risk of coronary artery disease, the recently developed new Framingham Risk Score/Profile systems are also used to predict 10-year or 30-year risk of general cardiovascular diseases [42, 43] (Fig. 1.6). The simple online tools for calculating the general cardiovascular risks are available on the website (http://www.framinghamheartstudy.org/risk) of the Framingham Heart Study (Box 1.3). In addition to the Framingham Risk Score systems, several other algorithms have been reported for predicting the total cardiovascular risk in various human populations [44]. These include the Systemic Coronary Risk Estimation (SCORE) [45], the Joint British Societies (JBS3) risk calculator [46], and the most recently proposed Pooled Cohort Equations by the American College of Cardiology and American Heart Association (ACC/AHA) [47, 48].

TABLE 1.10 The three levels of prevention of cardiovascular diseases

Level of prevention	Description
Primary prevention	Primary prevention aims to prevent the disease from occurring. Primary prevention reduces both the incidence and prevalence of a disease. Health promotion targeting on avoiding the risk factors of cardiovascular diseases is an example of primary prevention
Secondary prevention	The goal of secondary prevention is to find and treat disease early. In many cases, the disease can be cured if detected early. For example, patients with early stage of coronary artery disease and hypercholesterolemia are treated with a statin drug to prevent the occurrence of myocardial infarction
Tertiary prevention	Tertiary prevention targets the person who already has symptoms of the disease with the goals to slow down the disease, prevent the disease complications, and improve quality of life. For example, patients following myocardial infarction are treated with inhibitors of the renin–angiotensin–aldosterone system to prevent or retard the development of congestive heart failure

(A)

Age	HDL-C	Total C	SBP not treated	SBP treated	Smoker	Diabetic	Points
	60+		<120				−2
	50–59						−1
30–34	45–49	<160	120–129	<120	No	No	0
	35–44	160–199	130–139				1
35–39	<35	200–239	140–159	120–129			2
		240–279	160+	130–139		Yes	3
		280+		140–159	Yes		4
40–44				160+			5
45–49							6
							7
50–54							8
							9
55–59							10
60–64							11
65–69							12
							13
70–74							14
75+							15



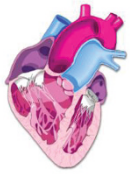
Points	Risk %	CV age
≤−3	<1	
−2	1.1	
−1	1.4	<30*
0	1.6	30
1	1.9	32
2	2.3	34
3	2.8	36
4	3.3	38
5	3.9	40
6	4.7	42
7	5.6	45

Points	Risk %	CV age
8	6.7	48
9	7.9	51
10	9.4	54
11	11.2	57
12	13.2	60
13	15.6	64
14	18.4	68
15	21.6	72
16	25.3	76
17	29.4	>80**
18+	>30	

FIGURE 1.6 General cardiovascular risk prediction in men (panel A) and women (panel B). This 10-year risk prediction model is based on Ref. [42]. The general cardiovascular diseases include coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure. As illustrated, six predictors are employed, including (i) age, (ii) diabetes, (iii) smoking, (iv) treated and untreated systolic blood pressure, (v) total cholesterol, and (vi) HDL cholesterol. Body mass index (BMI) can be used to replace lipids in a simpler model. In panel A, *, when the points are <0, the cardiovascular age is <30 years; **, when the points are ≥17, the cardiovascular age is >80 years. In panel B, *, when the points are <1, the cardiovascular age is <30 years.

(B)

Age	HDL-C	Total C	SBP not treated	SBP treated	Smoker	Diabetic	Points
			<120				−3
	60+						−2
	50–59			<120			−1
30–34	45–49	<160	120–129		No	No	0
	35–44	160–199	130–139				1
35–39	<35		140–149	120–129			2
		200–239		130–139	Yes		3
40–44		240–279	150–159			Yes	4
45–49		280+	160+	140–149			5
				150–159			6
50–54				160+			7
55–59							8
60–64							9
65–69							10
70–74							11
75+							12



Points	Risk %	CV age
≤−2	<1	
−1	1.0	
0	1.2	<30*
1	1.5	31
2	1.7	34
3	2.0	36
4	2.4	39
5	2.8	42
6	3.3	45
7	3.9	48
8	4.5	51
9	5.3	55

Points	Risk %	CV age
10	6.3	59
11	7.3	64
12	8.6	68
13	10.0	73
14	11.7	79
15	13.7	>80
16	15.9	
17	18.5	
18	21.5	
19	24.8	
20	28.5	
21+	>30	

FIGURE 1.6 (*Continued*)

BOX 1.3 FRAMINGHAM HEART STUDY

The **Framingham Heart Study** is a long-term, ongoing cardiovascular study on residents of the town of Framingham, Massachusetts. The study under the direction of the National Heart, Lung, and Blood Institute (NHLBI; then known as the National Heart Institute) began in 1948 with 5209 adult subjects from Framingham and is now on its third generation of participants. The origins of the study are closely linked to the cardiovascular health of President Franklin D. Roosevelt and his premature death from hypertensive heart disease and stroke in 1945 at the age of 63 [49]. At the time, little was known about the general causes of heart disease and stroke, but the death rates for cardiovascular diseases had been increasing steadily since the beginning of the century and had become an American epidemic. The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to cardiovascular diseases by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of cardiovascular diseases or suffered a heart attack or stroke. For more than 60 years, the Framingham Heart Study and the residents of Framingham, Massachusetts, have been synonymous with the remarkable advances made in the prevention of heart disease in the United States and throughout the world. More than 60 years of data collected from residents of Framingham have produced over 1000 scientific papers; identified major risk factors associated with heart disease, stroke, and other diseases (and of course the birth of the Framingham Risk Score, as described in Section 1.7.1); paved the way for researchers to undertake singular clinical trials based on Framingham findings; created a revolution in preventive medicine; and forever changed the way the medical community and general public view the genesis of disease. Having spent the past six decades looking at risk factors and lifestyle habits, researchers are now at the forefront of investigating how genes contribute to common metabolic disorders such as obesity, hypertension, diabetes, and even Alzheimer's disease [50, 51].

1.7.2 Evidence-Based Treatments

The entire medical profession strives to deliver care that is safe, timely, evidence based, efficient, equitable, and patient centered. Toward this goal, cardiology probably enjoys the greatest evidence base of any medical specialty [52]. The significant decline in the cardiovascular mortality in the United States and many other developed countries results from both prevention of the risk factor and effective treatment of the diseases. Remarkable progress has recently been made in the evidence-based treatments of cardiovascular diseases with pharmacological management set to assume an increasingly important role. Indeed, pharmacological agents not only play an important part in the treatment of the cardiovascular diseases but also in the management of risk factors of cardiovascular diseases. Pharmacological therapy has become an essential component of the armamentarium of evidence-based medicine for combating cardiovascular diseases. In fact, cardiovascular drugs are among the most widely used prescription drugs in the United States and other developed nations, as well as the developing world. Hence, a thorough understanding on the essentials and advances of cardiovascular pharmacology and therapeutics is of paramount importance for both prevention and treatment of cardiovascular diseases. Chapter 2 introduces the basic principles of pharmacology in general and cardiovascular pharmacology in particular to set a stage for the detailed discussion of the various topics in cardiovascular pharmacology and therapeutics throughout the rest of the book.

1.8 SUMMARY OF CHAPTER KEY POINTS

- The term cardiovascular diseases refers to a group of diseases involving the heart, blood vessels, or the sequelae of poor blood supply due to a decreased vascular supply and include diseases of the heart, vascular diseases of the brain, and diseases of other blood vessels.
- Cardiovascular diseases are classified in various ways, including schemes based on anatomical location and the involvement of atherosclerosis. The World Health Organization ICD-10 category represents the most comprehensive and most widely adopted classification scheme for human diseases, including cardiovascular diseases.
- Cardiovascular diseases are responsible for 48% of all global deaths due to noncommunicable diseases, and as such, they remain as a chief contributor to the global burden of disease.
- Globally, cardiovascular diseases (mainly ischemic heart disease and stroke) account for ~30% of all deaths, and the figure will surely increase in both developing and developed countries as risk factors for the diseases continue to increase.
- The development of cardiovascular diseases results from the complicated interactions between genes and environmental and dietary factors. The major cardiovascular disease risk factors include tobacco use, hypertension, high blood cholesterol, obesity, physical inactivity, and unhealthy diet, which have a high prevalence across the world and continue to increase.
- Prevention and control of cardiovascular diseases depend largely on how to effectively identify and manage the risk factors through population-based health promotion programs and initiatives at the community, national, and international levels.
- Risk management based on cardiovascular risk prediction and evidence-based treatments, including drug therapies, are indispensible components of the armamentarium for combating cardiovascular diseases and reducing their global burden.

1.9 SELF-ASSESSMENT QUESTIONS

1.9.1. According to a recent report of the Global Burden of Disease 2010 Study (Lancet 2012; 380:2095–128), there were 52.8 million deaths globally in 2010, of which 34.5 million deaths were caused by noncommunicable diseases, including cardiovascular diseases, cancer, and diabetes, among others. Cardiovascular diseases accounted for which of the following?
   A. ~5% of the total global deaths
   B. ~10% of the total global deaths
   C. ~15% of the total global deaths
   D. ~30% of the total global deaths
   E. ~50% of the total global deaths

1.9.2. According to the World Health Organization 2011 Global Atlas on Cardiovascular Disease Prevention and Control, which of the following is the number one cause of the death in the world?
   A. Congenital heart disease
   B. Heart failure
   C. Hypertension
   D. Ischemic heart disease
   E. Stroke

1.9.3. In a recent community-based Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) study (Circulation 2011; 123:850–7), the AHA construct of cardiovascular health and the AHA ideal health behaviors index and ideal health factors index were evaluated among 1933 participants (mean age 59 years; 44% blacks; 66% women). Out of the 1933 participants in the Heart SCORE study, how many participants met all seven components of the AHA definition of ideal cardiovascular health?
   A. 1
   B. 15
   C. 29
   D. 246
   E. 512

1.9.4. The development of cardiovascular diseases results from the complicated interactions between genes and environmental and dietary factors. There are many risk factors for developing cardiovascular diseases, which are classified into modifiable and nonmodifiable factors. Which of the following is not considered a modifiable risk factor for cardiovascular diseases?
   A. A diet rich in sea salt
   B. Chronic kidney disease
   C. Diabetes mellitus
   D. Moderate consumption of alcohol
   E. Smoking of <20 cigarettes daily

1.9.5. Declines in stroke death rate in the United States now rank stroke as which of the following?
   A. 3rd leading cause of death in the nation
   B. 4th leading cause of death in the nation
   C. 5th leading cause of death in the nation
   D. 6th leading cause of death in the nation
   E. 7th leading cause of death in the nation

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2

INTRODUCTION TO PRINCIPLES OF PHARMACOLOGY

2.1 OVERVIEW

In the foreword to the first edition of *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*, now a widely acclaimed text in its 3rd edition in medical pharmacology, Eugene Braunwald, a world-renowned cardiologist at Harvard Medical School, stated that "Almost every practicing physician prescribes drugs; most write many prescriptions every day. The learning of pharmacology, the science that deals with the action and use of drugs, is among the most important steps in becoming a physician. Rather than reflexly ordering a medication to treat a specific symptom or disease, modern therapeutics requires an understanding of the underlying mechanism of action of a pharmacological agent, how it influences and is influenced by the disease for which it is prescribed, and its capacity for causing both beneficial and harmful clinical effects." Indeed, pharmacology, as a biomedical discipline, focuses on the complex interactions between the drugs and living systems and has contributed substantially to the advances in the management of human diseases in general and cardiovascular diseases in particular. The discovery of new drugs and the rapid development of cardiovascular sciences in the past five decades have helped cardiovascular pharmacology and therapeutics become a major medical subspecialty that plays a central part in cardiovascular medicine. Knowledge in cardiovascular pharmacology and therapeutics is not only essential for the evidence-based treatment of patients with cardiovascular diseases but also important for cardiovascular disease prevention and promotion of public health. In this context, cardiovascular diseases are chief contributors to global burden of disease (Chapter 1). To lay a basis for understanding cardiovascular pharmacology and therapeutics, this chapter examines the general principles of pharmacology and therapeutics, beginning with defining pharmacology and related terms, followed by introducing the pharmacological paradigm as well as drug development and regulation. The chapter ends with a brief survey of the new developments and challenges of cardiovascular pharmacology and therapeutics.

2.2 DEFINITIONS AND HISTORY

2.2.1 What Is Pharmacology?

The term pharmacology is derived from the Greek words pharmakon (meaning a drug or medicine) and logos (meaning the truth about or a rational discussion). In general terms, pharmacology is the science dealing with drug action (including both beneficial and harmful effects) on biological systems. In its entirety, pharmacology embraces knowledge of sources, chemical properties, biological effects, and therapeutic uses of drugs. Pharmacology is a science that is fundamental not only to human clinical medicine but also to pharmacy, nursing, and dentistry, as well as veterinary medicine. Pharmacology taught in medical schools can be defined as a biomedical discipline that deals with the action and use of drugs in the diagnosis, treatment, or prevention of human diseases.

Cardiovascular Diseases: From Molecular Pharmacology to Evidence-Based Therapeutics, First Edition. Y. Robert Li.

2.2.2 Definitions of Related Terms

Although medical pharmacology has a focus on mechanisms of drug actions, it also emphasizes the clinical use of the drugs, better known as clinical pharmacology. Hence, medical pharmacology may be considered as a discipline that bridges the basic medical science and clinical medicine. The distinction between medical pharmacology and other related disciplines, such as pharmacotherapeutics, has becoming less obvious. Table 2.1 lists several different terms related to medical pharmacology.

2.2.3 A Brief History of Pharmacology

Historically, the roots of pharmacology go back to the ancient civilizations that used plants and plant extracts both in healing and as poisons. The accumulated total of this empirical knowledge, acquired by mankind through the ages, provided a foundation for the evolution of scientific pharmacology as it exists today. The well-known discovery of the beneficial effects of foxglove extracts for treating heart disease, the use of the bark of the willow and cinchona trees in treating fever, and the effectiveness of extracts of the poppy in the treatment of dysenteries are outstanding examples of such knowledge that have resulted in important advances in pharmacology.

The rise of organic chemistry in the last half of the nineteenth century, together with the development of physiology and, later, biochemistry, allowed empiricism to be discarded in favor of a rational approach, giving birth to modern pharmacology. The first published classic text, "Outline of Pharmacology," written by Oswald Schmiedeberg in 1878, set the momentum for today's pharmacology advancement throughout the world. Table 2.2 summarizes the major historic figures and events in the early development of modern pharmacology. The photos of the major historic figures are shown in Figure 2.1. Table 2.3 lists the Nobel Prize-winning research that has shaped modern pharmacology.

TABLE 2.1 Medical pharmacology and related terms

Term	Definition
Medical pharmacology	Medical pharmacology is the science that deals with the action and use of drugs in the diagnosis, treatment, or prevention of human diseases. Medical pharmacology includes basic pharmacology and clinical pharmacology. Basic pharmacology emphasizes the basic science principles, such as pharmacokinetics and pharmacodynamics, whereas clinical pharmacology is underpinned by the basic science of pharmacology with added focus on the application of pharmacological principles and methods in the clinical management of human diseases
Drug	The term drug is often defined in two ways: (i) the US Federal Food, Drug, and Cosmetic Act (FD&C Act) defines drugs, in part, by their intended use as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [FD&C Act, sec. 201(g)(1)]; and (ii) in pharmacology, a drug is defined as a natural product, chemical substance, or pharmaceutical preparation intended for administration to a human or animal to diagnose, treat, or prevent a disease
Pharmacotherapeutics	Pharmacotherapeutics is the medical science concerned with the use of drugs in the treatment of diseases, and its essence is clinical use of drugs. Pharmacology provides a rational basis for pharmacotherapeutics by explaining the mechanisms and effects of drugs on the body and the relationship between dose and drug response. Hence, pharmacotherapeutics and pharmacology are closely related and often intertwined. In this context, clinical pharmacology is even more closely intertwined with pharmacotherapeutics. The term pharmacotherapy refers to treatment of disease through the use of drugs
Pharmacy	Pharmacy is the science and profession concerned with the preparation, storage, dispensing, and proper use of drug products
Pharmaceutics	Pharmaceutics is concerned with the formulation and chemical properties of pharmaceutical products, such as tablets, liquid solutions and suspensions, and aerosols. Do not confuse pharmaceutics with pharmacotherapeutics
Pharmacognosy	Pharmacognosy is the study of drugs isolated from natural sources, including plants, microbes, animal tissues, and minerals
Nutraceutical	Nutraceutical is the term used to describe any substance that is considered a food or part of a food, including nutritional supplements that allege to provide health benefits
Functional food	Functional food refers to food that contains physiologically active compounds that provide health benefits beyond their nutrient contributions. The terms nutraceutical and functional food are often used interchangeably
Phytochemical	The term phytochemical refers to any nonnutrient compound in plant-derived foods that possesses biological activity in the body