# Contents

About the Companion Website vi  
Contributors vii  
Foreword xvi  
Preface xvii  
Acknowledgments xviii  

## Part I Principles and Techniques  1

### Section I Basic Knowledge  3

1. Atherogenesis and Inflammation  3  
   Umair Hayat, Vikas Thondapu, Tim Tsay, and Peter Barlis  
2. The Essentials of Femoral Vascular Access and Closure  17  
   Ted Feldman and Mohammad Sarraf  
3. Radial Artery, Alternative Arm Access, and Related Techniques  27  
   Thomas J. Ford, Martin K.C. Ng, Vikas Thondapu, and Peter Barlis  
4. Optimal Angiographic Views for Coronary Angioplasty  34  
   Gioel Gabrio Secco and Carlo Di Mario  
5. Material Selection  44  
   Sahil A. Parikh, Michele Pighi, and Carlo Di Mario  

### Section II Imaging and Physiology  59

6. Physiologic Assessment in the Cardiac Catheterization Laboratory: CFR, FFR, iFR, and Beyond  59  
   Sukhjinder Nijjer and Justin Davies  
7. Intravascular Ultrasound and Virtual Histology: Principles, Image Interpretation, and Clinical Applications  71  
   Adriano Caixeta, Akiko Maehara, and Gary S. Mintz  
8. Optical Coherence Tomography, Near-Infrared Spectroscopy, and Near-Infrared Fluorescence Molecular Imaging  91  
   Ismail Dogu Kilic, Roberta Serdoz, Enrico Fabris, Farouc Amin Jaffer, and Carlo Di Mario  
   Omosalewa O. Lalude, Francesca Pugliese, Pim J. de Feyter, and Stamatis Lerakis  
10. Cardiovascular Magnetic Resonance Imaging  126  
    Omosalewa O. Lalude and Stamatis Lerakis  

### Section III PCI in Different Clinical Settings  138

11. Stable Coronary Artery Disease  138  
   Abhiram Prasad and Bernard J. Gersh  
12. PCI Strategies in Acute Coronary Syndromes without ST Segment Elevation (NSTEMI)  148  
   Georgios E. Christakopoulos, Subhash Banerjee, and Emmanouil S. Brilakis  
13. Primary and Rescue PCI in Acute Myocardial Infarction and Elements of Myocardial Conditioning  155  
   Tayo Addo, Neil Swanson, and Anthony Gershlick  
   Bimmer E.P.M. Claessen, Dagnan Ouwend, and Josè P.S. Henriques  

### Section IV PCI in Different Lesion Types  168

15. Percutaneous Coronary Intervention in Unprotected Left Main  168  
   Gill Louise Buchanan, Alaide Chieffo, and Antonio Colombo  
16. Bifurcation Lesion Stenting  175  
   Yves Louvard, Thierry Lefevre, Bernard Chevalier, and Philippe Garot  
17. Risk Stratification Approach to Multivessel Coronary Artery Disease  185  
   Davide Capodanno and Corrado Tamburino  
18. Chronic Total Coronary Occlusion  190  
   Gerald S. Werner and Emmanouil S. Brilakis  
19. Percutaneous Coronary Intervention of Arterial and Vein Grafts  201  
   Bimmer E.P.M. Claessen, Josè P.S. Henriques, and George D. Dangas  
20. Interventional Approach in Small Vessel, Diffuse, and Tortuous Coronary Artery Disease  205  
   Robert Pyo  
21. In-Stent Restenosis in New Generation DES Era  213  
   Marco G. Mennuni and Patrizia Presbitero  

### Section V Special Techniques and Complications  224

22. Laser, Rotational, and Orbital Coronary Atherectomy  224  
   Kalob N. Axxress, Peter O’Kane, Robert Pyo, and Simon R. Redwood  
23. Thrombus-Containing Lesions  233  
   Giovanni Luigi De Maria and Adrian P. Banning  
24. Specialized Balloons in Percutaneous Coronary Intervention: Cutting, Scoring, Gliding, and Drug-Eluting Balloons  244  
   Bimmer E.P.M. Claessen, Josè P.S. Henriques, and George D. Dangas
Coronary Artery Dissections, Perforations, and the No-Reflow Phenomenon 248
Adriano Caixeta, Luiz Fernando Ybarra, Azeem Latib, Flavio Airoldi, Roxana Mehran, and George D. Dangas

Access Site Complications 267
Jose M. Wiley, Fernando Pastor, and Cristina Sanina

Renal Insufficiency and the Impact of Contrast Agents 274
Michael Donahue and Carlo Briguori

Radiation Management in Interventional Cardiology 282
Stephen Balter and Charles E. Chambers

Concepts of Cell Therapy and Myocardial Regeneration 290
Kevin O’Gallagher, Zoi Astroulakis, Alex Sirker, and Jonathan M. Hill

Section VI Clinical Trials in Coronary Heart Disease 296
Statistical Essentials in the Design and Analysis of Clinical Trials 296
Usman Baber and Stuart J. Pocock

Historical Perspective of Sirolimus and Paclitaxel-Eluting Stent Clinical Studies 301
Adriano Caixeta, Leonardo Guimarães, Philippe Généreux, and George D. Dangas

Cobalt-Chromium Everolimus-Eluting Stents 313
Vikas Thondapu, Yoshinobu Onuma, Bimmer E.P.M. Claessen, Patrick W. Serruys, and Peter Barlis

Platinum-Chromium Everolimus-Eluting Stents 326
Vikas Thondapu, Bimmer E.P.M. Claessen, George D. Dangas, Patrick W. Serruys, and Peter Barlis

Bioresorbable Stents 335
Gianluca Caiazzo, Alessio Mattesini, Ciro Indolfi, and Carlo Di Mario

The Biolimus Stent Family 344
Anna Franzone, Raffaele Piccolo, and Stephan Windecker

The Biotronik Stent Family 360
Anna Franzone, Raffaele Piccolo, and Stephan Windecker

Novel Drug-Eluting Stent Systems 368
J. Ribamar Costa, Jr., Adriano Caixeta, and Alexandre A.C. Abizaid

Part II Interventional Pharmacology 377
Section I Fundamentals of Interventional Pharmacology 379
Basics of Antiplatelet and Anticoagulant Therapy for Cardiovacular Disease 379
Piera Capranzano and Dominick J. Angiolillo

Balance of Ischemia and Bleeding in Selecting Antithrombotic Regimens 389
Bimmer E.P.M. Claessen and José P.S. Henriques

Oral Antiplatelet Agents in PCI 397
Jonathan A. Batt, Joseph R. Dunford, George D. Dangas, and Vijay Kanadian

Parenteral Anticoagulant Agents in PCI 408
Piera Capranzano, Corrado Tamburino, and George D. Dangas

Parenteral Antiplatelet Agents in PCI 415
Piera Capranzano, Giuseppe Gargiulo, and Corrado Tamburino

Role of Parenteral Agents in PCI for Stable Patients 421
Joanna Ghobrial, David A. Burke, and Duane S. Pinto

Vasoactive and Antiarrhythmic Drugs During PCI 432
Bimmer E.P.M. Claessen and José P.S. Henriques

The Optimal Duration of Dual Antiplatelet Therapy After PCI 436
Mikkel Malby Schoos, Roxana Mehran, and George D. Dangas

Triple Antiplatelet Therapy and Combinations with Oral Anticoagulants After PCI 443
Jonathan A. Batt, Joseph R. Dunford, Roxana Mehran, and Vijay Kanadian

Section III Pharmacological Testing 453
Peri-procedural Platelet Function Testing in Risk Stratification and Clinical Decision Making 453
Paul A. Gurbel, Fang Liu, Gailing Chen, and Udaya S. Tantry

Genetics and Pharmacogenetics in Interventional Cardiology 459
Hillary Johnston-Cox, Johan L.M. Björkegren, and Jason C. Kovacic

Monitoring and Reversal of Anticoagulation and Antiplatelet Agents 469
Gregory W. Yost and Steven R. Steinhubl

Part III Hypertension and Structural Heart Disease 485
Section I Systemic and Pulmonary Hypertension 487
Right Heart Catheterization and Pulmonary Hemodynamics 487
P. Christian Schulze

Treatment of Pulmonary Embolism: Medical, Surgical, and Percutaneous 491
Ian del Conde and Barry T. Katzen

Renal Denervation for Resistant Hypertension 499
Hitesh C. Patel, Carl Hayward, Sebastian Ewen, and Felix Mahfoud

Section II Structural Heart Interventions 507
Antithrombotic Strategies in Valvular and Structural Heart Disease Interventions 507
Mikkel Malby Schoos, Davide Capodanno, and George D. Dangas

Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy 517
Amir-Ali Fassa, George D. Dangas, and Ulrich Sigwart

Left Atrial Appendage Exclusion 525
Jorge G. Panizo and Jacob S. Koruth

Cryptogenic Stroke, Patent Foramen Ovale, and ASD Closure 530
Barry Love
Contents

57 Paravalvular Leak Closure and Ventricular Septal Defect Closure 540
Saurabh Sanon, Mackram F. Eleid, Allison K. Cabaika, and Charanjit S. Rihal

Section III Valvular Heart Disease Interventions 546

58 Aortic Valvuloplasty and Large-Bore Percutaneous Arterial Access 546
Matthew I. Tomey, Annapoorna S. Kini, Samin K. Sharma, and Jason C. Kovacic

59 Transfemoral Aortic Valve Implantation: Preparation, Implantation, and Complications 558
Brandon M. Jones, Samir R. Kapadia, Amar Krishnaswamy, Stephanie Mick, and E. Murat Tuzcu

60 Transsthoracic Aortic Valve Implantation 569
Giuseppe Bruschi, Kaleb N. Asrress, Paola Colombo, and Vinayak N. Bapat

61 New Aortic Valve Technologies 575
Dinnyre Alexandri Siqueira and Alexandre A.C. Abizaid

62 Transseptal Puncture 582
Alec Vahanian, Dominique Himbert, Fabrice Extramiana, Gregory Durocq, and Eric Brochet

63 Principles of Carpentier's Reconstructive Surgery in Degenerative Mitral Valve Disease 592
Farzan Filsoufi and Alain Carpentier

64 Mitral Valve Repair: MitraClip and Emerging Techniques 599
Ted Feldman, Mohammad Sarraf, Mayra Guerrero, and Francesco Maisano

65 Balloon Mitral Valvuloplasty 606
C.N. Manjunath, Nagaraja Mouorthy, and Upendra Kaul

66 Pulmonary Artery and Valve Catheter-Based Interventions 619
Kasey Chaszewski, Damien Kenny, and Ziyad M. Hijazi

67 Imaging for Planning and Guidance for Structural Heart Interventions 629
Ankit Parikh and Stamatis Lerakis

Part IV Vascular Disease for the Interventionalist 641

Section I Cerebrovascular Disease 643

68 Acute Stroke Intervention 643
Stefan C. Bertog, Iris Q. Grunwald, Anna Luisa Kuhn, Laura Vaskeleye, Ilona Hofmann, Sameer Gafoor, Markus Reinartz, Predrag Matic, and Horst Sievert

69 Carotid Artery Angioplasty and Stenting 653
Alberto Cremonesi, Shane Gieowarsingh, and Fausto Castriota

70 Cerebral Aneurysms: Diagnosis, Indications, and Strategies for Endovascular Treatment 671
Gyula Gál

Section II Aorta and Branch Diseases 677

71 Management of Acute Aortic Syndromes 677
Christoph A. Nienaber and Rachel E. Clough

72 Thoracic Endovascular Aortic Aneurysm Repair 687
Paul S. Lajos and Michael L. Marin

73 Endovascular Aortic Aneurysm Repair 692
William Beckerman, Paul S. Lajos, and Peter L. Farries

74 Acute and Chronic Mesenteric Ischemia 698
Robert J. Rosen, Amit Jain, and Jennifer Drury

75 Renal Artery Interventions 705
Mark Shipeng Yu, Kun Xiang, Steven T. Haller, and Christopher J. Cooper

76 Revascularization for Arteries in the Pelvis 713
Femi Philip and Jason H. Rogers

Section III Peripheral Arterial Disease 721

77 Iliac Interventions 721
Manish Taneja and Apoorva Gogna

78 Superficial Femoral Artery Interventions 726
Cristina Sanina, Pedro R. Cox-Alomar, Prakash Krishnan, and Jose M. Wiley

79 Popliteal Artery Interventions 733
Karthik Gujja, Gopi Punukollu, Vishal Kapur, and Prakash Krishnan

80 Below the Knee Interventions in Critical Limb Ischemia 738
Karthik Gujja, Katarzyna Nasiaidko, Arthur Tarricone, and Prakash Krishnan

81 Subclavian, Vertebral, and Upper Extremity Vascular Disease 748
Ian Del Conde, Cristina Sanina, and Jose M. Wiley

Section IV Venous Disease/Interventions 754

82 Antithrombotic Strategies in Endovascular Interventions: Current Status and Future Directions 754
Mehdi H. Shishehbor

83 Chronic Venous Insufficiency 759
Karthik Gujja, Cristina Sanina, and Jose M. Wiley

84 Cardiac Vein Anatomy and Transcoronary Sinus Catheter Interventions in Myocardial Ischemia 768
Werner Mohl, Levente Molnár, and Béla Merkely

Index 776
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Contributors

Alexandre A.C. Abizaid, MD, PhD
Director, Invasive Cardiology Department
Instituto Dante Pazzanese de Cardiologia (IDPC);
Hospital do Coração—Associação do Sanatório Sírio (HCOr);
Hospital Israelita Albert Einstein
São Paulo, Brazil

Tayo Addo, MD
Associate Professor of Medicine
University of Texas Southwestern Medical Center
Dallas, TX, USA

Flavio Airoldi, MD
Director
Interventional Cardiology Unit
IRCCS Multimedica
Sesto San Giovanni, Italy

Dominick J. Angiolillo, MD, PhD
Department of Medicine, Division of Cardiology
University of Florida College of Medicine—Jacksonville
Jacksonville, FL, USA

Kaleab N. Asrress, MA, PhD, MRCP
Department of Cardiology
St. Thomas’ Hospital;
King’s College London British Heart Foundation Centre of Excellence
The Rayne Institute, St. Thomas’ Hospital
London, UK

Zoë Astroulakis, MBBS, MRCP, PhD
Consultant in Interventional Cardiology
Department of Cardiology, St George’s Hospital
London, UK

Usman Baber, MD, MS
Director of Clinical Biometrics
Cardiovascular Institute Assistant Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Stephen Balter, PhD
Professor of Radiology and Medicine
Columbia University Medical Center
New York, NY, USA

Subhash Banerjee, MD
Chief of Cardiology
VA North Texas Health Care System;
Professor of Medicine
University of Texas Southwestern Medical Center
Dallas, TX, USA

Adrian P. Banning, MBBS, MD, FRCP, FESC
Consultant Cardiologist
Oxford Heart Centre, Oxford University Hospitals
John Radcliffe Hospital
Oxford, UK

Vinayak N. Bapat, MBBS, MS, FRCS.CTh
Department of Cardiology and Cardiothoracic Surgery
St Thomas’ Hospital;
King’s College London British Heart Foundation Centre of Excellence
The Rayne Institute, St. Thomas’ Hospital
London, UK

Peter Barlis, MBBS, MPH, PHD, FACC, FESC, FRACP
Professor of Medicine
Faculty of Medicine, Dentistry & Health Sciences
The University of Melbourne
Victoria, Australia

Jonathan A. Batty, BSc, MBChB
Institute of Cellular Medicine
Newcastle University;
The Royal Victoria Infirmary
Newcastle upon Tyne NHS Foundation Trust
Newcastle upon Tyne, UK

William Beckerman, MD
Resident in Vascular Surgery
Division of Vascular Surgery
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Stefan C. Bertog, MD
CardioVascular Center Frankfurt
Frankfurt, Germany

Johan L.M. Björkegren, MD, PhD
The Zena and Michael A. Wiener Cardiovascular Institute
and the Department of Genetics & Genomic Sciences
Institute of Genomics and Multiscale Biology
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Carlo Briguori, MD, PhD, FACC, FSCAI
Chief of Interventional Cardiology
Laboratory of Interventional Cardiology and Department of Cardiology
Clinica Mediterranea
Naples, Italy

Emmanouil S. Brilakis, MD, PhD
Minneapolis Heart Institute
Minneapolis, MN, USA;
Professor of Medicine
University of Texas Southwestern Medical Center
Dallas VA Medical Center
Dallas, TX, USA
Eric Brochet, MD
Cardiologist
Echocardiography Laboratory
Department of Cardiology
Hôpital Bichat-Claude Bernard
Paris, France

Giuseppe Bruschi, MD, FESC
Department of Cardiology and Cardiothoracic Surgery
Niguarda Ca’ Granda Hospital
Milan, Italy

Gill Louise Buchanan, MBChB
Department of Cardiology
North Cumbria University NHS Trust
Carlisle, UK

David A. Burke, MD
Division of Cardiovascular Medicine, Department of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA, USA

Allison K. Cabalka, MD
Division of Pediatric Cardiology
Mayo Clinic College of Medicine
Rochester, MN, USA

Gianluca Caiazzo, MD, PhD
Division of Cardiology, Department of Medical and Surgical Sciences
Magna Graecia University
Catanzaro, Italy;
National Institute of Health Research (NIHR)
Royal Brompton & Harefield NHS Foundation Trust
London, UK

Adriano Caixeta, MD, PhD
Interventional Cardiologist
Hospital Israelita Albert Einstein;
Professor of Medicine
Universidade Federal de São Paulo,
São Paulo, Brazil

Davide Capodanno, MD, PhD
Associate Professor of Cardiology
University of Catania;
Interventional Cardiologist
Ferrarotto Hospital
Catania, Italy

Piera Capranzano, MD
Cardiovascular Department
Ferrarotto Hospital, University of Catania
Catania, Italy

Alain Carpentier, MD, PhD
Hôpital Européen Georges-Pompidou
Paris, France

Fausto Castrioni, MD
Maria Cecilia Hospital
GVM Care & Research
Cotignola, Italy

Charles E. Chambers, MD
Professor of Medicine and Radiology
Penn State Hershey Medical Center
Hershey, PA, USA

Kasey Chaszczewski, MD
Rush University Medical Center
Chicago, IL, USA

Gailing Chen, MD
Sinai Center for Thrombosis Research
Cardiac Catheterization Laboratory
Baltimore, MD, USA

Bernard Chevalier, FESC
Institut Cardiovasculaire Paris Sud
Hôpital Privé Jacques Cartier, Massy;
Hôpital Privé Claude Galien
Quincy, France

Alaide Chieffo, MD
Consultant Interventional Cardiologist
Interventional Cardiology Unit
San Raffaele Scientific Hospital
Milan, Italy

Georgios E. Christakopoulos, MD
Research Fellow
VA North Texas Health Care System;
University of Texas Southwestern Medical Center
Dallas, TX, USA

Bimmer E.P.M. Claessen, MD, PhD
Department of Cardiology
Academic Medical Center—University of Amsterdam
Amsterdam, The Netherlands

Rachel E. Clough, MD
University Heart Center Rostock
Department of Internal Medicine
Cardiology, Pulmonology, Intensive Care Medicine
Rostock School of Medicine
Rostock, Germany

Antonio Colombo, MD
Interventional Cardiology Unit
San Raffaele Scientific Hospital
Milan, Italy

Paola Colombo, MD, PhD
Department of Cardiology and Cardiothoracic Surgery
Niguarda Ca’ Granda Hospital
Milan, Italy

Christopher J. Cooper, MD
Department of Medicine, Cardiovascular Medicine
University of Toledo
Toledo, OH, USA

J. Ribamar Costa, Jr., PhD
Chief of the Medical Section of Coronary Intervention of the Instituto Dante Pizzanesi de Cardiologia (IDPC);
Hospital do Coração—Associação do Sanatório Sirio (HCor)
São Paulo, Brazil

Pedro R. Cox-Alomar, MD, MPH, FACC
Interventional Cardiology Fellow
Division of Cardiology
University of Florida College of Medicine
UF Health Medical Center
Jacksonville, FL, USA
Alberto Cremonesi, MD
Maria Cecilia Hospital
GVM Care & Research
Cotignola, Italy

George D. Dangas, MD, PhD, FACC, FSCAI, FESC, FAHA
Professor of Medicine
Director, Cardiovascular Innovation
Department of Cardiology
Mount Sinai Medical Center
New York, NY
USA

Justin Davies, BSc, MBBS, MRCP, PhD
Imperial College London
London, UK

Giovanni Luigi De Maria, MD
Oxford Heart Centre, Oxford University Hospitals
John Radcliffe Hospital
Oxford, UK

Ian del Conde, MD, FACC
Miami Cardiac and Vascular Institute
Miami, FL, USA

Carlo Di Mario, MD, PhD, FRCP, FACC, FSCAI, FESC
Consultant Cardiologist
National Institute of Health Research (NIHR)
Royal Brompton & Harefield NHS Foundation Trust, London;
Professor of Clinical Cardiology
National Heart & Lung Institute Imperial College London
London, UK

Michael Donahue, MD
Interventional Cardiologist
Laboratory of Interventional Cardiology and Department of Cardiology
Clinica Mediterranea
Naples, Italy

Jennifer Drury
Physician Assistant
Lenox Hill Heart and Vascular Institute
New York, NY
USA

Gregory Ducrocq, MD
Hôpital Bichat-Claude Bernard
Paris, France

Joseph R. Dunford, MRes
Institute of Cellular Medicine
Newcastle University
Newcastle upon Tyne, UK

Mackram F. Eleid, MD
Division of Cardiovascular Diseases
Mayo Clinic College of Medicine
Rochester, MN, USA

Sebastian Ewen, MD
Klinik für Innere Medizin III
Universitätsklinikum des Saarlandes
Homburg-Saar, Germany

Fabrice Extramiana, MD
Hôpital Bichat-Claude Bernard
Paris, France

Enrico Fabris, MD
Interventional Cardiologist
National Institute of Health Research (NIHR)
Royal Brompton & Harefield NHS Foundation Trust, London;
NHMI Imperial College London
London, UK;
Cardiovascular Department
Ospedali Riuniti and University of Trieste
Trieste, Italy

Peter L. Faries, MD, FACS
The Franz W. Sichel Professor of Surgery
Chief, Division of Vascular Surgery
Professor of Surgery & Radiology
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Amir-Ali Fassa, MD
La Tour Hospital
Geneva, Switzerland

Ted Feldman, MD, FESC, FACC, MSCI
Director, Cardiac Catheterization Laboratories
Evanston Hospital
NorthShore University HealthSystem
Evanston, IL, USA

Pim J. de Feyter, MD, PhD, FESC, FACC
Professor of Cardiac Imaging
Departments of Cardiology and Radiology
Erasmus MC University Medical Center
Rotterdam, The Netherlands

Farzan Filsoufi, MD
Professor
Department of Cardiovascular Surgery
Icahn School of Medicine at Mount Sinai
New York, NY
USA

Thomas J. Ford, MBChB
Department of Cardiology
St. George Hospital;
Faculty of Medicine
University of New South Wales
Sydney, New South Wales
Australia

Anna Franzone, MD
Department of Cardiology
Bern University Hospital
Bern, Switzerland

Sameer Gafoor, MD
CardioVascular Center Frankfurt
Frankfurt, Germany;
Swedish Medical Center
Seattle, WA, USA

Gyula Gál, MD
Department of Radiology, Section of Neuroradiology
Odense University Hospital
Odense, Denmark
Giuseppe Gargiulo, MD
Cardiovascular Department
Ferrarotto Hospital
University of Catania
Catania, Italy

Philippe Garot, FESC
Institut Cardiovasculaire Paris Sud
Hôpital Privé Jacques Cartier, Massy;
Hôpital Privé Claude Galien
Quincy, France

Philippe Généreux, MD
Clinical Instructor
Division of Cardiology
Center for Interventional Vascular Therapy
Columbia University Medical Center
New York, NY, USA

Bernard J. Gersh, MBChB, DPhil, FACC
Professor of Medicine
Mayo Clinic and Mayo Clinic College of Medicine
Rochester, MN, USA

Anthony Gershlick, MBBS, BSc, FRCP
University of Leicester
Leicester, UK

Joanna Ghibrial, MD, MS
Division of Cardiovascular Medicine
Department of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA, USA

Shane Gieowarsingh, MBBS, MET
Maria Cecilia Hospital
GVM Care & Research
Cotignola, Italy

Apoorva Gogna, MBBS, FRCR
Consultant, Interventional Radiology
Singapore General Hospital
Singapore

Iris Q. Grunwald, MD, PhD
Post Graduate Medical Institute
Anglia Ruskin University
Chelmsford, UK;
Southend University Hospital
Southend-on-Sea, UK

Mayra Guerrero, MD, FACC, FSCAI
NorthShore University HealthSystem
Evanston, IL, USA

Leonardo Guimarães, MD
Interventional Cardiologist
Hospital Israelita Albert Einstein;
Universidade Federal de São Paulo
São Paulo, Brazil

Karthik Gujja, MD, MPH
Assistant Professor of Medicine
Icahn School of Medicine at Mount Sinai;
Assistant Director of Endovascular Fellowship
The Zeta and Michael A. Weiner Cardiovascular Institute
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Paul A. Gurbel, MD
Director, Inova Center for Thrombosis
Research and Drug Development
Inova Heart and Vascular Institute
Falls Church, VA, USA

Steven T. Haller, PhD
Department of Medicine
Cardiovascular Medicine
University of Toledo
Toledo, OH, USA

Umair Hayat
Melbourne Medical School
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne
Victoria, Australia

Carl Hayward, MB, BChir, MRCP, MA
Cardiology Research Fellow
National Institute of Health Research (NIHR)
Royal Brompton & Harefield NHS Foundation Trust
London, UK

José P.S. Henriques, MD, PhD
Department of Cardiology
Academic Medical Center—University of Amsterdam
Amsterdam, The Netherlands

Ziyad M. Hijazi, MD, MPH, MSCAI
Professor of Pediatrics
Weill Cornell Medicine
Chair, Department of Pediatrics
Sidra Medical and Research Center
Doha, Qatar

Jonathan M. Hill, MD
Department of Cardiology
King’s College Hospital NHS Foundation Trust
London, UK

Dominique Himbert, MD
Cardiologist
Department of Cardiology
Hôpital Bichat-Claude Bernard
Paris, France

Ilona Hofmann, MD
CardioVascular Center Frankfurt
Frankfurt, Germany

Ciro Indolfi, MD
Division of Cardiology, Department of Medical and Surgical Sciences
Magna Graecia University
Catanzaro, Italy

Farouc Amin Jaffer, MD, PhD
Associate Professor
Cardiology Division
Massachusetts General Hospital, Harvard Medical School
Boston, MA, USA

Amit Jain, MD
Lenox Hill Heart and Vascular Institute
New York, NY, USA
Hillary Johnston-Cox, MD, PhD
The Zena and Michael A. Wiener Cardiovascular Institute and the Department of Genetics & Genomic Sciences
Institute of Genomics and Multiscale Biology
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Brandon M. Jones, MD
Fellow in Cardiovascular Medicine and Interventional Cardiology
Robert and Suzanne Tomsich Department of Cardiovascular Medicine
Cleveland Clinic
Cleveland, OH, USA

Samir R. Kapadia, MD
Director, Sones Cardiac Catheterization Laboratory
Section Head, Interventional Cardiology
Professor of Medicine
Robert and Suzanne Tomsich Department of Cardiovascular Medicine
Cleveland Clinic
Cleveland, OH, USA

Vishal Kapur, MD, FACC
Assistant Professor of Cardiology
The Zena and Michael A. Weiner Cardiovascular Institute
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Barry T. Katzen, MD
Miami Cardiac and Vascular Institute
Miami, FL, USA

Upendra Kaul, MD, DM, FCSI, FSCAI, FACC, FAMS
Executive Director and Dean Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Damien Kenny, MB, MD, FACC, FSCAI
Consultant Cardiologist
Our Lady’s Children’s Hospital
Dublin, Ireland

Ismail Dogu Kilic, MD
Department of Cardiology
Pamukkale University Hospitals
Denizli, Turkey

Annapoorna S. Kini, MD
The Zena and Michael A. Wiener Cardiovascular Institute
The Marie-Josée and Henry R. Kravis Cardiovascular Health Center
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Jacob S. Koruth, MD
Director, Experimental Lab
Helmley Electrophysiology Center; Assistant Professor of Medicine and Cardiology
Mount Sinai Hospital
New York, NY, USA

Jason C. Kovacic, MD, PhD
The Zena and Michael A. Wiener Cardiovascular Institute
The Marie-Josée and Henry R. Kravis Cardiovascular Health Center
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Prakash Krishnan, MD, FACC, FSCAI
Assistant Professor of Medicine—Cardiology and Radiology
Icahn School of Medicine at Mount Sinai;
Director of Endovascular Services
The Zena and Michael A. Wiener Cardiovascular Institute
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Amar Krishnaswamy, MD
Associate Program Director, Interventional Cardiology
Robert and Susan Tomsich Department of Cardiovascular Medicine
Cleveland Clinic
Cleveland, OH, USA

Anna Luisa Kühn, MD, PhD
Department of Radiology
University of Massachusetts Medical School
Worcester, MA, USA

Vijay Kunadian, MBBS, MD, FRCP, FESC, FACC
Institute of Cellular Medicine
Faculty of Medical Sciences, Newcastle University
Newcastle upon Tyne;
Freeman Hospital Newcastle upon Tyne Hospital NHS Foundation Trust
Newcastle upon Tyne, UK

Paul S. Lajos MD, RPVI
Associate Chief of Vascular Surgery
Mount Sinai Queens;
Division of Vascular Surgery
Assistant Professor of Surgery & Radiology
Department of Surgery
The Mount Sinai Hospital
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Omosalewa O. Lalude, MBBS, FACC
Medical Director, Adult Cardiac Imaging
Memorial Healthcare System
Hollywood, FL, USA

Azeem Latib, MBBCh
Interventional Cardiologist
Interventional Cardiology Unit
San Raffaele Scientific Institute
Milan, Italy

Thierry Lefevre, FESC, FSCAI
Institut Cardiovasculaire Paris Sud
Hôpital Privé Claude Galien
Massy;
Hôpital Privé Claude Galien
Quincy, France

Stamatios Lerakis, MD, PhD
Professor of Medicine (Cardiology), Radiology and Imaging Sciences
Adjunct Professor of Biomedical Engineering
Emory University School of Medicine and Georgia Institute of Technology
Director of Imaging for the Emory Structural and Valve Heart Center
Director of Cardiac MRI at Emory University Hospital and Emory Clinic
Atlanta, GA, USA

Fang Liu, MD
Sinai Center for Thrombosis Research
Cardiac Catheterization Laboratory
Baltimore, MD, USA
Yves Louvard, FSCAI
Institut Cardiovasculaire Paris Sud
Hôpital Privé Jacques Cartier
Massy;
Hôpital Privé Claude Galien
Quincy, France

Barry Love, MD
Assistant Professor of Pediatrics and Medicine
Icahn School of Medicine
Mount Sinai Medical Center
New York, NY, USA

Akiko Maehara, MD
Columbia University Medical Center;
Cardiovascular Research Foundation
New York, NY, USA

Felix Mahfoud, MD
Klinik für Innere Medizin III
Universitätsklinikum des Saarlandes
Homburg-Saar, Germany;
Harvard-MIT Biomedical Engineering
Institute of Medical Engineering and Science
Cambridge, MA, USA

Francesco Maisano, MD, FESC
Division of Cardiac and Vascular Surgery
University Hospital Zurich
Zurich, Switzerland

C.N. Manjunath, MD, DM
Professor and Head of Department of Cardiology
Sri Jayadeva Institute of Cardiovascular Sciences and Research
Bangalore, India

Michael L. Marin, MD, FACS
The Jacobson Professor of Surgery
Chairman, Department of Surgery
Icahn School of Medicine at Mount Sinai
Surgeon-In-Chief
Mount Sinai Health System
New York, NY, USA

Predrag Matic, MD
CardioVascular Center Frankfurt
Frankfurt, Germany

Alessio Mattesini, MD
Department of Heart and Vessels
AOUC Careggi
Florence, Italy

Roxana Mehran, MD
Department of Cardiology
Mount Sinai Medical Center
New York, NY, USA

Marco G. Mennuni, MD
Interventional Cardiologist
Department of Cardiology
Humanitas Research Hospital
Rozzano, Milan, Italy

Béla Merkely, MD, PhD, DSc
Chairman and Director
Heart and Vascular Center, Semmelweis University
Budapest, Hungary

Stephanie Mick, MD
Department of Cardiovascular Surgery
Cleveland Clinic
Cleveland, OH, USA

Gary S. Mintz, MD
Chief Medical Officer
Columbia University Medical Center;
Cardiovascular Research Foundation
New York, NY, USA

Werner Mohl, MD, PhD
Professor of Surgery
Department of Cardiac Surgery
Medical University of Vienna
Vienna, Austria

Levente Molnár, MD
Assistant Lecturer
Semmelweis University
Budapest, Hungary

Nagaraja Moorthy, MD, DM
Assistant Professor
Sri Jayadeva Institute of Cardiovascular Sciences and Research
Bangalore, India

Katarzyna Nasiadko, MD, MHA
Research Assistant
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Martin K.C. Ng, PhD, MBBS
University of New South Wales Medical School,
The University of Sydney;
Department of Cardiology, Royal Prince Alfred Hospital
Sydney, New South Wales
Australia

Christoph A. Nienaber, MD, PhD
University Heart Center Rostock, Department of Internal Medicine I
Cardiology, Pulmology, Intensive Care Medicine
Rostock School of Medicine
Rostock, Germany

Sukhjinder Nijjer, BSc, MBChB, MRCP, PhD
Hammersmith Hospital
Imperial College Healthcare NHS Trust
London, UK

Kevin O’Gallagher, BA, MBBS, MRCP
Registrar in Interventional Cardiology
Department of Cardiology, King's College Hospital NHS Foundation Trust
London, UK

Peter O’Kane, MD
Dorset Heart Centre
Royal Bournemouth Hospital
Bournemouth, UK

Yoshinobu Onuma, MD
Research Fellow
Thoraxcenter
Erasmus Medical Center
Rotterdam, The Netherlands
Dagmar Ouweneel, MSc
Department of Cardiology
Academic Medical Center—University of Amsterdam
Amsterdam, The Netherlands

Jorge G. Panizo, MD
Helmsley Electrophysiology Center
Mount Sinai Hospital
New York, NY, USA

Ankit Parikh, MD
Emory University School of Medicine
Atlanta, GA, USA

Sahil A. Parikh, MD, FACC, FSCAI
Assistant Professor of Medicine
Case Western Reserve University School of Medicine
Director, Center for Research and Innovation
Director, Interventional Cardiology Fellowship Program
Director, Experimental Interventional Cardiology Laboratory
University Hospitals Case Medical Center, Harrington Heart & Vascular Institute
Cleveland, OH, USA

Fernando Pastor, MD
Medical Director & Director Cardiac Catheterizations Laboratory
Instituto Cardiovascular Cuyo
Sanatorio La Merced
Villa Mercedes, Argentina

Hitesh C. Patel, BSc, MB, BS, MRCP
Cardiology Research Fellow
National Institute of Health Research (NIHR)
Royal Brompton & Harefield NHS Foundation Trust
London, UK

Femi Philip, MD
Division of Cardiovascular Medicine
University of California, Davis Medical Center
Sacramento, CA, USA

Raffaele Piccolo, MD
Department of Cardiology
Bern University Hospital
Bern, Switzerland

Michele Pighi, MD
National Institute of Health Research (NIHR)
Royal Brompton & Harefield NHS Foundation Trust
London, UK

Duane S. Pinto, MD, MPH
Division of Cardiovascular Medicine
Department of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA, USA

Stuart J. Pocock, PhD
Professor and Chair
London School of Hygiene and Tropical Medicine
University of London
London, UK

Abhiram Prasad, MD, FRCP, FESC, FACC
Professor of Interventional Cardiology
St George’s, University of London
London, UK

Patrizia Presbitero, MD
Senior Consultant in Interventional Cardiology
Department of Cardiology
Humanitas Research Hospital
Rozzano, Milan, Italy

Francesca Pugliese, MD
Erasmus MC University Medical Center
Rotterdam, The Netherlands

Gopi Punukollu, MD
Interventional Cardiology
Lenox Hill Hospital (North Shore LIJ)
New York, NY, USA

Robert Pyo, MD
Montefiore Medical Center
Albert Einstein College of Medicine
New York, NY, USA

Simon R. Redwood, MB, BS, MD, FRCP, FACC
Professor of Interventional Cardiology
Consultant Interventional Cardiologist
Department of Cardiology
St. Thomas’ Hospital;
King’s College London British Heart Foundation Centre of Excellence
The Rayne Institute, St Thomas’ Hospital
London, UK

Markus Reinartz, MD
CardioVascular Center Frankfurt
Frankfurt, Germany;
Herz- Jesu-Krankenhaus
Dernbach, Germany

Charanjit S. Rihal, MD, MBA
Division of Cardiovascular Diseases
Mayo Clinic College of Medicine
Rochester, MN, USA

Jason H. Rogers, MD
Director, Interventional Cardiology
Division of Cardiovascular Medicine
University of California, Davis Medical Center
Sacramento, CA, USA

Robert J. Rosen, MD
Lenox Hill Heart and Vascular Institute
New York, NY, USA

Cristina Sanina, MD
Postdoctoral Fellow, ISCI
University of Miami Miller School of Medicine
Miami, FL, USA

Saurabh Sanon, MD, FACC
Division of Cardiovascular Diseases
Mayo Clinic College of Medicine
Rochester, MN, USA

Mohammad Sarraf, MD
NorthShore University HealthSystem
Evanston, IL, USA

Mikkel Malby Schoos, MD, PhD
Department of Cardiology
Zealand University Hospital
Denmark
Contributors

P. Christian Schulze, MD, PhD
Department of Internal Medicine I
Division of Cardiology, Angiology
Pneumology and Intensive Medical Care
Friedrich-Schiller-University Jena
Jena, Germany

Gioel Gabrio Secco, MD, PhD
Interventional Cardiologist
Department of Cardiology
Santi Antonio e Biagio e Cesare Arrigo Hospital
Alessandria, Italy

Roberta Serdoz, MD
National Institute of Health Research (NIHR)
Royal Brompton & Harefield NHS Foundation Trust, London;
NHLI Imperial College London
London, UK

Patrick W. Serruys, MD, PhD
Faculty of Medicine
National Heart & Lung Institute
Imperial College London
London, UK

Samin K. Sharma, MD
The Zena and Michael A. Wiener Cardiovascular Institute
The Marie-Josée and Henry R. Kravis Cardiovascular Health Center
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Mehdi H. Shishehbor, DO, MPH, PhD
Director, Endovascular Services
Associate Program Director
Interventional Cardiology
Heart & Vascular Institute
Cleveland Clinic
Cleveland, OH, USA

Horst Sievert, MD, PhD
CardioVascular Center Frankfurt
Frankfurt, Germany;
Anglia Ruskin University
Chelmsford
Essex, UK

Ulrich Sigwart
Emeritus Professor
Geneva University Hospitals
Geneva, Switzerland

Dimytri Alexandre Siqueira, MD, PhD
Dante Pazzanese Institute of Cardiology
São Paulo, Brazil

Alex Sirker, MA (Cantab), MB, BChir, MRCP, PhD
Consultant in Interventional Cardiology
Department of Cardiology, UCLH and St Bartholomew's Hospital
London, UK

Steven R. Steinhubl, MD
Scripps Translational Science Institute
San Diego, CA, USA

Neil Swanson, MBChB
University of Leicester
Leicester, UK

Corrado Tamburino, MD, PhD
Professor of Cardiology
University of Catania;
Director, Cardio-Thoracic-Vascular Department
Ferrarotto Hospital
Catania, Italy

Manish Taneja, MBBS, FRCR
Specialist in Interventional Radiology and Interventional Neuroradiology
Raffles Hospital, Singapore

Udaya S. Tantry, PhD
Director, Thrombosis Research Lab
Inova Center for Thrombosis Research and Drug Development
Inova Heart and Vascular Institute
Falls Church, VA, USA

Arthur Tarricone, BS
Senior Associate Researcher
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Vikas Thondapu
Melbourne Medical School
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne
Victoria, Australia

Matthew I. Tomey, MD
Assistant Professor of Medicine (Cardiology)
The Zena and Michael A. Wiener Cardiovascular Institute, and The Marie-Josée and Henry R. Kravis Cardiovascular Health Center
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Tim Tsay
Melbourne Medical School
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne
Victoria, Australia

E. Murat Tuzcu, MD
Professor of Medicine, Interventional Cardiology
Chief Academic Officer
Chief, Department of Cardiovascular Medicine
Cleveland Clinic
Abu Dhabi, United Arab Emirates

Alec Vahanian, MD, FESC, FACC
Head of Cardiology
Hôpital Bichat-Claude Bernard
Paris, France

Laura Vaskelyte, MD
CardioVascular Center Frankfurt
Frankfurt, Germany

Jose M. Wiley, MD, MPH, FACC, FACP, FSCAI
Associate Professor of Clinical Medicine
Albert Einstein College of Medicine
Director of Endovascular Interventions
Division of Cardiology
Montefiore Einstein Center for Heart & Vascular Care
Bronx, NY, USA
Stephan Windecker, MD
Department of Cardiology
Bern University Hospital
Bern, Switzerland

Kun Xiang, MD, PhD
Department of Medicine, Cardiovascular Medicine
University of Toledo
Toledo, OH, USA

Luiz Fernando Ybarra, MD
Interventional Cardiologist
Hospital Israelita Albert Einstein;
Universidade Federal de São Paulo
São Paulo, Brazil

Gregory W. Yost, DO
Department of Cardiology
Geisinger Medical Center
Danville, PA, USA

Mark Shipeng Yu, MD
Department of Medicine, Cardiovascular Medicine
University of Toledo
Toledo, OH, USA
The development of interventional cardiology has followed the evolutionary trend of internal medicine. After World War II and during the latter part of the twentieth century, the number of subspecialties in the field of Internal Medicine exploded. The "Great Internal Medicine" became Cardiology, Pneumonology, Gastroenterology, Endocrinology, and so on.

Interventional cardiology was originally created by Andreas Grünzig when, for the first time in a conscious patient, he applied the technique of percutaneous transluminal angioplasty: the whole intervention consisted of "inflating" a balloon inside the narrowed section of a coronary artery. It took almost two decades to diversify the approach of the percutaneous treatment of coronary artery disease with devices such as directional atherectomy, rotational atherectomy, and stenting.

The ground-breaking work in congenital treatment, the first pulmonary balloon angioplasty, the first closure of an atrial septum defect, almost went unnoticed by the "mature" interventional cardiologist. It was not until Alain Cribier's pioneering work that the field of adult valvular intervention ushered in the specialty of interventional cardiology outside the coronary arteries.

In the 1990s the term TCT was coined (transcatheter treatment) and this further evolved into the concept of percutaneous coronary intervention (PCI), which today englobes and comprises intracranial treatment, carotid treatment, aortic arch reconstruction, descending aorta, femoral, popliteal, pedal artery, most of the congenital abnormalities including ASD, VSD, patent ductus arteriosus, and also left atrial appendage and most recently the extraordinary explosion of devices to treat aortic stenosis, aortic regurgitation, and mitral valve stenosis … as well as others such as the alcoholization of the interventricular septum in hypertrophic cardiomyopathy.

As a consequence of this diversification, we see highly specialized doctors in interventional cardiology, who dedicate their time to total chronic occlusion, bifurcation, aortic stenosis with TAVR, mitral clips, mitral valve replacement, and so on.

What is striking is that the development of a highly specialized subspecialty requires an in-depth knowledge of very specific details to efficiently and safely perform these interventions. For instance, the transseptal punctures for left appendage closure or clip implantation are quite different and necessitate 3D imaging online with precise measurement in 3D dimension of the site of the puncture, which has to be a few millimeters below, above, at the back, in the front of the septum, and so on. Thus, the new generation gets involved in a very granular analysis of the syndromes, techniques, type of lesion, and type of imaging, and may, at some point, lose the “helicopter view of the field.” Therefore we must commend the editors of the second edition of the Interventional Cardiology for having a very broad and wide description of the field, which is an increasingly challenging endeavor.

It would be easy to be laudative about the content. It is apparent that all the authors have done their utmost to cover the field. It is always very challenging to start and maintain a so-called “textbook.” In my personal experience as an editor/co-editor of 42 (text) books; I can frankly say that a textbook in the field is a most exacting activity, in the sense that only a few great names have been able to repeat the experience multiple times during their lifetime and their textbook became such a historical entity that the baton was taken up by other people.

So once more I can only congratulate the editors for having conceived, constructed, and finalized the expanded second edition of this textbook. A textbook is a matter of endurance and repetition, and while it might be easy to criticize the content, the real question is this: will these three magnificent editors be able to continue the work of updating their textbook throughout their careers, because that’s what really gives a sense of purpose to a textbook. I sincerely hope that they will.

Patrick W. Serruys, MD, PhD
January 2016
There is no doubt that our specialty has been expanding in every direction at a fast pace in recent years. Just in the 5 years since publication of the first edition of *Interventional Cardiology*, almost its entire content has been revised extensively. The updated edition includes not only current data and critical new information on the most important subjects, but also introduces new subspecialties that have been developing in the intervening years. Additionally, specialists from other areas of medicine and surgery are taking part in the treatment of patients with interventional, percutaneous, minimally invasive methods and techniques. The technological advances are vast and highlight the overall growth of cardiovascular interventions.

In this edition, we have been fortunate to have a group of internationally recognized authorities in many fields contributing chapters describing the use of these techniques in a wide range of cardiovascular diseases.

Accordingly, we have expanded considerably the second edition of this textbook to cover four major sections: coronary interventions, interventional pharmacology, structural heart interventions, and endovascular therapy. We believe that the reader will find this approach useful and practical. Each section includes key subjects presented in an organized way: starting with the pathophysiological background and relevant pathology, followed by mechanisms of treatment, device description, procedural techniques, follow-up care, risks, contraindications, and complications, where applicable. The inclusion of multiple choice questions with each online chapter allows both self-assessment as well as completion of accredited learning hours.

The modular presentation of this textbook, both as a printed book, and as an e-book CD-ROM or web-based program reflects the efforts of the publisher and the editors to reach out to many generations of physicians in training. The evolution of specialty certification and recertification has indeed made life learning a reality in our era. Therefore, the present textbook must also fulfill the quest to approach the new and tech-savvy learner, those ahead of an initial certification examination, those in advanced clinical practice who need practical instruction for a certain specialized subject, as well as those who have been practicing for a long time and need to refresh their knowledge with or without a recertification examination ahead of them. We have tried our best, and we certainly hope the reader will concur.

George D. Dangas  
Carlo Di Mario  
Nicholas N. Kipshidze
Acknowledgments

In a time when interventional cardiology has become too complex to be mastered by one or even three individuals, we decided to involve the best scholars in the field to cover the various topics of this book: without their help we could not have achieved this final result.

Our masters have taught us more than to push catheters. They made us love our profession and love teaching; we are delighted that many of them also contributed to this textbook.

Our Fellows have told us with their questions and doubts that not everything can be found in the many existing textbooks and the Internet. They inspired us to embark on this endeavor and acted as a continuous source of inspiration to draw enough attention to practical details.

Finally, we have neglected our spouses and children to spend long hours in front of a computer screen. We are confident that our wives already understand us and we hope one day our children will see this textbook on the shelves of the family library, read some pages, and forgive us.

George D. Dangas
Carlo Di Mario
Nicholas N. Kipshidze
PART I

Principles and Techniques
Atherosclerosis and its clinical consequences are the leading cause of death in Western nations [1]. Several factors have been implicated in the evolution, progression, and destabilization of atherosclerotic plaque highlighting its multifaceted nature. Atherosclerosis, now considered a chronic inflammatory disease, begins at a young age and progresses slowly for decades [2–4]. The clinical symptoms of atheroma occur in adults and usually involve plaque rupture and thrombosis [5–7].

While several advances have helped curb some of the complications resulting from atherosclerosis, this disease still represents an ongoing challenge with several new insights raising optimism that help to improve clinical outcomes is at hand. This chapter reviews the pathogenesis of atherosclerosis and the inflammatory cascades leading to plaque progression and destabilization. New coronary imaging modalities and developments in computer modeling are critiqued as tools to help improve the understanding of cardiovascular diseases.

**Pathogenesis of atherosclerosis**

Atherosclerosis is an inflammatory fibro-proliferative process in which plaque forms in the intima, bringing about stenosis or thrombosis and hence ischemia [8–10]. Though the exact initiator of plaque formation remains unknown, there is a general consensus that the triggering episode is endothelial damage, which could be caused by factors such as cigarette smoke toxins, hypertension, or immune injury [4,11–15]. Damaged cells become more permeable, ultimately causing subendothelial macrophages to consume circulating low density lipoproteins (LDL) which are altered in the intima to induce further endothelial damage [8,9,16]. More macrophages are then recruited, after which they remain in the intima as lipid-rich foam cells [9,10,17–19]. Meanwhile, in an attempt to restore endothelial function, smooth muscle cells migrate from the media to the intima to proliferate and generate a connective tissue matrix to cap the lipid core, further thickening the lesion [8,19,20]. Plaques enlarge as the process becomes chronic, classified as stable or unstable (Figures 1.1 and 1.2), either of which can lead to clinical sequelae [8,17,21].

**Clinical features**

The first indication of coronary artery disease (CAD) may be sudden death, or patients can present with silent ischemia, stable angina, or an acute coronary syndrome (ACS) [22]. ACSs comprise a range of syndromes resulting from atherosclerotic plaque disruption or rupture and are divided into unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) [21,23,24]. An unstable plaque, characterized by a large lipid core covered by a thin and unstable fibrous cap, is prone to rupture [21,25–27]. The sudden rupture can cause thrombus formation, in turn leading to ACS (Figure 1.2) [26,28,29]. Conversely, a stable plaque has a thick fibrous cap which is not easily ruptured (Figure 1.1), causing the chronic condition of stable angina through episodes of ischemia experienced upon physical exertion [25,27,30].

**Consequences of atherosclerosis**

The risk of major thrombotic and thromboembolic complications of atherosclerosis appears to be related more to the stability of atheromatous plaques than to the extent of disease [31,32]. Stable angina is associated with smooth fibrous coronary artery plaques (stable plaque), whereas unstable angina, acute myocardial infarction (AMI), and sudden cardiac death are almost invariably associated with destabilization of plaques [29]. Similarly, in patients with carotid artery atherosclerotic disease, plaque irregularity and rupture are closely associated with cerebral ischemic events, and patients with irregular or ulcerated plaque demonstrate a higher risk of ischemic stroke irrespective of the degree of luminal stenosis [33].

Much attention has been placed on trying to identify plaques at high risk of disruption leading to thrombosis. Such “vulnerable plaques” have also been areas of intense research using novel intracoronary imaging modalities: optical coherence tomography (OCT) [6,29]. OCT offers the advantages over intravascular ultrasound or angiography of ultra-high resolution and superiority in imaging the vessel wall and lumen interface [34–36].
Figure 1.1 Stable atherosclerotic plaque characterized by the presence of a low inflammatory infiltrate. This type of lesion is constituted by a lipid core (extracellular lipid, cholesterol crystals, and necrotic debris) covered by a thick fibrous cap consisting principally of smooth muscle cells (SMC) in a collagenous–proteoglycan matrix, with varying degrees of infiltration by macrophages and T lymphocytes. HDL, high density lipoprotein.

Figure 1.2 Unstable atherosclerotic plaque characterized by the presence of a thin fibrous cap rich in inflammatory macrophagic foam cells and T lymphocytes. Rupture of the fibrous cap at the shoulder region has resulted in thrombus formation.
Considerable data exist to sustain the hypothesis that several morphologic and molecular markers identifying unstable plaques could be expressed during plaque vulnerability. As shown by a number of anatomical and clinical studies, these vulnerable plaques are more often associated with rupture and thrombosis than stable plaques covered by a thin fibrous cap and show an extensive inflammatory infiltrate [28,37].

Unlike the stable plaque that shows a chronic inflammatory infiltrate, the vulnerable and ruptured plaque is characterized by features of acute inflammation [37,38]. There are a large number of studies showing that “active” inflammation mainly involves T lymphocytes and macrophages which are activated toward a pathway of inflammatory response, secrete cytokines and lytic enzymes which in turn cause thinning of the fibrous cap, predisposing to plaque rupture. Recent research has furnished new insight into the molecular mechanisms that cause transition from a stable to an unstable phase of atherosclerosis and points to inflammation as the playmaker in the events leading to plaque destabilization and suggest that alterations in shear stress may also play a pivotal part [39,40].

A current challenge is to identify morphological and molecular markers able to discriminate stable plaques from vulnerable ones allowing the stratification of “high risk” patients for acute cardiac and cerebrovascular events before clinical syndromes develop. Bearing this aim in mind, this chapter focuses on cellular and molecular mechanisms affecting plaque progression and serum markers correlated to plaque inflammation.

**Insights from coronary imaging**

Traditionally, coronary angiography has been the gold standard to detect extent and severity of CAD. These findings form the foundation of the interventionist’s clinical decision-making process and whether to proceed to percutaneous therapy. It is widely acknowledged, however, that angiography has several limitations. First, it maintains a relatively low image resolution. Second, it represents a luminogram of the artery and stenosis. Therefore little detail is provided as to the composition of the underlying plaque causing the stenosis and, finally, it is a 2D imaging method used to assess what are complex 3D structures.

**Intravascular ultrasound**

Intravascular ultrasound (IVUS) utilizes ultrasound waves that reflect off vascular tissues to yield real-time images [41,42]. While angiography only portrays a luminal silhouette [41], IVUS, with a resolution of 100–150 μm, captures details not retrievable with angiography—cross-sections of the lumen and vessel wall, even a differentiation of its layers [43–46]. Thus, IVUS enables study of the atherosclerotic process through the visualization of plaque in the vessel wall [41,47–49]. Indeed, the technology has demonstrated a greater prevalence of atherosclerosis than initially claimed with angiography [44].

**Optical coherence tomography**

OCT, the optical analog of IVUS, employs the reflection of near-infrared (NIR) light instead of sound. Initially applied in ophthalmology, advancement in the technology has now enabled OCT to capture non-transparent tissues such as coronary vessels [50,51]. OCT offers real-time, *in vivo* and *in situ* cross-sectional imaging of vascular structures with a resolution 10-fold that of IVUS (15 μm versus 150 μm) and a penetration depth similar to that of histology [34,43,50–53].

By virtue of its superior resolution, OCT can provide near-histological analysis of atherosclerotic plaques in real time (Figure 1.3). OCT definition of thin cap fibroatheroma (TCFA) follows the findings of autopsy studies of sudden death patients that had revealed the presence of fibrous caps <65 μm in the majority of plaques that had ruptured. These thin ruptured caps were also found to have an infiltrate of macrophages [54]. Whereas OCT is well placed in precisely defining the thinness of fibrous cap, macrophage infiltration seen as punctate, signal-rich spots at the junction of fibrous cap and lipid pool has been described less consistently. Previous autopsy studies had also shown that plaque rupture, erosion, and calcified nodules were the three leading underlying mechanisms for luminal thrombosis with a frequency of 65%, 30%, and 5%, respectively [25]. In recent years OCT has enabled this type of information to be obtained *in vivo* and has confirmed similar prevalence of plaque morphologies in patients presenting with STEMI and NSTEMI [55].

Plaque rupture on OCT is identified by a clear-cut disruption in the signal-rich thin fibrous cap overlying a signal-poor necrotic core resulting in extrusion of highly thrombogenic material into the lumen. Plaque erosion on the other hand is identified by the presence of luminal thrombus adjacent to a plaque that has an irregular but intact, thicker fibrous cap. Such plaques are mostly devoid of necrotic core. Calcified nodules are the least common etiology in ACS and are less well defined. They are recognized by sharp nodules protruding into the lumen causing discontinuation of the fibrous cap (Figure 1.4).

In patients with stable CAD, coronary imaging can provide lesion level information and help to show the changes in plaque microstructure in response to pharmacotherapies. Kataoka et al. [56] evaluated 293 and 122 lipid and fibrous plaques in 280 stable statin-treated patients with CAD and reported that patients with LDL-C levels <50 mg/dL were less likely to have lipid plaques, and had more features of plaque stability such as thicker fibrous caps and smaller lipid arcs.

**The vulnerable plaque**

Atherosclerotic lesions, according to the classification of the American Heart Association modified by Virmani et al. [29], are divided in two groups: (i) non-atherosclerotic intimal lesions and (ii) progressive atherosclerotic lesions which include stable, vulnerable, and thrombotic plaques.

The different pathologic characterization of atherosclerotic lesions largely depends on the thickness of the fibrous cap and its grade of inflammatory infiltrate, which is in turn largely constituted by macrophages and activated T lymphocytes. Typically, the accumulating plaque burden is initially accommodated by an adaptive positive remodeling with expansion of the vessel external elastic lamina and minimal changes in lumen size [57,58]. The plaque contains monocyte-derived macrophages, smooth muscle cells, and T lymphocytes. Interaction between these cells types and the connective tissue appears to determine the development and progression of the plaque itself, including important complications such as thrombosis and rupture.

The lesions classified as vulnerable or TCFA identify a plaque prone to rupture and thrombosis characterized by a large necrotic core containing numerous cholesterol clefts. The overlying cap is thin and rich in inflammatory cells, macrophages, and T lymphocytes with few smooth muscle cells [28,29,59]. Burke et al. [54] identified a cut-off value for cap thickness of 65 μm to define a vulnerable coronary plaque. Despite the predominant hypothesis...
focusing on the responsibility of a specific vulnerable atherosclerotic plaque rupture [5,7] for acute coronary syndromes, some pathophysiologic, clinical, and angiographic observations seem to suggest the possibility that the principal cause of coronary instability is not to be found in the vulnerability of a single atherosclerotic plaque, but in the presence of multiple vulnerable plaques in the entire coronary tree, correlated with the presence of a diffuse inflammatory process [37,38,60,61].

Within this context, recent angiographic studies have demonstrated the presence of multiple vulnerable atheromatous plaques in patients with unstable angina [20,62] and in those affected by transmural myocardial infarction [61]. Recently, by means of flow
cytometry Spagnoli et al. [38] have demonstrated the presence of an activated and multicentric inflammatory infiltrate in the coronary vessels of individuals who died of AMI. Similar results have been obtained by Buffon et al. [60], who, through the determination of the neutrophil myeloperoxidase activity, have proved the presence of a diffuse inflammation in the coronary vessels in individuals affected by unstable angina. These results have been confirmed by a morphological study which demonstrated the presence of a high inflammatory infiltrate constituted by macrophages and T lymphocytes activated in the whole coronary tree, also present in the stable plaques of individuals who died of AMI. These plaques showed a two- to fourfold higher inflammatory infiltrate than aged-matched individuals dying from non-cardiac causes with chronic stable angina (SA) or without clinical cardiac history (CTRL), respectively [37]. Moreover, it has also been demonstrated that activated T lymphocytes infiltrate the myocardium both in the peri-infarcted area and in remote unaffected myocardial regions in patients who died of a first myocardial infarction [63].

The simultaneous occurrence of diffuse coronary and myocardial inflammation in these patients further supports the concept that both coronary and myocardial vulnerabilities concur in the pathogenesis of fatal AMI.

AMI—at least associated with unfavorable prognosis—is therefore likely to be the consequence of a diffuse “active” chronic inflammatory process which determines the destabilization of both the entire coronary tree and the whole myocardium, not only the part of it affected by infarction. The causes of the diffuse inflammation associated with myocardial infarction are scarcely known. The presence of activated T lymphocytes suggests the “in situ” presence of an antigenic stimulus which triggers adaptive immunity.

Role of inflammation in the natural history of atherosclerosis

Inception of the plaque

Endothelial injury has been proposed to be an early and clinically relevant pathophysiologic event in the atherosclerotic process [4,32]. Patients with endothelial dysfunction have an increased risk for future cardiovascular events including stroke [64]. Endothelial dysfunction was described as the ignition step in atherogenesis. From this point on, an inflammatory response leads to the development of the plaque.

Endothelial damage can be caused by physical and chemical forces, by infective agents or by oxidized LDL (ox-LDL). Dysfunctional endothelium expresses P-selectin (stimulation by agonists such as thrombin) and E-selectin (induced by IL-1 or TNF-α). Expression of intercellular adhesion molecule-1 (ICAM-1) both by macrophages and endothelium and vascular adhesion molecule-1 (VCAM-1) by endothelial cells is induced by inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-1 (TNF-α), and γ-interferon (IFNγ).

Monocytes recalled in the subintimal space ingest lipoproteins and morph into macrophages. These generate reactive oxygen species (ROS), which convert ox-LDL into highly oxidized LDL. Macrophages upload ox-LDL via scavenger receptors until foam cells form. Foam cells with leukocytes migrate at the site of damage and generate the fatty streak. The loss of biologic activity of endothelium determines nitric oxide (NO) reduction together with increased expression of prothrombotic factors, proinflammatory adhesion molecules cytokines, and chemotactic factors. Cytokines may decrease NO bioavailability increasing the production of ROS. ROS reduces NO activity both directly, reacting with endothelial cells, and indirectly via oxidative modification of eNOS or guanylyl cyclase [65]. Low NO bioavailability can upregulate VCAM-1 in the endothelial cell layer that binds monocytes and lymphocytes in the first step of invasion of the vascular wall, via induction of nuclear factor κB (NFκB) expression [66]. In addition, NO inhibits leukocyte adhesion [67] and NO reduction results in induction of monocyte chemotactic protein-1 (MCP-1) expression which recruits monocytes [68]. NO is in a sensitive balance with endothelin-1 (ET-1) regulating vascular tone [69]. Plasma ET-1 concentrations are increased in patients with advanced atherosclerosis and correlate with the severity of the disease [70,71]. In addition to its vasoconstrictor activity, ET-1 also promotes leukocyte adhesion [72] and thrombus formation [73]. Dysfunctional endothelium expresses P-selectin (stimulation by agonists such as trombin) and E-selectin (induced by IL-1 or TNF-α) [74]. The expression of both ICAM-1 by macrophages and endothelium, and VCAM-1 by endothelial cells is induced by inflammatory cytokines such as IL-1, TNF-α, and IFNγ. Endothelial cells also produce monocyte chemotactic protein-1 (MCP-1), monocyte colony-stimulating factor, and IL-6 which further amplify the inflammatory cascade [75]. IL-6 production by smooth muscle cells represents the main stimulus for C-reactive protein (CRP) production [3]. Recent evidence suggests that CRP may contribute to the proinflammatory state of the plaque both mediating recruitment of monocytes and stimulating monocytes to release IL-1, IL-6, and TNF-α [76]. The damaged endothelium allows the passage of lipids into the subendothelial space. Fatty streaks represent the first step in the atherosclerotic process.

Evolver fibro-atheromatous plaque

The atheroma evolution is modulated by innate and adaptive immune responses [3,77,78]. The most important receptors for innate immunity in atherothrombosis are the scavenger receptors and the toll-like receptors (TLRs) [79]. Adaptive immunity is much more specific than innate immunity but may take several days or even weeks to become fully mobilized. It involves an organized immune response leading to generation of T- and B-cell receptors and immunoglobulins, which can recognize foreign antigens [80].

Stable plaque

Macrophages take up lipid deposited in the intima via a number of receptors, including scavenger receptor-A, and CD36. Deregulated uptake of modified LDL through scavenger receptors leads to cholesterol accumulation and “foam cell” formation. The lipid laden macrophages (foam cells) forming the fatty streak secrete proinflammatory cytokines that amplify the local inflammatory response in the lesion, matrix metalloproteinases (MMPs), tissue factor into the local matrix, as well as growth factors, which stimulate the smooth muscle replication responsible for lesion growth. Macrophages colony-stimulating factor (M-CSF) acts as the main stimulator in this process, next to granulocyte-macrophage stimulating factor (MGGM-CSF) and IL-2 for lymphocytes [81]. Lymphocytes enter the intima by binding adhesion molecules: VCAM-1, P-selectin, ICAM-1, MCP-1 (CCL2), IL-8 (CXCL8) [75]. Such infiltrate constituted mainly by CD4+ T lymphocytes recognize antigens bound to MHC class II molecules involved in antigen presentation to T lymphocytes thus provoking an immune response [2]. The major histocompatibility complex molecules (MHC II) are expressed by endothelial cells, macrophages, and vascular smooth muscle cells in proximity to activated T lymphocytes in the atherosclerotic plaque. Proinflammatory cytokines manage a central transcriptional control
Repeated inflammatory stimuli induce foam cells to secrete growth factors that induce proliferation and migration of SMCs into the intima. The continuous influx of cells in the subintimal space convert the fatty streak in a more complex and advanced lesion in which inflammatory cells (monocytes/macrophages, lymphocytes), SMCs, necrotic debris mainly resulting from cell death, ox-LDL elicit a chronic inflammatory response by adaptive immune system. SMCs form a thick fibrous cap that cover the necrotic core and avoid the exposition of thrombogenic material to the bloodstream. The volume of lesion grows and protrudes into the arterial lumen causing variable degrees of lumen stenosis. These lesions are advanced complicated "stable" atherosclerotic lesions, asymptomatic and often unrecognized [82,83].

**Vulnerable plaque: a shift toward Th1 pattern**

Early phases of the plaque development are characterized by an acute innate immune response against exogenous (infectious) and endogenous non-infectious stimuli. Specific antigens activate adaptive immune system leading to proliferation of T and B cells. A first burst of activation might occur in regional lymph nodes by dendritic cells (DCs) trafficking from the plaque to the lymph node. Subsequent cycles of activation can be sustained by interaction of activated/memory T cells re-entering in the plaque by selective binding to endothelial cell surface adhesion molecules with plaque macrophages expressing MHC class II molecules. In this phase of the atherogenic process the selective recruitment of a specific subtype of CD4+ cells play a major part in determining the future development of the lesion. Two subtypes of CD4+ cells have a juxtaposed role: Th1 and Th2 cells [84].

Th1 cells secreting proinflammatory cytokines, such as IFNγ, promote macrophage activation, inflammation, and atherosclerosis, whereas Th2 cells (cytokine pattern IL-4, IL-5, and IL-10) mediate antibody production and generally have anti-inflammatory and antiatherogenic effects [64]. Therefore the switch to a selective recruitment of Th1 lymphocyte represents a key point toward plaque vulnerability and disruption. T cells in the plaque may encounter antigens such as ox-LDL. Moreover, T-cell response can be triggered by heat shock proteins of endogenous or microbial origin [85]. It is still unknown why the initial inflammatory response becomes a chronic inflammatory condition. However, when the plaque microenvironment triggers the selective recruitment and activation of Th1 cells they in turn determine a potent inflammatory cascade.

The combination of IFNγ and TNF-α upregulates the expression of fractalkine (CX3CL1) [86]. IL-1 and TNFα-activated endothelium express also fractalkine (membrane bound form) which directly mediates the capture and adhesion of CX3CR1 expressing leukocytes providing a further pathway for leukocyte activation [87]. This cytokine network promotes the development of the Th1 pathway which is strongly proinflammatory and induces macrophage activation, superoxide production, and protease activity.

A limited number of T cells, following the Th1 pathway, initiates the production of large amounts of molecules downstream in the cytokine cascade orchestrating the transition from the stable to unstable plaque [77,88].

Within the plaque, inflammatory cells such as foam cells and monocyte-derived macrophages are induced to produce matrix-degrading enzymes, cytokines, and growth factors strictly implicated in extracellular matrix homeostasis. In particular, cytokines such as IFNγ suppress collagen synthesis, a major component of the fibrous cap [75]. Moreover, infiltration of mononuclear cells results in release of proteases which causes plaque disruption [89]. The production of ROS within the atherosclerotic plaque has important implications for its structural integrity [65]. Deregulated oxidant production has the potential to promote the elaboration and activation of matrix degrading enzymes in the fibrous cap of the plaque. Moreover, impaired NO function coupled with oxidative excess can activate MMPs [90], namely MMP-2 and MMP-9, which weaken the fibrous cap. Another mechanism that can determine the thinning of the fibrous cap is the apoptosis of smooth muscle cells. In fact, there is evidence for extensive apoptosis of SMCs within the cap of advanced atherosclerosis, as well as those cultured from plaques [32,91].

A very important role, not yet well studied, is that of dendritic cells, namely cells specialized in antigen presentation with a key role in the induction of primary immune response and in the regulation of T-lymphocyte differentiation, as well as in mechanisms of central and peripheral tolerance aiming at the elimination of T lymphocytes that are potentially self-reactive toward self-antigens [92,93]. A characteristic of dendritic cells is also the ability to polarize T-cell responses toward a Th-helper phenotype (Th1) in response to bacterial antigens. Molecules expressed by activated T lymphocytes, like CD40L, OX40, stimulate the release from dendritic cells of chemokines (fractalkines) able to attract other lymphocytes toward the inflammation site, amplifying the immune response [94].

Patients with ACS are characterized by the expansion of an unusual subset of T cells, CD4+CD28null T cells, with functional activities that predispose for vascular injury [95,96]. CD4+CD28null T cells are a population of lymphocytes rarely found in healthy individuals. Disease-associated expansions of these cells have been reported in inflammatory disorders such as rheumatoid arthritis. CD4+CD28null T cells are characterized by their ability to produce high amounts of IFNγ [96]. Equally importantly, CD4+CD28null T cells have been distinguished from classic Th cells by virtue of their ability to function as cytotoxic effector cells. Possible targets in the plaque are SMCs and endothelial cells, as recently shown [97]. In vivo, CD4+CD28null cells have a tendency to proliferate with the frequent emergence of oligoclonality, raising the possibility of continuous antigenic stimulation, as it is the case in certain autoimmune disorders and in chronic infections. The demonstration of oligoclonality within the CD4+CD28null T-cell subsets and sharing of T-cell receptor sequences in expanded T-cell clones of patients with ACS strongly support the notion that these cells have expanded and are activated in response to a common antigenic challenge [98]. CD4+CD28null T cells are long-lived cells. Clonality and longevity of these cells are associated with defects in apoptotic pathways [99]. Moreover, CD28 is relevant for the expansion of apoptotic T cells, thus the absence of this molecule contributes to the senescence of lymphocytes. The excessive expansion of a pool of senescent T lymphocytes might compromise the efficacy of the immune responses direct against exogenous antigens as well as determine autoimmune responses.
Recently, a subpopulation of \( T \) CD4\(^+\) cells, expressing IL-2 receptor, CD25 membrane marker, has been pointed out. Such lymphocytes represent 7–10\% of \( T \) CD4\(^+\) cells and their homeostasis is due to some co-stimulatory molecules, such as CD28 receptor expressed by \( T \) cells and B7 molecules expressed by dendritic cells [100]. The current knowledge of the role of this specific subset of \( T \) cells in human atherogenesis is still incomplete, even though a very recent study carried out on mice has demonstrated an antiatherogenic effect of \( T \) CD4\(^+\)CD25\(^+\) cells [101].

Th1 cells and \( T \) regulatory 1 cells have been demonstrated to play opposite roles in rupture of atherosclerotic lesion. The role of novel subset of \( T \) regulatory cells, known as CD4\(^+\)CD25\(^-\)Foxp3\(^+\) cells, has been recently studied in CAD. Han et al. [102] found that the reduction of CD4\(^+\)CD25\(^-\)Foxp3\(^+\) \( T \) lymphocytes was consistent with the expansion of Th1 cells in patients with unstable CAD. The reversed development between CD4\(^+\)CD25\(^-\) Tregs and Th1 cells might contribute to plaque destabilization.

### Serum markers correlated to plaque inflammation

In recent years, a number of studies have correlated different serologic biomarkers with cardiovascular disease [4,103] leading to a rapid increase in the number of biomarkers available (Table 1.1). These biomarkers are useful in that they can identify a population at risk of an acute ischemic event and detect the presence of so-called vulnerable plaques and/or vulnerable patients [104,105]. Ideally, a biomarker must have certain characteristics to be a potential predictor of incident or prevalent vascular disease. Measurements have to be reproducible in multiple independent samples, the method for determination should be standardized, variability controlled, and the sensitivity and specificity should be good. In addition, the biomarker should be independent from other established risk markers, substantively improve the prediction of risk with established risk factors, be associated with cardiovascular events in multiple population cohorts and clinical trials, and the cost of the assays has to be acceptable. Finally, to be clinically useful a biomarker should correctly reflect the underlying biological process associated with plaque burden and progression.

Traditional biomarkers for cardiovascular risk include LDL cholesterol and glucose. However, 50\% of heart attacks and strokes occur in individuals who have normal LDL cholesterol, and 20\% of major adverse events occur in patients with no accepted risk factors [106]. Therefore, in light of changing atherosclerotic models, vulnerable blood may be better described as blood that has an increased level of activity of plasma determinants of plaque progression and rupture.

In this context, proposed biomarkers fall into nine general categories: inflammatory markers, markers for oxidative stress, markers of plaque erosion and thrombosis, lipid-associated markers, markers of endothelial dysfunction, metabolic markers, markers of neovascularization, and genetic markers. The last six biomarker categories are not treated in this chapter but only listed in Table 1.1. Some of these markers may indeed reflect the natural history of atherosclerotic plaque growth and may not be directly related to an increased risk of cardiovascular events. On the contrary, other markers are more related to complex plaque morphological features and may reflect an active process within the plaque which is in turn related to the onset of local complications and onset of acute clinical events.

However, it is important to emphasize that, in any individual patient, it is not yet clear how these biomarkers relate to quantitative risk of major adverse cardiovascular events. The best outcomes may be achieved by a panel of markers that will capture all of the different processes involved in plaque progression and plaque rupture, and that will enable clinicians to quantify an individual patient's true cardiovascular risk. In all likelihood, a combination of genetic (representing heredity) and serum markers (representing the net interaction between heredity and environment) will ultimately be the ones that should be utilized in primary prevention. Finally, different non-invasive and invasive imaging techniques may be coupled with biomarkers detection to increase the specificity, sensitivity, and overall predictive value of each potential diagnostic technique.

### Markers of inflammation

Markers of inflammation include CRP, inflammatory cytokines soluble CD40L (sCD40L), soluble vascular adhesion molecules (sVCAM), and TNF.

CRP is a circulating pentraxin that has a major role in the human innate immune response [107] and provides a stable plasma biomarker for low grade systemic inflammation. CRP is produced predominantly in the liver as part of the acute phase response. However, CRP is also expressed in SMCs within diseased atherosclerotic arteries [108] and has been implicated in multiple aspects of atherogenesis and plaque vulnerability, including expression of adhesion molecules, induction of NO, altered complement function, and inhibition of intrinsic fibrinolysis [109]. CRP is considered to be an independent predictor of unfavorable cardiovascular events in patients with atherosclerotic disease. Beyond the ability of CRP to predict risk among both primary and secondary prevention patients, interest in it has increased with the recognition that statin-induced reduction of CRP is associated with less progression in adverse cardiovascular events that is independent of the lipid-associated changes [110] and that the efficacy of statin therapy may be related to the underlying level of vascular inflammation as detected by high-sensitivity CRP (hs-CRP). Among patients with stable angina and established CAD, plasma levels of hs-CRP have consequently been shown associated with recurrent risk of cardiovascular events [111,112]. Similarly, during acute coronary ischemia, levels of hs-CRP are predictive of high vascular risk even if troponin levels are non-detectable, suggesting that inflammation is associated with plaque vulnerability even in the absence of detectable myocardial necrosis [113,114]. Despite these data, the most relevant use of hs-CRP remains in the setting of primary prevention. To date, over two dozen large-scale prospective studies have shown baseline levels of hs-CRP to independently predict future myocardial infarction, stroke, cardiovascular death, and incidence of peripheral arterial disease [115,116]. Moreover, eight major prospective studies have had adequate power to evaluate hs-CRP after adjustment for all Framingham covariates, and all have confirmed the independence of hs-CRP [117]. Despite this evidence, it is important to recognize that there remain no firm data to date that lowering CRP levels per se will lower vascular risk. Further, as with other biomarkers of inflammation, it remains controversial whether CRP has a direct causal role in atherogenesis [118], and ongoing work with targeted CRP-lowering agents are required to fully test this hypothesis. However, the clinical utility of hs-CRP has been well established, and on the basis of data available through 2002, the Centers for Disease Control and Prevention and the American Heart Association endorsed the use of hs-CRP as an adjunct to global risk prediction, particularly among those at “intermediate risk” [119]. Data available since 2002 strongly reinforce these recommendations and suggest

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
expansion to lower risk groups, as well as those taking statin therapy. Perhaps most importantly, data for hs-CRP provides evidence that biomarkers beyond those traditionally used for vascular risk detection and monitoring can have important clinical roles in prevention and treatment.

Cellular adhesion molecules can be considered potential markers of vulnerability because such molecules are activated by inflammatory cytokines and then released by the endothelium [120]. These molecules represent the one available marker to assess endothelial activation and vascular inflammation. The Physicians’ Health Study evaluated more than 14,000 healthy subjects and demonstrated ICAM-1 expression positive correlation with cardiovascular risk and showed that subjects in the higher quartile of ICAM-1 expression showed 1.8 times higher risk than subjects in the lower quartile [121]. Furthermore, soluble ICAM-1 and VCAM-1 levels showed a positive correlation with atherosclerosis disease burden [122]. IL-6 is expressed during the early phases of inflammation and it is the principal stimulus for CRP liver production. In addition, CD40 ligand, a molecule expressed on cellular membrane, is a TNFα homologue which stimulates activated macrophages proteolytic substances production [123]. CD40 and CD40L have been found on platelets and several other cell types in functional-bound and soluble (sCD40L) forms. Although many platelet-derived factors have been identified, recent evidence suggests that CD40L is actively involved in the pathogenesis of ACS. CD40L drives the inflammatory response through the interaction between CD40L on activated platelets and the CD40 receptor on endothelial cells. Such interactions facilitate increased expression of adhesion molecules on the surface of endothelial cells and release of various stimulatory chemokines. These events, in turn, facilitate activation of circulating monocytes as a trigger of atherosclerosis. Beyond known proinflammatory and thrombotic properties of CD40L, experimental evidence suggests that CD40L-induced platelet activation leads to the production of reactive oxygen and nitrogen species, which are able to prevent endothelial cell migration and angiogenesis [124]. As a consequence of inhibiting endothelial cell recovery, the risk of subsequent coronary events may be greater. Clinical studies have supported the involvement of CD40L in ACS and the prognostic value in ACS populations. Levels of sCD40L have been shown to be an independent predictor of

### Table 1.1 Serologic markers of vulnerable plaque/patient.

<table>
<thead>
<tr>
<th>Reflecting metabolic and immune disorders</th>
<th>Reflecting hypercoagulability</th>
<th>Reflecting complex atherosclerotic plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal lipoprotein profile (i.e., high LDL, low HDL, lipoprotein [a], etc.)</td>
<td>Markers of blood hypercoagulability (i.e., fibrinogen, α-dimer, factor V Leiden)</td>
<td>Morphology/structure</td>
</tr>
<tr>
<td>Non-specific markers of inflammation (hs-CRP, CD40L, ICAM-1, VCAM, leukocytosis and other immuno-related serologic markers which may not be specific for atherosclerosis and plaque inflammation)</td>
<td>Increased platelet activation and aggregation (i.e., gene polymorphism of platelet glycoproteins IIb/IIIa, la/IIa, and Ib/IX)</td>
<td>• Cap thickness</td>
</tr>
<tr>
<td>Serum markers of metabolic syndrome (diabetes or hypertriglyceridemia)</td>
<td>Increased coagulation factors (i.e., clotting of factors V, VII, VIII, XIII, von Willebrand factor)</td>
<td>• Lipid core size</td>
</tr>
<tr>
<td>Specific markers of immune activation (i.e., anti-LDL antibody, anti-HSP antibody)</td>
<td>Decreased anticoagulation factors (i.e., proteins S and C, thrombomodulin, antithrombin III)</td>
<td>• Percentage stenosis</td>
</tr>
<tr>
<td>Markers of lipid peroxidation (i.e., ox-LDL and ox-HDL)</td>
<td>Decreased endogenous fibrinolysis activity (i.e., reduced tissue plasminogen activator, increased type I PAI, PAI polymorphisms)</td>
<td>• Remodeling (positive vs. negative)</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>Prothrombin mutation (i.e., G20210A)</td>
<td>• Color (yellow, red)</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>Thrombogenic factors (i.e., anticaldrioplin antibodies, thrombocytosis, sickle cell disease, diabetes, hypercholesterolemia)</td>
<td>• Collagen content vs. lipid content</td>
</tr>
<tr>
<td>Circulating apoptosis markers (i.e., Fas/Fas ligand)</td>
<td>Transient hypercoagulability (i.e., smoking, dehydration, infection)</td>
<td>• Calcification burden and pattern</td>
</tr>
<tr>
<td>ADMA/DDAH/</td>
<td></td>
<td>• Shear stress</td>
</tr>
<tr>
<td>Circulating NEFA</td>
<td></td>
<td>Activity/function</td>
</tr>
</tbody>
</table>

ADMA, asymmetric dimethylarginine; CRP, C-reactive protein; DDAH, dimethylarginine dimethylaminohydrolase; HDL, high density lipoprotein; HSP, heat shock protein; ICAM, intercellular adhesion molecule; LDL, low density lipoprotein; NEFA, non-esterified fatty acids; PAI, plasminogen activator; PAPP-A, pregnancy-associated plasma protein A; VCAM, vascular adhesion molecule.