Interventional Cardiology
Companion DVD-ROM

This book is accompanied by a companion DVD with:

- 33 additional cases with video clips
- Table of Contents for DVD—
  1. GC Support in Bifurcational Lesion
  2. Poor Support during SVG
  3. Flush CTO of RCA with Poor Support
  4. MSCT for intermediate Lesion Severity
  5. Intermediate Lesion Severity
  6. Intermediate Lesion Severity after CABG
  7. IVUS to Guide Distal GW Reentry in CTO Recanalisation
  8. Atypical Chest Pain after Stent
  9. CTO Reverse CART
  10. Stenting Strategy for CTO
  11. Wire Exit during CTO Recanalisation
  12. Final Steps in Retrograde Recanalisation
  13. CTO Antegrade Approach Failure
  14. Angina After CABG
  15. Left Main Stenosis
  16. OCT Bifurcation Lesion
  17. LAD Bifurcation Lesion V Stenting
  18. Multivessel Disease CTO Complication
  19. Multivessel Disease High Risk PCI
  20. Multivessel Disease CABG Impella
  21. Multivessel Disease & ACS
  22. Multivessel Multilesion Treatment
  23. In-stent Restenosis after BMS
  24. Incomplete Stent Expansion
  25. Late Stent Thrombosis
  26. Primary PCI
  27. Post DES Aneurysm
  28. Coronary Perforation
  29. Coronary Spasm
  30. New Stent Device for SVG Lesion
  31. Anomalous Origin of LCX
  32. Anterograde Approach to CTO of RCA
  33. Degenerated SVG Lesion

Case contributions by Drs. Di Mario and Tyczynski
Contents

Contributors, vii
Acknowledgements, xiii
Foreword by Patrick W. Serruys, xiv
Foreword by Martin B. Leon, xv
Preface, xvi

Part I Principles and Techniques
1 Interventional Cardiology Training, 3
   Carlo Di Mario and Joseph Babb
2 Atherogenesis and Inflammation, 10
   Giuseppe Sangiorgi, Alessandro Mauriello, Santi Trimarchi, Elena Bonanno, and Luigi Giusto Spagnoli
3 The Essentials of Vascular Access and Closure, 30
   Ted Feldman and Gerald Yong
4 Optimal Angiographic Views for Coronary Angioplasty, 44
   Carl Schultz and Carlo Di Mario
5 Material Selection, 58
   Carl Schultz, Rohit Khurana, and Carlo Di Mario
6 Physiologic Assessment in the Cardiac Catheterization Laboratory, 74
   Narbeh Melikian and Martyn R. Thomas
7 Quantitative Coronary and Vascular Angiography, 90
   Joan C. Tuinenburg, Gerhard Koning, and Johan H.C. Reiber

Part II Interventional Pharmacology
8 Oral Antiplatelet Agents in PCI, 103
   Annunziata Nusca and Germano Di Sciascio
9 Heparin, LMWH, GIIb/IIIa, and Direct Thrombin Inhibitors, 110
   Eric Heller and George D. Dangas

Part III Complementary Imaging Techniques
10 Intravascular Ultrasound: Principles, Image Interpretation, and Clinical Applications, 147
   Adriano Caixeta, Akiko Maehara, and Gary S. Mintz
11 Principles of Intra-coronary Optical Coherence Tomography, 172
   Peter Barlis, Jun Tanigawa, Patrick W. Serruys, and Evelyn Regar
12 Multislice Computed Tomography of Coronary Arteries, 179
   Francesca Pugliese and Pim J. de Feyter
13 Cardiac Magnetic Resonance Imaging, 198
   Amgad N. Makaryus and Steven D. Wolff

Part IV Indications in Acute and Chronic Syndromes
14 Stable Angina, 215
   Abhiram Prasad and Bernard J. Gersh
15 Indications in Acute Coronary Syndromes Without ST Elevation (NSTE-ACS), 232
   Christian W. Hamm and Albrecht Elsaesser
16 Primary and Rescue PCI in Acute Myocardial Infarction, 242
   Neil Swanson and Anthony Gershlick
Part V Approaching Complex Coronary Interventions

17 Chronic Total Coronary Occlusion, 265
   Gerald S. Werner

18 Percutaneous Coronary Intervention in Unprotected Left Main, 280
   Alaide Chieffo, Valeria Magni, and Antonio Colombo

19 Bifurcation Lesions, 298
   Leif Thuesen

20 Approach to Multivessel Coronary Artery Disease, 312
   Bryan P. Yan, Andrew E. Ajani, and David J. Clark

Part VI Interventional Techniques

21 Rotational Atherectomy, 325
   Saidi A. Mohiddin and Martin T. Rothman

22 Thrombectomy and Embolic Protection, 338
   William J. van Gaal and Adrian P. Banning

23 Carotid Artery Angioplasty and Stenting, 354
   Alberto Cremonesi, Shane Gieowarsingh, Estêvão C. de Campos Martins, and Fausto Castriota

24 Aortic Valve Disease Interventions, 374
   Srinivas Iyengar and Martin B. Leon

25 Transseptal Puncture, 383
   Alec Vahanian, Dominique Himbert, and Eric Brochet

26 Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy, 394
   Amir-Ali Fassa and Ulrich Sigwart

27 Cell Therapy, 406
   Zoë Astroulakis, Alex Sirker, and Jonathan M. Hill

Part VII Complications

28 No Reflow, 419
   Azem Latib and Flavio Airoldi

29 The Management of Cardiogenic Shock, 433
   John Edmond and Andreas Baumbach

30 In-stent Restenosis in the DES Era, 442
   Jiro Aoki, Adriano Caixeta, George D. Dangas, and Roxana Mehran

31 Renal Insufficiency and the Impact of Contrast Agents, 464
   Carlo Briguori

32 Coronary Artery Dissection and Perforation, 476
   Adriano Caixeta, Eugenia Nikolsky, Alexandra J. Lansky, Roxana Mehran, and George D. Dangas

Part VIII Clinical Trials

33 Statistical Essentials in the Design and Analysis of Clinical Trials, 493
   Stuart J. Pocock

34 Sirolimus and Paclitaxel Eluting Stent Clinical Studies, 502
   Ajay J. Kirtane, Adriano Caixeta, Philippe Généreux, Rikesh Patel, & Jeffrey W. Moses

35 Zotarolimus Eluting Stent Clinical Studies, 519
   William Wijns and Marco Valgimigli

36 Everolimus Eluting Coronary Stents: Clinical Trials, 528
   Neville Kukreja, Yoshinobu Onuma, and Patrick W. Serruys

37 Novel Drug Eluting Stent Systems, 539
   Adriano Caixeta, Alexandre Abizaid, George D. Dangas, & Martin B. Leon

Index, 556

Question and Answer contributions by Drs. Tayo Addo and George D. Dangas.
Contributors

Alexandre Abizaid, MD, PhD
Chief of Coronary Interventions
Institute Dante Pazzanese of Cardiology
São Paulo
Brazil

Tayo Addo, MD
Assistant Professor of Medicine
Southwestern Medical Center
Dallas, TX
USA

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

Andrew E. Ajani, MD, MBBS, FRACP, FJFICM
Associate Professor
Interventional Cardiologist
Director of Coronary Care Unit
Director of Physician Training
Royal Melbourne Hospital
Melbourne, VIC
Australia

Jiro Aoki, MD, PhD
Interventional Cardiologist
Division of Cardiology
Mitsol Memorial Hospital
Tokyo
Japan

Zoë Astroulakis, MBBS, MRCP
Clinical Research Fellow
Department of Cardiology
King’s College London
James Black Centre
London
UK

Joseph Babb, MD
Professor of Medicine
Director, Interventional Cardiology Fellowship
Department of Cardiovascular Sciences
East Carolina University Brody School of Medicine
Greenville, NC
USA

Adrian P. Banning, MD, FRCP, FESC
Consultant Cardiologist
Department of Cardiology
John Radcliffe Hospital
Oxford
UK

Peter Barlis, MBBS, MPH, FCSANZ, FESC, FRACP, PhD
Associate Professor of Medicine
Faculty of Medicine, Dentistry & Health Sciences
The University of Melbourne
Consultant & Interventional Cardiologist
The Northern Hospital
Melbourne, VIC
Australia

Andreas Baumbach, MD, FRCP, FESC
Consultant Cardiologist
Bristol Heart Institute
University Hospitals Bristol
Bristol
UK

Elena Bonanno, MD
Assistant Professor Pathology
Department of Pathology
University of Rome Tor Vergata
Rome
Italy

Carlo Briguori, MD, PhD
Chief of Laboratory
Laboratory of Interventional Cardiology
Clinica Mediterranea
Naples
Laboratory of Interventional Cardiology
“Vita e Salute” University School of Medicine
Milan
Italy

Eric Brochet, MD
Cardiologist
Echocardiography Laboratory
Department of Cardiology
Bichat Hospital
Paris
France
Adriano Caixeta, MD, PhD
Postdoctoral Research Fellow
Center for Interventional Vascular Therapy
Columbia University Medical Center
Clinical Trial Center
Cardiovascular Research Foundation
New York, NY
USA

Estêvão C. de Campos Martins, MD
Interventional Cardio-Angiology Unit
GVM Hospitals of Care and Research
Cotignola (RA)
Italy

Fausto Castriota, MD
Interventional Cardio-Angiology Unit
GVM Hospitals of Care and Research
Cotignola (RA)
Italy

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

David J. Clark, MD, FRACP
Director of Interventional Research
Austin Hospital
Melbourne, VIC
Australia

Antonio Colombo, MD
San Raffaele Scientific Institute and EMO Centro
Cuore Columbus
Milan
Italy

Alberto Cremonesi, MD
Interventional Cardio-Angiology Unit
GVM Hospitals of Care and Research
Cotignola (RA)
Italy

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

Carlo Di Mario, MD, PhD, FRCP, FSCAI, FESC
Professor of Cardiology
National Heart & Lung Institute Imperial College London
Consultant Cardiologist
Royal Brompton Hospital
Professor of Clinical Cardiology
Imperial College London
London
UK

Germano Di Sciascio, MD, FACC, FESC
Professor of Cardiology
Department of Cardiovascular Sciences
Campus Bio-Medico University of Rome
Rome
Italy

John Edmond, MD, MRCP
Consultant Interventional Cardiologist
Bristol Heart Institute
University Hospitals Bristol
Bristol
UK

Albrecht Elsaesser, MD
Head of the Department of Cardiology
Heart Center
Oldenburg Medical Center
Oldenburg
Germany

Amir-Ali Fassa, MD
Interventional Cardiology Fellow
Cardiology Service
Geneva University Hospitals
Geneva
Switzerland

Ted Feldman, MD, FSCAI
Director, Cardiac Catheterization Laboratory
Cardiology Division
Evanston Hospital
Evanston, IL
USA

Giuseppe Ferrante, MD
Cardiologist
Institute of Cardiology
Catholic University of the Sacred Heart
Rome
Italy

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
Francesca del Furia, MD
Research Fellow
Royal Brompton Hospital
London
UK

William J. van Gaal, MBBS, FRACP, MSc, FESC, FCSANZ
Director of Cardiology
The Northern Hospital
Epping, VIC
Australia

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, FRCP, FACC
Professor of Medicine
The Division of Cardiovascular Diseases and Department of Internal Medicine
Mayo Clinic and Mayo Foundation
Rochester, MN
USA

Anthony Gershlick, MBBS, BSc, FRCP
Professor of Interventional Cardiology
Glenfield Hospital
Leicester
UK

Shane Gieowarsingh, MBBS, MET
Master of Endovascular Techniques Fellow
Interventional Cardio-Angiology Unit
GVM Hospitals of Care and Research
Cotignola (RA)
Italy

Christian W. Hamm, MD
Medical Director
Heart and Thorax Center
Kerckhoff-Klinik
Bad Nauheim
Germany

Eric Heller, MD
Instructor in Clinical Medicine
Columbia University Medical Center
New York, NY
USA

Jonathan M. Hill, MD
Consultant Cardiologist
Department of Cardiology
King’s Health Partners
London
UK

Dominique Himbert, MD
Cardiologist
Department of Cardiology
Bichat Hospital
Paris
France

Srinivas Iyengar, MD
Clinical Instructor
Division of Cardiology
New York-Presbyterian Hospital
Columbia University Medical Center
New York, NY
USA

Rohit Khurana, MD, MRCP
Department of Cardiology
Imperial College Health Trust
London
UK

Ajay J. Kirtane, MD, ScM
Assistant Professor of Clinical Medicine
Center for Interventional Vascular Therapy
Columbia University Medical Center
New York-Presbyterian Hospital
New York, NY
USA

Gerhard Koning, MSc
Senior Scientific Researcher
Division of Image Processing (LKEB)
Department of Radiology
Leiden University Medical Center
Leiden
The Netherlands

Neville Kukreja, MA, MRCP
Research Fellow
Lister Hospital
Stevenage
UK

Alexandra J. Lansky, MD
Associate Professor of Clinical Medicine
Columbia University Medical Center
Joint Chief Scientific Officer, Clinical Trial Center & Director, Women’s Cardiovascular Health Initiative
Cardiovascular Research Foundation
New York, NY
USA
Contributors

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

Martin B. Leon, MD
Professor of Medicine and Associate Director
Center for Interventional Vascular Therapy
Columbia University Medical Center
Founder & Chairman Emeritus
Cardiovascular Research Foundation
New York, NY
USA

Akiko Maehara, MD
Director of Intravascular Imaging &
Physiology Core Laboratories
Associate Director of MRI Core Laboratories
Cardiovascular Research Foundation
Assistant Professor, Columbia University Medical Center
New York, NY
USA

Valeria Magni, MD
Research Fellow
Invasive Cardiology Unit
San Raffaele Hospital
Milan
Italy

Amgad N. Makaryus, MD, FACC,
FACP, FASE
Director of Cardiac CT and MRI
Department of Cardiology
North Shore University Hospital
NYU School of Medicine
Manhasset, NY
USA

Alessandro Mauriello, MD
Associate Professor of Pathology
Department of Pathology
University of Rome Tor Vergata
Rome
Italy

Roxana Mehran, MD
Associate Professor of Medicine
Columbia University College of Physicians and Surgeons
Director of Outcomes Research
Center for Interventional Vascular Therapy
Columbia University Medical Center
Joint Chief Scientific Officer
Cardiovascular Research Foundation
New York, NY
USA

Narbeh Melikian, MD, MRCP
Clinical Lecturer in Cardiology and Interventional Cardiologist
Cardiology Department
King’s College London School of Medicine and
King’s College Hospital Foundation Trust
London
UK

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

Saidi A. Mohiddin, MBChB
Specialist Registrar in Cardiology,
Barts and The London NHS Trust
The London Chest Hospital
London
UK

Jeffrey W. Moses, MD
Professor of Medicine
Columbia University Medical Center
Director Center for Intravascular Therapy (CIVT)
Director Adult Cardiac Catheterization Laboratories
New York-Presbyterian Hospital
New York, NY
USA

Eugenia Nikolsky, MD, PhD
Columbia University Medical Center
Cardiovascular Research Foundation
New York, NY
USA
Rambam Health Care Campus
Heart Institute
Haifa
Israel

Annunziata Nusca, MD
Interventional Cardiologist
Department of Cardiovascular Sciences
Campus Bio-Medico University of Rome
Rome
Italy

Yoshinobu Onuma, MD
Research Fellow
Thoraxcenter
Erasmus Medical Center
Rotterdam
The Netherlands
Rikesh Patel, MD
Postdoctoral Residency Fellow
Department of Medicine
Columbia University Medical Center
New York-Presbyterian Hospital
New York, NY
USA

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

Abhiram Prasad, MD, FRCP, FACC, FESC
Professor of Medicine
Consultant, Cardiac Catheterization Laboratory
The Division of Cardiovascular Diseases and Department of Internal Medicine
Mayo Clinic and Mayo Foundation
Rochester, MN
USA

Francesca Pugliese, MD
Consultant Cardiac Radiologist
Cardiothoracic Centre Basildon University Hospital
Basildon
UK
Hon. Consultant
Royal Brompton Hospital and Imperial College Healthcare Trust
London
UK
Clinical Researcher
Erasmus MC University Medical Center
Rotterdam
The Netherlands

Evelyn Regar, MD, PhD
Interventional Cardiologist
Thoraxcenter
Erasmus Medical Center
Rotterdam
The Netherlands

Johan H.C. Reiber, PhD
Professor of Medical Imaging
Division of Image Processing (LKEB)
Department of Radiology
Leiden University Medical Center
Leiden
The Netherlands

Martin T. Rothman, FRCP, FACC, FESC
Professor of Interventional Cardiology
Director of Cardiac Research & Development
Barts and The London NHS Trust
The London Chest Hospital
London
UK

Giuseppe Sangiorgi, MD, FESC, FSCAI
Assistant Professor of Cardiology
Director, Cardiac Catheterization Laboratory
University of Modena
Department of Pathology
University of Rome
Italy

Carl Schultz, MD, PhD
Interventional Cardiologist
Department of Cardiology
Thoraxcenter
Erasmus Medical Center
Rotterdam
The Netherlands

Patrick W. Serruys, MD, PhD
Professor of Cardiology
Thoraxcenter
Erasmus Medical Center
Rotterdam
The Netherlands

Ulrich Sigwart, MD, FACC, EFESC, FRCP
Professor and Chairman Emeritus
Cardiology Service
Geneva University Hospitals
Geneva
Switzerland

Alex Sirker, MB, BChir, MRCP
Specialist Registrar in Cardiology and Clinical Research Fellow
Department of Cardiology
King’s College London
James Black Centre
London
UK

Luigi Giusto Spagnoli, MD
Professor of Pathology and Director
Pathology Department
University of Rome Tor Vergata
Rome
Italy

Neil Swanson, MBChB
Consultant Cardiologist
James Cook University Hospital
Middlesbrough
UK

Jun Tanigawa, MD, PhD
First Department of Internal Medicine
Osaka Medical College
Takatsuki, Osaka
Japan
Martyn R. Thomas, MD, MBBS, FRCP
Clinical Director
Cardiothoracic Centre and Consultant
Interventional Cardiologist
Cardiology Department
St Thomas' Hospital
London
UK

Leif Thuesen, MD, DMSc, FESC
Director, Cardiac Catheterization Laboratory
Department of Cardiology
Aarhus University Hospital
Skejby
Denmark

Santi Trimarchi, MD
Assistant Professor of Vascular Surgery
Department of Vascular Surgery
IRCCS Policlinico San Donato
San Donato Milanese
Milan
Italy

Joan C. Tuinenburg, MSc
Scientific Researcher
Division of Image Processing (LKEB)
Department of Radiology
Leiden University Medical Center
Leiden
The Netherlands

Pawel Tyczynski, MD, PhD
Cardiologist
Department of Coronary Artery Disease
Institute of Cardiology
Warsaw
Poland
Recipient of the EAPCI Training Grant in Interventional Cardiology
Royal Brompton Hospital
London
UK

Alec Vahanian, MD, FESC, FACC
Head of Cardiology
Bichat Hospital
Paris
France

Marco Valgimigli, MD, PhD
Senior Interventional Cardiologist
Cardiovascular Institute
University of Ferrara
Ferrara
Italy

Gerald S. Werner, MD, FACC, FESC
Professor of Cardiology and Director
Cardiology & Intensive Care
Klinikum Darmstadt
Darmstadt
Germany

William Wijns, MD, PhD
Senior Interventional Cardiologist
Cardiovascular Center Aalst
Moorselbaan
Aalst
Belgium

Steven D. Wolff, MD, PhD
Director of Advanced Cardiovascular Imaging
Assistant Professor of Medicine and Radiology
Columbia University, College of Physicians and Surgeons
New York, NY
USA

Bryan P. Yan, MBBS, FRACP
Assistant Professor
Division of Cardiology, Prince of Wales Hospital
Department of Medicine & Therapeutics
The Chinese University of Hong Kong
Hong Kong
China

Gerald Yong, MBBS (Hons), FRACP
Interventional Fellow
Cardiology Division
Evanston Hospital
Evanston, IL
USA
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 in 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.

Carlo Di Mario  
George D. Dangas  
Peter Barlis
Foreword

By Patrick W. Serruys

Interventional cardiology has grown dramatically since the early days of Andreas Gruntzig, and today coronary angioplasty is the most commonly performed intervention in medicine. It remains an impossible task for today’s interventional cardiologist to stay abreast of all developments and Carlo Di Mario, George Dangas and Peter Barlis must therefore be commended for assembling a distinguished field of experts who share their vast knowledge and experience in this rapidly changing field.

The importance of sound technique and an understanding of the principles of interventional cardiology cannot be overstated, and Part I provides crucial information for both the junior cardiologist starting on the long road of training in interventional cardiology, and the more seasoned experienced interventional cardiologist who will still find their knowledge enhanced. As we enter a new decade, the cath lab is increasingly becoming a high-tech environment as we strive to obtain the best results for our patients, and decisions are no long based on just plain ‘luminography.’ The editors must therefore be congratulated for providing an indispensable chapter on complementary imaging; techniques which still remain novel to many of us. The complexity of lesions being treated in the cath lab is ever increasing, and Part V provides essential reading on the fundamental aspects of treating these lesions, by operators dealing with lesions day in day out.

The wealth of information that this book provides means it will suitably grace any cath lab and personal library.

Patrick W. Serruys,
Thoraxcenter, Rotterdam, The Netherlands
2010
Foreword

By Martin B. Leon

For the past three decades the discipline of interventional cardiology has evolved from a simple balloon procedure, to a valued collection of less-invasive therapies, and currently into a clearly defined subspecialty that provides worthwhile treatment alternatives to millions of patients around the world each year. Importantly, the spirit of interventional cardiology has always embraced evolutionary change, with a strong emphasis on both technical expertise in the catheterization laboratory and clinical decision-making enhanced by evidence-based medicine. These are crucial times in the life history of interventional cardiology with many challenges, including the socioeconomic burdens of procedural therapies in many parts of the world. A vital component to preserve and grow the specialty requires a commitment to the education and training of the next generation of interventional physicians. In the past, most textbooks in interventional cardiology have focused on broad academic and clinical overviews or selective niche topics (e.g. chronic total occlusions or drug-eluting stents). The unique significance of “Interventional Cardiology: Principles and Practice” is that this is the first legitimate textbook which targets the education and training of young coronary interventionalists, spanning the range from fellows, to junior faculty, to clinical practitioners. Interestingly, the design and nature of the textbook also lends itself to a much wider readership; the expanding mass of healthcare professionals (e.g. cardiovascular nurses, technologists) who desire a formal updated reference text in the field of interventional cardiology.

The textbook, edited by Drs. Di Mario, Dangas and Barlis, is thoughtfully organized and provides an engaging balance of factual data and practical clinical insights. The authors are an amalgam of well known international thought leaders, next generation budding stars, and early stage interventionalists who have recently completed training experiences. This provocative blend of author expertise results in a textbook which certainly provides the necessary knowledge content from “brand name” individuals, but also allows a spirited digression into areas of practical clinical relevance which are of great importance to younger trainees. The chapter progression moves seamlessly from fundamental principles, to general and specific interventional techniques, to adjunctive pharmacology, to indications for treatment, to complications, and concludes with a worthwhile session on many of the seminal interventional clinical trials. The content is an admixture of standard topics required to master clinical interventional practice and many of the newest and most novel potential therapies of the future, such as transcatheter valve and cell-based therapies.

In the dynamic subspecialty of interventional cardiology, wherein rapid evolutionary and even revolutionary changes are expected in a telescoped time horizon (usually in very few years), there needs to be a comprehensive, modern era textbook which provides an educational and training experience for dedicated individuals who crave to master basic and advance skills or simply desire a formal in-depth introduction into the field. “Interventional Cardiology: Principles and Practice” nicely fills this critical gap and should be embraced as a major success, supporting and complementing the dynamism of the subspecialty.

Martin B. Leon,
Center for Interventional Vascular Therapy,
NewYork-Presbyterian Hospital/Columbia University Medical Center,
New York, USA
2010
Preface

The idea for the generation of this book has been the continuous encouragement from the attendees of the Interventional Cardiology review courses we have been holding regularly both in the United States and Europe. The genesis of the subspecialty of cardiology has paralleled the exponential development of techniques and equipment to provide minimally invasive interventional therapies to patients with cardiovascular disease. The proper administration of such therapies requires a unique set of qualifications as well as special understanding of the disease entities and the interventions used. In many ways, this is not simply something in-between classic surgery and medical therapy, but demands skills and knowledge of both classic entities. The immediate therapeutic results and their relationship to rational hemodynamic and pathophysiologic algorithms attract the attention of both trainees and teachers for life. The fast pace of evidence based decision making is a challenge which requires continuous knowledge updates to all involved.

This subspecialty has been a recognized one in the United States since 1999 with the advent of the first Board Examination and the ensuing Certifications. Although other places of the world have not yet set up a formal teaching pathway, this should be expected soon, since this specialty is practiced widely everywhere. Therefore, a comprehensive review of this discipline is in high demand. We have been fortunate to have initiated the review courses in 1998 in the USA and in 2006 in Europe and have firmly believed all along that a written instruction should ideally complement the live teaching methods.

We are quite pleased to provide the present book to all those seeking initial or repeat certification in Interventional Cardiology. Furthermore, we would also encourage anyone outside the formal specialty (e.g. cardiac or vascular surgeons, radiologists, etc) who have keen interest in interventional therapies to complement their practical instruction with structured studying. We have worked with our review courses faculty in this task, and we would like to thank all of the co-authors for their contributions of carefully written narratives, illustrative figures, organized tables and inquisitive question-answer sections.

Finally, we would like to thank our Publisher for the high quality of the final product and once again thank our students, teachers and colleagues of the international community of academic interventional cardiologists for the continuous inspiration they have provided to us.

Carlo Di Mario
George D. Dangas
Peter Barlis
PART I

Principles and Techniques
CHAPTER 1

Interventional Cardiology Training

Carlo Di Mario¹, & Joseph Babb²
¹Royal Brompton Hospital, London, UK
²East Carolina University Brody School of Medicine, Greenville, NC, USA

Introduction

The treatment of coronary artery disease has undergone rapid evolution, with many groundbreaking innovations introduced in the last years. Angioplasty is now the first option in the acute phase of myocardial infarction, allows rapid control and early discharge of patients with acute coronary syndromes, and has eroded the prevalent use of bypass surgery in stable angina and silent ischemia. The drastic reduction of restenosis observed with the use of drug eluting stents makes percutaneous revascularization a viable option in complex lesions, including multivessel and left main disease, with ongoing clinical trials of comparison with surgery. Interventional cardiology has expanded its field of application from coronary arteries to structural heart disease and other degenerative atherosclerotic changes such as peripheral artery disease. If laser and directional atherectomy have almost disappeared from the therapeutic armamentarium, other devices such as Rotablator, cutting balloon, filters, and thromboaspiration devices have become a welcome addition in selected cases as preparation to balloon dilatation and stent implantation. Aspirin and heparin were the only options available 15 years ago and are now complemented or substituted by a variety of antiplatelet and antithrombin agents. Another important change transforming the practice of interventional cardiology has been the increasing pressure of healthcare systems, forcing interventionalists to use strict interpretation of guidelines for indications, meticulously document procedures and complications in databases open to review from health providers and the general public, acquire management skills to optimize resource utilization, motivate and enhance performance of the team, build stable referral networks.

Specific mandatory training is implemented in few countries around the world. With these few exceptions, all cardiologists but also many other medical specialists (radiologists, cardiac and vascular surgeons) are legally entitled to perform percutaneous interventional procedures after successful completion of training in their main specialty without any specific knowledge and experience in the interventional field. In this chapter, the different reality of interventional training in Europe and the United States is examined to help Fellows understand the similarities and differences and to stimulate growth and improvement on both sides of the Atlantic.

Principles of Medical Training Applied to Interventional Cardiology

As for most doctors, the three cornerstones of the training required for a successful interventionalist are knowledge, professional skills and professionalism. The most knowledgeable cardiologist with a complete background spanning from pathophysiology
of coronary artery disease to the results of the most recent trials will be unable to work safely if s/he has not achieved sufficient practical experience of a variety of procedures, assisted and coached by qualified supervisors. Similarly, a physician combining good theoretical knowledge and hands-on experience can still be inefficient and dangerous if s/he does not use in his/her practice respect and human compassion towards his/her patients and does not have the ability to select and motivate his/her team. Training in interventional cardiology must pay attention to these three complementary essential aspects of the education process and must develop reliable methods of assessment to certify the progress made and indicate the additional steps required to become an independent professional. As the undergraduate and postgraduate medical education is different in the various countries also the curriculum of Interventional Cardiology training must adapt to the different background which explains differences among countries. In this chapter we limited our observations to Europe and the United States.

The State of Interventional Cardiology Training in Europe

The training of specialists in interventional cardiology is not formally regulated in any European countries. Most countries, however, offer a period of one to two years’ training in interventional cardiology and the appointment of cardiologists expected to carry out angioplasties and other interventional procedures is in practice restricted at a level of interviews/local credentials required by hospitals to candidates who prove they have successfully completed this training. Still, no official certificates with binding legal value are issued. The official approval of a new Specialty called Interventional Cardiology requires a direct decision of the National Governments since this legislation is demanded to individual countries. The European Community only checks compatibility with the principles governing the community of member states. One such principle is the promotion of free movement of workers, including professionals. It is understandable, therefore, that the European Commission, the Government of the Union, seeks advice from a body representing all the Medical Colleges of the Member states, called UEMS (European Union of Medical Specialists). This supernational representation has allowed in the past a radical review of the denomination and duration of training in the different post-graduate medical Specialty areas. The complexity of the process required, involving the consultation of all the Departments of Health and Education, Universities and Medical Colleges, is one of the factors explaining the reluctance to introduce too frequent new changes. In most European countries, cardiology training is constituted by a period of training in internal medicine (1–2 years) and 3–4 years’ training in Cardiology, covering the different invasive and non-invasive fields. The ability to perform diagnostic coronary angiography and right and left cardiac catheterization is still part of the general training for all Cardiologists in most European countries, with a minimum number of procedures often indicated in the curriculum of trainees in general cardiology. This is reflected by the Core Curriculum in Cardiology, recently published by the Education Committee of the European Society of Cardiology [1]. In the Curriculum a minimum of 300 catheterizations as first operator is required. For diagnostic catheterization (right and left, with coronary angiography and left ventriculography) the level required (III) implies that the trainee is able to “independently perform the procedure unaided” at the end of his/her training. Also percutaneous interventions are part of the techniques required, with a lower number (50) and a Level II which indicates “practical experience but not as independent operator”. The Core Curriculum, promoted and implemented by the European Society of Cardiology and recently updated, implicitly recognizes that percutaneous interventions are part of a different Subspecialty training.

To promote the application of the Curriculum and issue the Diploma of European Cardiologist, a certificate not required to practice in individual countries but helpful to move across different European countries, a permanent body joining the expertise provided by the European Society of Cardiology and the authority of the UEMS has been created. This permanent Committee, called European Board of the Specialty in Cardiology, has already endorsed the concept that practice of activities like interventional cardiology, electrophysiol-
ogy and pacing, cardiovascular imaging, require a specific and additional training and has set the general rules regulating its organization, devolving to each individual Working Group or Association the development of the specific educational content of the programs.

**The European Curriculum and Syllabus**

After several meetings between members of the ESC WG of Interventional Cardiology and the chairmen of the national interventional societies, a Committee was nominated to finalize a Curriculum and Syllabus for interventional cardiology training in Europe. The final document has been published in EuroIntervention in 2006 [2]. The intention of the curriculum is to identify an educational process for specialists in interventional cardiology in Europe. The curriculum mandates a two-year program divided into four semesters, with the trainee starting to prepare the patient for the intervention, including diagnostic angiography, and assist the supervisor or another experienced interventionalist performing the angioplasty procedure. It was recommended that the trainee starts working as primary operator for simple angioplasties under close supervision and assists in the most complex angioplasty procedures (bifurcations, thrombus containing lesions, chronic occlusions, diffuse disease, severe calcifications, etc.) till s/he reaches a level of confidence allowing him/her to work as primary and independent operator in both simple and complex coronary interventional procedures.

Apprenticeship learning is defined as the mainstay of the training process in interventional cardiology. Candidates are required to be involved in procedure planning, assessment of indications and contraindications, and specific establishment of the individual patient risks based on clinical and angiographic characteristics. The performance of supervised angioplasty procedures is regulated with the goal of a progressive increase of the candidate involvement and direct handling of angioplasties of increasing complexity. A parallel formal learning is also required, ensuring that the candidate achieves sufficient knowledge of all the subjects included in the Syllabus. Trainees are required to attend at least 30 full days (240 hours) in two years of accredited formal sessions locally, nationally or abroad, including attendance of study days and post graduate courses, national and international courses in Interventional Cardiology, including live courses. Distance learning through journals, textbooks and the Internet is also encouraged and certified. In the Curriculum it is indicated that all trainees must be exposed by the training program to research in interventional cardiology.

It is a formidable challenge to ensure homogeneous high standard training when no central European government can enforce it and in the absence of any legal recognition of this training. The solution proposed by EBSC and approved by the EAPCI and most National Interventional Cardiological Societies and interventional groups is the development of web based platforms dedicated to subspecialty training, with the scientific and educational content determined by EAPCI within a general scheme valid for all the Subspecialities approved by EBSC [3]. The platform is currently under development and will offer to the trainee the possibility to document attendance of accredited formal training courses and to record their catheter lab based procedures [4]. The website will ask for mandatory reports of Directly Observed Procedures, appraisal from the program director, a 360 degrees assessment involving medical colleagues but also nurses, radiographers, technicians and patients. The final judgment should report the trainee’s ability to interact with cath lab staff and colleagues, attention to minimize patient risk and attitude to discuss complex procedures with more expert colleagues, ability to make independent appropriate choices and cope with emergency situations. No final summative examination is envisioned at the end of the training, but multiple choice questions (MCQ) are embedded into a first section testing theoretical knowledge and covering all items included in the Syllabus, and a second series of MCQ in present under “Skills”, using real or simulated clinical cases to appraise practical experience.

Training centers are asked to fulfill technical and staffing requirements such as having an independent interventional cardiology unit, allowing the trainee to follow the patient from the beginning to the completion of the interventional treatment, having a volume of at least 800 coronary angioplasties per year including acute coronary syndromes and primary angioplasty for acute
myocardial infarction. At least two certified supervisors must be available, with an experience of at least 1,000 coronary interventions and more than five years experience mainly dedicated to interventional cardiology.

These activities have already promoted changes de facto or via a legal governmental approval of the training programs of interventional cardiology in most European countries. A final year of subspecialist training after a common trunk of three years in general cardiology has been adopted in most countries, with an additional year of fellowship encouraged. The emphasis posed by the EAPCI and the National groups of interventional cardiology on education and training [5] has gained the consensus of all the components within cardiology. Trainees enthusiastically subscribe to the dedicated courses organized for fellows, modeled after similar initiatives of the US Society for Cardiac Angiography and Interventions. Europe, the cradle of modern interventional cardiology, is being reinvigorated to ensure this tradition is continued by competent and dedicated physicians, sharing common knowledge, skills and professionalism throughout Europe.

The State of Interventional Cardiology Training in the USA

The development of training and education in interventional cardiology in the United States followed a path similar to that in Europe. Initial training in percutaneous transluminal coronary angioplasty (PTCA) occurred via attendance at a live demonstration course in Zurich given by Dr. Andreas Gruentzig and his colleagues. At that time (late 1970s, very early 1980s), there was only one manufacturer of PTCA equipment in the USA. Initially they would not sell equipment to hospitals unless the operator had a diploma from attendance at a Gruentzig course and the hospital had Institutional Review Board (IRB) approval to perform PTCA. As the procedure gained acceptance and Dr. Gruentzig moved from Zurich to Emory University in Atlanta, Georgia, more “Courses in Angioplasty” began to appear and more companies began selling PTCA equipment. With this, the requirement for IRB approval of the procedure disappeared and certification of an individual as “PTCA competent” was left to the discretion of individual hospital credentialing committees.

PTCA became accepted very quickly as an appropriate alternative to coronary artery bypass grafting (CABG) for a select number of patients. Add to this the pioneering work of Dr. Geoffrey Hartzler in late 1980 in performing “direct” angioplasty (as he termed it) in acute myocardial infarction, and the impetus to expand the field of angioplasty was very strong indeed. On the job training through attendance at live demonstration courses and preceptorships rapidly expanded the number of physicians performing angioplasty. PTCA procedures were, by necessity, performed only in hospitals which had an open heart surgery program as the requirement for urgent CABG due to coronary dissection or acute closure was not infrequent in this pre-stent, pre-glycoprotein 2b/3a era. Since a large proportion of these hospitals with on-site CABG and PTCA programs were teaching hospitals with training programs in cardiology, exposure to PTCA became a regular part of basic cardiology training. The core training program in cardiology consisted of three years of internal medicine training followed by three years of cardiology training. The core training program in cardiology covered all aspects of non-invasive and invasive cardiology. As a result, new graduates of programs having PTCA on site began to be certified by their program directors as being capable of performing PTCA.

In this early era, there was no nationally specified curriculum of training in interventional cardiology and, as a result, this process was essentially an unstructured apprenticeship. The graduates of these programs were products of a highly varied educational experience, some with excellent cognitive as well as technical exposure and some with limited cognitive and/or technical exposure.

As the field grew and patient and technical complexity increased, programs began to electively add an additional year of training for persons wishing to pursue careers in interventional cardiology. According to survey results, by 1993 approximately half of the then approved cardiology training programs were requiring an additional year of training if graduates wished certification in interventional procedures [6].
This rapid growth led both The Society for Cardiovascular Angiography and Interventions and The American College of Cardiology to discuss in the early 1990s a means to structure and codify the interventional cardiology training process. An added impetus was the concern that patient outcomes might be compromised by low volume operators with limited training, especially if performing in low volume hospitals. This was supported by several publications which showed a clear relationship between lower operator volumes and increased rates of emergency coronary artery bypass surgery in both the pre-stent and stent eras [7,8].

As a result, a group of interventional leaders began conversation with the American Board of Internal Medicine (ABIM), the American Board of Medical Specialties (ABMS), and the Accreditation Council for Graduate Medical Education (ACGME) about creating a new subspecialty of interventional cardiology. It is requisite that all these bodies interact in order to create a new medical specialty, designate an approved training pathway, and offer certification of competence in that specialty.

In order to recognize a new specialty area, the ACGME requires the following criteria be met:

1. The new specialty signifies the differentiation of a new specialty based on major new concepts in medical science.
2. The new specialty is based on substantial advancement in medical science. The necessary training must be sufficiently complex or extended that it is not feasible to include it in established training programs.
3. There will be sufficient interest and resources available to establish the critical mass of quality training programs with long term commitments for successful integrating of the graduates in the health care system nationally.
4. The new discipline is recognized as legitimate and significant by the medical profession in general and the closely related specialties in particular for a consensus of the training required to perform in this new field.
5. That training in the new field is recognized as the single pathway to the competent preparation of a practitioner in this discipline.

Additionally, the ACGME requires that a number of other criteria be fulfilled to warrant a new training pathway. Detailed information on these requirements is available on the ACGME website. [9] As is evident, the creation of a new accredited subspecialty is a highly structured and codified process requiring much thought, effort, and coordination with other specialty areas. As a result of these extensive discussions, in 1999 the ACGME began reviewing and certifying training programs in interventional cardiology.

In addition to these ACGME training requirements, the ABIM had to find, amongst other things, that the specified body of knowledge is testable and objectively assessable. In 1999, the ABIM created a Certificate of Added Qualification in Interventional Cardiology (now simply called Certification in Interventional Cardiology), and the first examinations were given in the autumn of that year. To be eligible, a candidate had to hold a valid existing board certification in internal medicine and cardiovascular diseases. The candidate then applied through either the practice pathway (no formal interventional fellowship) or the training pathway (with formal interventional fellowship) meeting specified procedural requirements. The practice pathway ended with the 2003 examination. Thereafter, all applicants had to qualify via the training pathway with graduation from an ACGME approved interventional fellowship experience. The reason for this somewhat complex interweaving of eligible training pathways was to allow existing practitioners without formal interventional training to take IC boards until the training pipeline was established.

The IC examination is a timed multiple choice format examination given over two days. At the present, the question content is divided as follows:

- Case selection 25%
- Procedural techniques 25%
- Imaging 15%
- Pharmacology 15%
- Basic science 15%
- Miscellaneous 5%

Detailed information on content is available on the ABIM website [10] At the time of writing, the ABIM is preparing to utilize simulation in upcoming examinations in order to more adequately assess examinees technical skills and intra-procedure decision making.
Training and education are living processes undergoing constant evolution. In 2004 the ACGME promulgated new educational guidelines for all graduate medical education programs in the US and specified that all training had to comply with the six core competencies which are part of the Outcomes Project. These are:

- Medical Knowledge (MK)
- Patient Care (PC)
- Practice Based Learning and Improvement (PBLI)
- Systems Based Practice (SBP)
- Professionalism (P)
- Interpersonal and Communication Skills (ICS)

Details regarding these, procedural exposure, conferencing, research, and other ACGME requirements are available at their website [11].

As a result of these highly structured and codified requirements, training and credentialing in the US has achieved a high standard of excellence. The requirement of a structured didactic curriculum along with case conferences, basic science, conferences, morbidity and mortality conferences, and a required research project assure each trainee of a comprehensive and intensive training experience. The trainee is accepted in the program for one purpose only—to educate him/her. The notion of an unstructured apprenticeship built around clinical service to the mentor is no longer acceptable.

The next challenge to be faced is how to accommodate training for non-coronary interventions and structural heart disease within the existing framework. Note that according to the existing training documents, current IC training is specifically focused on coronary intervention. Adding this to the existing IC curriculum would require additional conversations with the ACGME, ABIM, and ABMS as they would have to agree to this plan according to the criteria enumerated above. Regardless of the outcome of these discussions, some form of formal, structured education beyond coronary intervention seems both likely and necessary.

In summary, the process of training and credentialing in interventional cardiology in the United States has evolved into a highly structured and codified process. Such training was initially obtained in the context of the basic three-year curriculum in cardiology and then developed into an additional year of training at many institutions but without clearly outlined expectations of didactic or clinical content. These unstructured apprenticeships then evolved into the current system of ACGME approved training in interventional cardiology beginning in 1999. In the same year, the ABIM began administering written examinations in interventional cardiology to provide “board certification” in the sub-sub-specialty. Until 2003 one could take these examinations via the practice pathway which required no formal training in IC but substantial experience. Thereafter, only graduates of ACGME approved IC programs were eligible for these examinations which provide a 10-year time-limited certification. At the end of that time, the applicant must re-take the examinations to maintain certification. As the field of IC continues to evolve, it seems highly likely that the current guidelines will be modified to include specified training in non-coronary interventions and/or structural heart disease with curricula and certifying examinations to match.

**Conclusion**

Interventional cardiovascular practice remains a dynamic, evolving and demanding subspecialty of cardiology which requires significant personal commitment to training and significant system resources to provide properly structured training. The evolution of similar systems in Europe suggests that this formalized process is superior to unstructured apprenticeships/fellowships and there may come a day when a truly international program of training and certification may be available.

**References**


CHAPTER 2

Atherogenesis and Inflammation

Giuseppe Sangiorgi, Alessandro Mauriello, Santi Trimarchi, Elena Bonanno, & Luigi Giusto Spagnoli

1 Cardiac Catheterization Laboratory, University of Modena, Italy
2 University of Rome Tor Vergata, Rome, Italy
3 IRCCS Policlinico San Donato, Milanese, Italy

Introduction

Atherosclerosis and its clinical consequences are the leading cause of death in Western nations. Mechanisms that lead to the formation of the atherosclerotic plaque are numerous. Atherosclerosis, by now considered a chronic inflammatory disease, begins in young age and progresses slowly for decades [1–3]. The clinical symptoms of atheroma occur in adult age and usually involve plaque rupture and thrombosis [4–6].

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 [7,8]. 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 to destabilisation of plaques [9]. 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 [10].

Many efforts have been recently performed to identifying plaques at high risk of disruption leading to thrombosis, generally defined as “vulnerable plaques” [5,9]. Several data sustain the hypothesis that some 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 associated with rupture and thrombosis, as compared to the stable ones covered by a thin fibrous cap and show an extensive inflammatory infiltrate [11,12].

Unlike the stable plaque that shows a chronic inflammatory infiltrate, the vulnerable and ruptured plaque is characterised by a chronic inflammation [13,12]. 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.

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 that aim in mind, this chapter will focus on cellular and molecular mechanisms affecting plaque progression and serum markers correlated to plaque inflammation.

**The Vulnerable Plaque**

Atherosclerotic lesions, according to the classification of the American Heart Association modified recently by Virmani et al. [9], are divided in two groups: (a) non-atherosclerotic intimal lesions and (b) 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 remodelling with expansion of the vessel external elastic lamina and minimal changes in lumen size [15]. The plaque contains monocyte-derived macrophages, smooth muscle cells, and T lymphocytes. Interaction between these cell 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 thin cap fibrous atheroma (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 [9,11,16]. Burke et al. identified a cut-off value for cap thickness of 65 microns to define a vulnerable coronary plaque [17]. With regard to carotid plaque vulnerability, our observations identified a thickness of 165 microns for differentiating stable from unstable carotid lesions (pers. comm.).

Despite the predominant hypothesis focusing on the responsibility of a specific vulnerable atherosclerotic plaque rupture [4,6] 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 [12,13,18,19].

Within this context, recent angiographic studies have demonstrated the presence of multiple vulnerable atheromatous plaques in patients with unstable angina [20] and in those affected by transmural myocardial infarction [19]. Recently by means of flow cytometry we have demonstrated the presence of an activated and multicentric inflammatory infiltrate in the coronary vessels of individuals who died of acute myocardial infarction [13]. Similar results have been obtained by Buffon et al., 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 [18]. These results have been confirmed by a morphological study of our group which demonstrated the presence of a high inflammatory infiltrate constituted by macrophagic cells and T lymphocytes activated in the whole coronary tree, also present in the stable plaques of individuals who died of acute myocardial infarction. These plaques showed a two- to four-fold higher inflammatory infiltrate than aged-matched individuals dying from non-cardiac causes with chronic stable angina (SA) or without clinical cardiac history (CTRL), respectively [12]. Moreover, we have recently demonstrated that activated T lymphocytes infiltrate the myocardium both in the peri-infarctual area and in remote unaffected myocardial regions in patients who died of a first myocardial infarction [21]. 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.

Acute myocardial infarction—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 [3,8]. Patients with endothelial dysfunction have an increased risk for future cardiovascular events including stroke [22]. 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 trombin) 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 IL-1, TNFα, and IFNγ. Endothelial cells also produce MCP-1, monocyte colony-stimulating factor and IL-6 which further amplify the inflammatory cascade [33]. IL-6 production by smooth muscle cells represents the main stimulus for C-reactive protein (CRP) production [2]. Recent evidence suggests that CRP may contribute to the proinflammatory state of the plaque both mediating monocytes recruitment and stimulating monocytes to release IL-1, IL-6, TNFα [34]. The damaged endothelium allows the passage of lipids into the subendothelial space. Fatty streaks represent the first step in the atherosclerotic process.

Evolving Fibro-atheromatous Plaque
The atheroma evolution is modulated by innate and adaptive immune responses [2,35,36]. The most important receptors for innate immunity in atherothrombosis are the scavenger receptors and the toll-like receptors (TLRs) [37]. Adaptive immunity is much more specific than innate immunity but may take several days or even weeks to be fully mobilized. It involves an organized immune response leading to generation of T and B cell receptors and immunoglobulins, which can recognize foreign antigens [38].

Stable Plaque
Macrophages take up lipid deposited in the intima via a number of receptors, including scavenger