

3

---

**PROGRESS  
IN CARDIOLOGY**

**PAUL N. YU**

**JOHN F. GOODWIN**

---

3

# PROGRESS IN CARDIOLOGY

*Edited by*

PAUL N. YU, M.D.

*Sarah McCort Ward Professor of Medicine and Head,  
Cardiology Unit, University of  
Rochester School of Medicine and Dentistry,  
Rochester, New York*

*and*

JOHN F. GOODWIN, M.D.

*Professor of Clinical Cardiology,  
Royal Postgraduate Medical School,  
London, England*



LEA & FEBIGER • Philadelphia, 1974

OTHER BOOKS IN THE SERIES

*Progress in Cardiology 1—1972*

*Progress in Cardiology 2—1973*

Library of Congress Cataloging in Publication Data  
Main entry under title:

Progress in cardiology.

Includes bibliographies.

1. Cardiology. I. Yu, Paul N., 1915- ed.  
II. Goodwin, John F., ed. [DNLM: 1. Cardiology—  
Yearbooks. W1 PR667P]  
RC667.P75 616.1'2 77-157474  
ISBN 0-8121-0326-2 (v. 1)  
ISBN 0-8121-0409-9 (v. 2)  
ISBN 0-8121-0451-X (v. 3)

Copyright © 1974 by LEA & FEBIGER. Copyright under the International Copyright Union. All Rights Reserved. *This book is protected by copyright. No part of it may be reproduced in any manner or by any means without written permission from the publisher.*

Published in Great Britain by Henry Kimpton Publishers, London

Printed in the United States of America

This volume is dedicated to our wives,  
Hing and Barbara, for their understanding,  
encouragement and support throughout the  
years.

## PREFACE

The third volume of *Progress in Cardiology* follows the pattern laid down for the first two volumes. It consists of 12 chapters contributed by authors from four continents. The material covers a wide spectrum of timely topics in cardiology.

The volume begins with a comprehensive review of the epidemiology and prevention of coronary artery disease. Risk factors and their prevention are succinctly discussed and critically evaluated. The second chapter is an excellent description of the formation and conduction of the cardiac electrical impulse, an understanding of which is fundamental to the interpretation and management of the cardiac arrhythmias. This is followed by a richly illustrated chapter on the pathogenesis and mechanism of ventricular arrhythmias, in which a unified concept for the genesis of ventricular arrhythmias is proposed. The next chapter provides us with up-to-date information concerning the physiology of exercise, the criteria for interpretation of exercise tests, and the precautions to be

observed during testing. The fifth chapter describes the care of patients in the important first hour after the onset of acute myocardial infarction. This chapter summarizes the author's experience in the operation of mobile coronary care units in Belfast, which serves as a model for prehospital care of acute myocardial infarction. The results are impressive and suggest a significant role for mobile units in the early prevention and management of cardiac arrhythmias and reduction in the incidence of cardiogenic shock and overall mortality.

The chapter on the renin-angiotensin system emphasizes the important role of this system in hypertension, with respect to pathophysiological, diagnostic and therapeutic considerations. Further investigation in this field will undoubtedly enhance our understanding and management of hypertension and related conditions. The chapter on the Eisenmenger syndrome describes the authors' experience with a large number of patients with this condition. The patho-

physiology and differential diagnosis of the syndrome are authoritatively discussed. The evaluation of drugs which affect heart muscle, with special reference to the principles and methodology for drug evaluation, comprises the eighth chapter. In Chapter 9, long-term surgical results and the advantages and disadvantages of various types of prosthetic valves are thoroughly appraised. Follow-up study has now clearly established the value of valve replacement in improving both longevity and the quality of patients' lives.

Chapter 10 is a critical review of the long-term use of specific agents for prevention of thromboembolic disease. It is now possible to use therapeutic agents judiciously for management of this condition over a period of many years. The principles, diagnostic value and limitations of echocardiography are admirably reviewed in the following chapter. Clinical evaluation of many types of con-

genital and acquired heart disease has been greatly facilitated by this noninvasive diagnostic tool. In the last chapter, the measurement of lung water is discussed. The author reviews the merits and limitations of the technique now widely used in clinical investigation and reports the quantity of lung water in various types of cardiac and pulmonary diseases. The quantitative relationships of lung water to patients' clinical status and to hemodynamic findings are of special interest.

All chapters for Volume 4 have already been committed. We sincerely hope that *Progress in Cardiology* will continue to publish a variety of valuable reviews in the field of cardiology, contributed by investigators from many parts of the world.

*Rochester, New York*  
*London, England*

PAUL N. YU  
JOHN F. GOODWIN

## ACKNOWLEDGMENT

We are grateful to all authors of the previous and current volumes for the excellence of their contributions.

We wish to acknowledge our profound indebtedness to Miss Sharon Frederick and Miss Janet Brewer for their devoted secretarial service. They have been most thorough and meticulous in handling correspondence, manuscripts and galley proofs.

In the past five years it has been our great pleasure to work with the staff of Lea & Febiger. We wish to thank Mr. R. Kenneth Bussy, Mr. Francis C. Lea, Jr., Mr. Thomas Colaiezzi and Mrs. Rosemary Pattison for their cooperation and assistance.

P.N.Y.  
J.F.G.

## CONTRIBUTORS

A. A. J. Adgey, M.B., M.R.C.P.  
Physician, Cardiac Department  
Royal Victoria Hospital  
Belfast, Ireland

Henry Blackburn, M.D.  
Professor of Medicine  
School of Medicine  
Director, Laboratory of Physiological Hygiene  
School of Public Health  
University of Minnesota  
Minneapolis, Minnesota

Robert A. Bruce, M.D.  
Professor of Medicine  
Co-Director, Division of Cardiology  
University of Washington  
Seattle, Washington

J. S. Geddes, B.Sc., M.D., M.R.C.P.  
Physician, Cardiac Department  
Royal Victoria Hospital  
Belfast, Ireland

John F. Goodwin, M.D., F.R.C.P., F.A.C.C.  
Professor of Clinical Cardiology  
Royal Postgraduate Medical School  
London, England

Raymond Gramiak, M.D.  
Professor of Diagnostic Radiology  
University of Rochester School of Medicine  
Rochester, New York

K. A. Hallidie-Smith, M.B., B.S., M.R.C.P., D.C.H.  
Pediatric Cardiologist  
Royal Postgraduate Medical School  
London, England

J. D. Harry, B.Sc., Ph.D., M.B., B.S.  
Lecturer in Medicine  
Cardiovascular Unit  
Killingbeck Hospital, Leeds General Infirmary  
and the University of Leeds  
Leeds, England

Thomas N. James, M.D.  
Professor and Chairman, Department of Medicine  
Professor of Pathology  
Director, Cardiovascular Research and Training  
Center  
University of Alabama School of Medicine  
Birmingham, Alabama

R. J. Linden, Ph.D., D.Sc., M.B., Ch.B., M.R.C.P.  
Professor of Applied Physiology  
Director, Cardiovascular Unit  
Killingbeck Hospital, Leeds General Infirmary  
and the University of Leeds  
Leeds, England

William A. H. MacLean, M.D.  
Instructor in Medicine  
University of Alabama School of Medicine  
Birmingham, Alabama

## xii Contributors

R. Michael McCredie, M.D., M.R.C.P., F.R.C.P.  
(Edin.), M.R.A.C.P.  
Cardiologist, the Prince Henry Hospital  
Little Bay, New South Wales, Australia

Philippe Meyer, M.D.  
Professor in Experimental Medicine  
Director, Physiology and Pharmacology Research  
Unit  
INSERM U7  
Hospital Necker  
Paris, France

J. F. Pantridge, M.C., M.D., F.R.C.P.,  
Professor of Cardiology, Queen's University  
Physician-in-Charge, Cardiac Department  
Royal Victoria Hospital  
Belfast, Ireland

D. John Parker, M.B., Ch.B., M.R.C.P., F.R.C.S.,  
F.R.C.S.E.  
Senior Lecturer, Cardiothoracic Institute  
Consultant Surgeon, National Heart Hospital  
London, England

W. Robert Pitney, M.D. (Melb.), F.R.A.C.P.,  
F.R.C.P.A.  
Professor of Medicine  
St. George Hospital and the University of New  
South Wales  
Kogarah, New South Wales, Australia

Donald N. Ross, M.B., Ch.B., F.R.C.S.  
Director of Surgery, Cardiothoracic Institute  
Consultant Surgeon, National Heart Hospital and  
Guy's Hospital  
London, England

Leo Schamroth, M.D. (Rand.), D.Sc., F.R.C.P.,  
(Edin.), F.R.C.P. (Glasg.), F.A.C.C.  
Professor of Medicine and Chief Physician  
Baragwanath Hospital and the University of  
Witwatersrand  
Johannesburg, Republic of South Africa

Pravin M. Shah, M.D.  
Associate Professor of Medicine and Pediatrics  
University of Rochester School of Medicine  
Rochester, New York

Albert L. Waldo, M.D.  
Associate Professor of Medicine  
University of Alabama School of Medicine  
Birmingham, Alabama

S. W. Webb, B.Sc., M.B., M.R.C.P.  
Senior Registrar, Cardiac Department  
Royal Victoria Hospital  
Belfast, Ireland

# CONTENTS

**1. PROGRESS IN THE EPIDEMIOLOGY AND PREVENTION OF CORONARY HEART DISEASE . . . . . 1**  
*(Henry Blackburn)*

- The Problem . . . . . 1
- The Frequency of CHD . . . . . 3
- Population Differences in CHD Frequency . . . . . 4
- Risk Factors for CHD . . . . . 5
  - Diet as a Risk Factor . . . . . 5
  - Overweight and Obesity as Risk Factors . . . . . 14
  - Hypertension as a Risk Factor . . . . . 15
  - Tobacco Smoking as a Risk Factor . . . . . 16
  - Glucose Tolerance as a Risk Factor . . . . . 17
  - Sedentary Habits as a Risk Factor . . . . . 17
  - Soft Water as a Risk Factor . . . . . 19
  - Personality, Behavior and Stress as Risk Factors . . . . . 20
  - Heredity and Family History as Risk Factors . . . . . 22
- Risk Factors for Sudden Death . . . . . 22
- Advances in Risk Appraisal . . . . . 23
- Strengths and Limitations of the Risk-factor Approach . . . . . 24
- Other Problems in the Use and Interpretation of Risk Factors
  - and the Risk Concept . . . . . 25
- Risk-factor Modification . . . . . 27
- Professional Attitudes about the Cause and Prevention of CHD . . . . . 27
  - The Academic Attitude . . . . . 27
  - The Pragmatic Attitude . . . . . 28

The Nihilistic View of CHD Prevention . . . . .	29
Atherosclerosis, a Pediatric Problem? . . . . .	31
The Future . . . . .	33
<b>2. FORMATION AND CONDUCTION OF THE CARDIAC ELECTRICAL IMPULSE . . . . .</b>	<b>37</b>
<i>(William A. H. MacLean, Albert L. Waldo, and Thomas N. James)</i>	
The Sinus Node. . . . .	37
Embryology . . . . .	38
Anatomy . . . . .	39
Innervation . . . . .	40
Electrophysiology . . . . .	42
Pathology . . . . .	44
Internodal and Interatrial Pathways . . . . .	44
Anatomy . . . . .	45
Electrophysiological Studies . . . . .	46
The Atrioventricular Node . . . . .	49
Embryology . . . . .	49
Anatomy . . . . .	49
Innervation . . . . .	51
Electrophysiology . . . . .	52
Pathology . . . . .	55
The His Bundle, Bundle Branches, and Purkinje System . . . . .	56
Embryology . . . . .	56
Anatomy . . . . .	57
Innervation . . . . .	60
Electrophysiology . . . . .	60
Pathology . . . . .	63
Conclusion . . . . .	65
<b>3. THE PATHOGENESIS AND MECHANISM OF VENTRICULAR ARRHYTHMIAS . . . . .</b>	<b>75</b>
<i>(Leo Schamroth)</i>	
The Electrocardiographic Expression . . . . .	75
Ventricular Escape (Idioventricular) Rhythm . . . . .	75
Ventricular Parasystole . . . . .	76
Ventricular Extrasystoles . . . . .	77
The Genesis of Ventricular Extrasystoles . . . . .	85
Ventricular Tachycardia . . . . .	91
Ventricular Fibrillation . . . . .	95
The Physiological Expression . . . . .	96
The Action Potential of a Nonpacemaking Cell . . . . .	96
The Action Potential of a Pacemaking Cell . . . . .	97
The Physiological Expression of Ectopic Ventricular Rhythms . . . . .	98
Ventricular Extrasystoles . . . . .	98
Extrasystolic Ventricular Tachycardia . . . . .	104
Idioventricular Rhythm: Ventricular Escape Rhythm . . . . .	106

Idioventricular Tachycardia . . . . . 106  
 Parasystolic Ventricular Rhythm . . . . . 106  
 Postulates . . . . . 107  
 The Unifying Concept . . . . . 107  
 The Biochemical Expression . . . . . 108  
 Acknowledgments . . . . . 109  
 Appendix . . . . . 109

**4. PROGRESS IN EXERCISE CARDIOLOGY . . . . . 113**

*(Robert A. Bruce)*

Cardiovascular Implications of Different Types of Exercise . . . . . 114  
 Classification of Exercise Tests . . . . . 116  
     Physical Types . . . . . 116  
     Physiological Types . . . . . 117  
     Standardization of Submaximal Tests . . . . . 117  
     Types of Maximal Tests . . . . . 118  
 Hazards and Safety Precautions . . . . . 121  
 Maximal Oxygen Uptake . . . . . 122  
     Definition and Significance of Maximal Oxygen Uptake . . . . . 122  
     Variations in Measurement of  $V_{O_{2max}}$  . . . . . 124  
     Reliability and Predictability of  $V_{O_{2max}}$  . . . . . 124  
     Estimation of  $V_{O_{2max}}$  in Man, When Both Physical Activity and  
         Cardiovascular Health Status are Known . . . . . 125  
     Relative Approach to  $V_{O_{2max}}$  with Multistage-treadmill Protocol . . . . . 125  
     Appraisal and Comparability of Relative Aerobic Requirements . . . . . 126  
     Relationship of Relative Aerobic Requirements to Regulatory  
         Mechanisms . . . . . 127  
     Longitudinal versus Cross-sectional Differences in  $V_{O_{2max}}$  . . . . . 127  
     Definition of Functional Aerobic Impairment . . . . . 128  
     Nomographic Derivation of FAI . . . . . 129  
 Cardiovascular Mechanisms of Functional Aerobic Impairment and  
     Relative Submaximal Stress . . . . . 130  
     Circulatory Mechanisms . . . . . 130  
     Cardiac Mechanisms in Cardiovascular Patients . . . . . 131  
     Submaximal Exercise Stresses . . . . . 135  
 Hemodynamic Responses to Exercise . . . . . 137  
     Normal Responses . . . . . 137  
     Responses in Cardiac Patients . . . . . 139  
     Regulation and Mechanisms of Impairment during Submaximal  
         Exercise . . . . . 139  
     Validity of Pressure Recordings . . . . . 141  
     Maximal Exercise . . . . . 142  
     Effects of Bed Rest . . . . . 143  
     Hemodynamic Comparison of Exercise Responses to Work on  
         Bicycle or Treadmill . . . . . 144  
 Exercise Electrocardiography . . . . . 145  
     Purposes, Criteria and Mortality Risks . . . . . 145  
     Exertional Arrhythmias . . . . . 146

Clinical and Epidemiological Correlates of S-T Depression . . . . . 147

Pathophysiological Considerations . . . . . 150

Sensitivity and Specificity of Clinical Interpretations of  
S-T Segment Depression . . . . . 151

ECG Lead Systems and Computer Analysis of S-T Segment  
Depression . . . . . 151

Morphological Correlations by Coronary Arteriography . . . . . 154

Effects of Nitroglycerin . . . . . 156

Physical Training or Exercise Conditioning . . . . . 156

Physiological Adaptations . . . . . 157

Clinical Aspects . . . . . 160

Initial Guidelines for Indications and Contraindications . . . . . 163

Guidelines for Vigorous Exercise Conditioning of Physical Training . . . . . 164

Requirements . . . . . 164

Practical Modifications in Relation to Clinical Classification  
of Functional Capacity . . . . . 165

Exercise Evaluation of Cardiac Therapy . . . . . 167

Acknowledgments . . . . . 168

Appendix . . . . . 169

**5. THE FIRST HOUR AFTER THE ONSET OF ACUTE MYOCARDIAL INFARCTION . . . . . 173**

*(J. F. Pantridge, S. W. Webb, A. A. J. Adgey, and J. S. Geddes)*

Management of the Acute Phase of Myocardial Infarction . . . . . 182

**6. THE ROLE OF THE RENIN-ANGIOTENSIN SYSTEM IN THE PATHOGENESIS OF HIGH BLOOD PRESSURE . . . . . 189**

*(Philippe Meyer)*

Role of Angiotensin in Maintenance and Control of Normal Blood  
Pressure . . . . . 192

Inhibition of the Renin-angiotensin Reaction . . . . . 192

Inhibition of the Conversion of Angiotensin I to Angiotensin II . . . . . 192

Inhibition of the Interaction of Angiotensin at Receptor Sites  
in Vascular Smooth Muscles . . . . . 193

Neutralization of Circulating Angiotensin II . . . . . 193

The Role of Angiotensin in the Pathogenesis of Experimental  
Renal Hypertension . . . . . 194

Experimental Renal Hypertension . . . . . 194

Experimental Malignant Hypertension . . . . . 199

Conclusions and Interpretations . . . . . 199

The Role of Angiotensin in the Pathogenesis of Human Renal  
Hypertension . . . . . 200

Human Renovascular Hypertension . . . . . 200

Malignant Hypertension . . . . . 203

Chronic Renal Insufficiency . . . . . 203

The Role of Angiotensin in the Pathogenesis of Sodium Hypertension . . . . . 204

Acknowledgments . . . . . 205

Addendum . . . . . 205

<b>7. THE EISENMENGER SYNDROME</b>	211
<i>(K. A. Hallidie-Smith and J. F. Goodwin)</i>	
Incidence	213
Susceptibility	213
Pulmonary Vasculature in the Fetus and Newborn Infant	213
The Pulmonary Circulation in the Fetus and Newborn	213
Pathogenesis	213
Post-tricuspid Shunts	215
Transposition of the Great Arteries	216
Pretricuspid Shunts	216
Symptoms and Complications	217
Quality of Life	218
Age at Death	218
Risk Factors and Causes of Death	218
Pregnancy	219
Treatment	220
Prevention	221
<b>8. THE EVALUATION OF DRUGS AFFECTING THE HEART</b>	227
<i>(R. J. Linden and J. D. Harry)</i>	
General Considerations about the Evaluation of Drugs which	
Affect the Heart	228
Action of Propranolol on the Heart	229
Does Propranolol "Depress" the Myocardium?	229
Conclusion	232
Mode of Study Advocated	232
Preparations of Isolated Papillary Muscle	233
Controlled Large Animal Experiments	234
Investigations in Man	240
Value to Man of Models Developed from Laboratory Experimentation	241
Effects of Sympathetic Nerve Stimulation which is Deleterious to	
the Patient—Beta-adrenoreceptor Blockade in Angina Pectoris	242
Selectivity and Intrinsic Sympathomimetic Activity of	
Beta-adrenoreceptor Blocking Drugs	243
The Variability of the Action of Beta-adrenoreceptor	
Blocking Drugs in Man	244
Value of Predictions of Responses to Drugs in Chronic Disease	246
General Conclusions	247
<b>9. CURRENT ASPECTS OF VALVE REPLACEMENT</b>	253
<i>(Donald N. Ross and D. John Parker)</i>	
Conservative Management	254
Valve Stenosis	254
Valve Regurgitation	254
Surgical Techniques for Valve Replacement	256
Aortic Valve Replacement	256
Mitral Valve Replacement	256
Tricuspid Valve Replacement	258

Pulmonary Valve Replacement . . . . .	258
Biological Valve Replacement . . . . .	258
Homograft Aortic Valve Replacement . . . . .	258
Pulmonary Autograft Valve . . . . .	260
Homografts in the Mitral and Tricuspid Positions . . . . .	262
Homograft Right Ventricular Outflow Tract Reconstruction . . . . .	263
Other Tissue Valves . . . . .	263
Heterograft Valves . . . . .	263
Summary . . . . .	264
Prosthetic Valve Replacement . . . . .	264
Aortic Valve Replacement . . . . .	264
Mitral Valve Replacement . . . . .	265
Tricuspid Valve Replacement . . . . .	265
Other Valves . . . . .	265
Summary . . . . .	265
Associated Problems . . . . .	266
Coronary Artery Disease and Valve Replacement . . . . .	266
Endocarditis and Valve Replacement . . . . .	267
Future Prospects . . . . .	268

**10. LONG-TERM THERAPY IN THE PREVENTION OF THROMBOSIS . . . . . 275**

*(W. R. Pitney)*

Oral Anticoagulants . . . . .	277
Mechanism of Action . . . . .	277
Choice of Agents . . . . .	277
Indications for Oral Anticoagulant Therapy . . . . .	278
Oral Anticoagulants in Pregnancy . . . . .	281
Practical Aspects of Oral Anticoagulant Therapy . . . . .	282
Laboratory Control of Oral Anticoagulant Therapy . . . . .	283
Agents which Affect Platelet Behavior . . . . .	284
Aspirin . . . . .	284
Pyrimidopyrimidine Compounds . . . . .	285
Clofibrate . . . . .	285
Other Agents which Affect Platelets . . . . .	286
Pharmacological Enhancement of Fibrinolysis . . . . .	286
Conclusions . . . . .	287

**11. CLINICAL USEFULNESS OF ECHOCARDIOGRAPHY . . . . . 293**

*(Pravin M. Shah and Raymond Gramiak)*

Historical Outline . . . . .	293
Basic Principles . . . . .	294
Echocardiographic Technique . . . . .	295
Echocardiographic Findings in Normal Adult Subjects . . . . .	298
Echo Findings in Disease . . . . .	301
Rheumatic Mitral Valve Disease . . . . .	301
Nonrheumatic Mitral Regurgitation . . . . .	305
Cardiomyopathies . . . . .	310
Aortic Valve Disease . . . . .	318

Aortic Root Dissection . . . . .	320
Pericardial Effusion . . . . .	320
Left Atrial Myxoma . . . . .	320
Congenital Heart Disease . . . . .	322
Pulmonary Hypertension . . . . .	326
Left Ventricular Function . . . . .	326
Future Technical Developments in Ultrasound Cardiography . . . . .	327
<b>12. THE MEASUREMENT OF LUNG WATER . . . . .</b>	<b>331</b>
<i>(R. M. McCredie)</i>	
Morphological and Physiological Considerations . . . . .	331
Principle of Methods . . . . .	332
Choice of Indicators . . . . .	334
Sources of Error . . . . .	334
What is the Water Space Measured? . . . . .	339
Applications of Lung Water Measurements . . . . .	340
Normal Values . . . . .	340
Lung Water in Disease . . . . .	340

## Chapter 1

# PROGRESS IN THE EPIDEMIOLOGY AND PREVENTION OF CORONARY HEART DISEASE\*

Henry Blackburn, M.D.

The classical “up-the-river-from-New-Orleans” version of the history of American jazz is a logical and accurate one, as far as it goes, but it misses much of the emotional turmoil, the side battles, and the excitement of the whole development. Similarly, this view of the recent progress in cardiological thought about the epidemiology and prevention of coronary heart disease (CHD) is concerned not with a classical review of the evidence but rather with the present intellectual excitement, questions, and controversies. It is a problem-oriented and personal approach rather than a traditional one. Excellent and thoroughgoing recent reviews of the epidemiological evidence and the status of CHD prevention are available and highly recommended.<sup>17,18,64,68,69,73</sup>

The present state of progress in cardiovascular epidemiology includes the overriding

\* Some of the data and conclusions herein were obtained through support from National Heart and Lung Institute awards (HE 04997; HL 04697; PH 86-64-110; HE 11898; HE 10194), and from the American Heart Association, the Ober Charitable Trust Fund, and the Mutual Service Scholarship in Preventive Cardiology.

demonstration that there are vast differences in the frequency of CHD among populations and that the risk of the disease varies enormously according to the burden of individual or population risk characteristics. Cardiology, in concert with disciplines from preventive medicine, has arrived at the stage of knowledge in which major preventive trials are considered indicated and imperative.<sup>75</sup> These will demonstrate whether individuals and populations at apparently high risk can be converted to lower levels of risk by direct intervention on the risk factors, that is, by prophylactic treatment. These ideas, simple like most important ideas, confront the medical profession and the public with one of their finest challenges. It is now a part of the mainstream of cardiology to participate in this adventure, to test whether significant reduction is possible of one of the most costly of man's diseases.

### THE PROBLEM

The essentiality of a preventive approach to CHD is clear from what we know of the insidious nature of the atherosclerotic process,