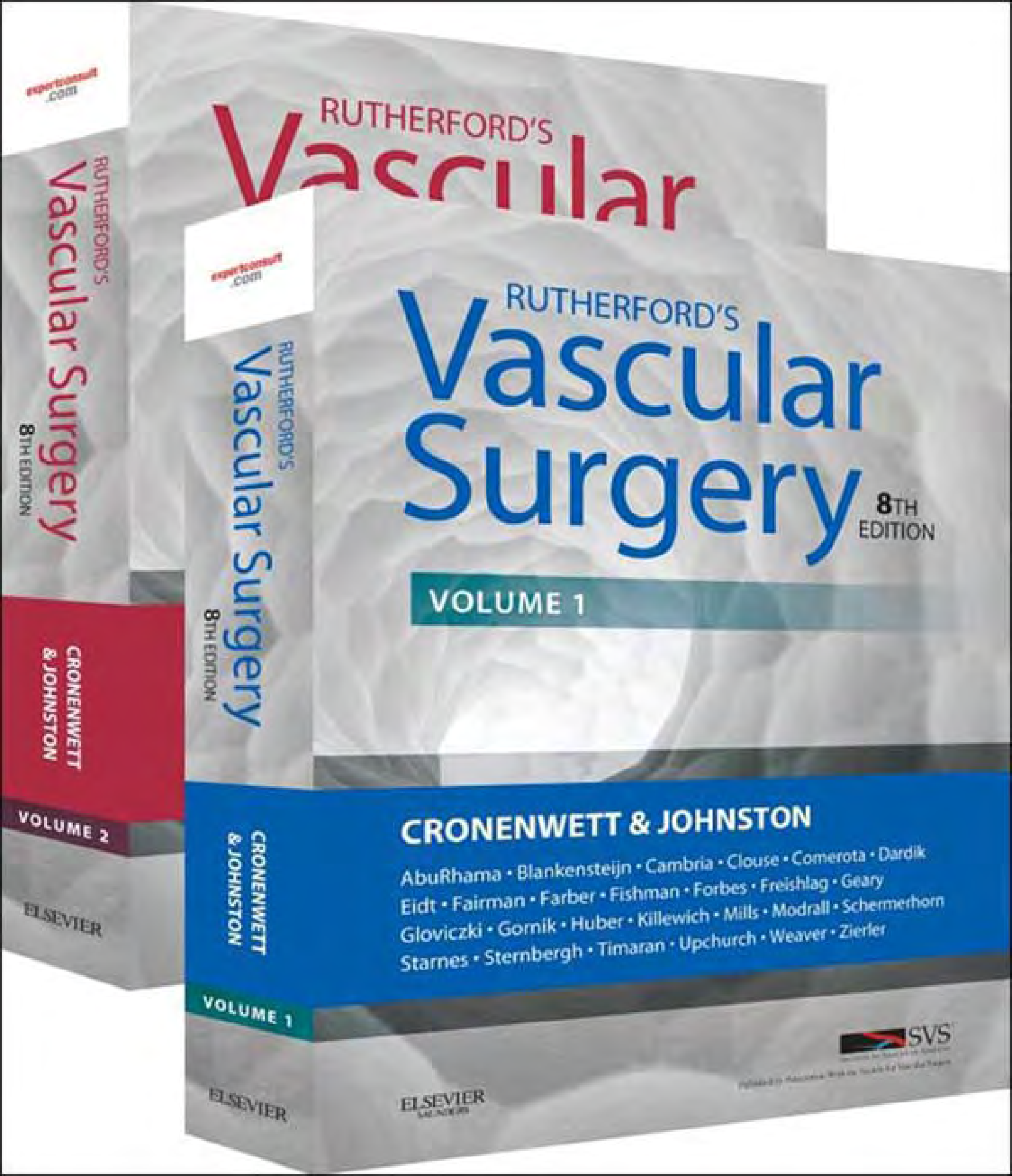
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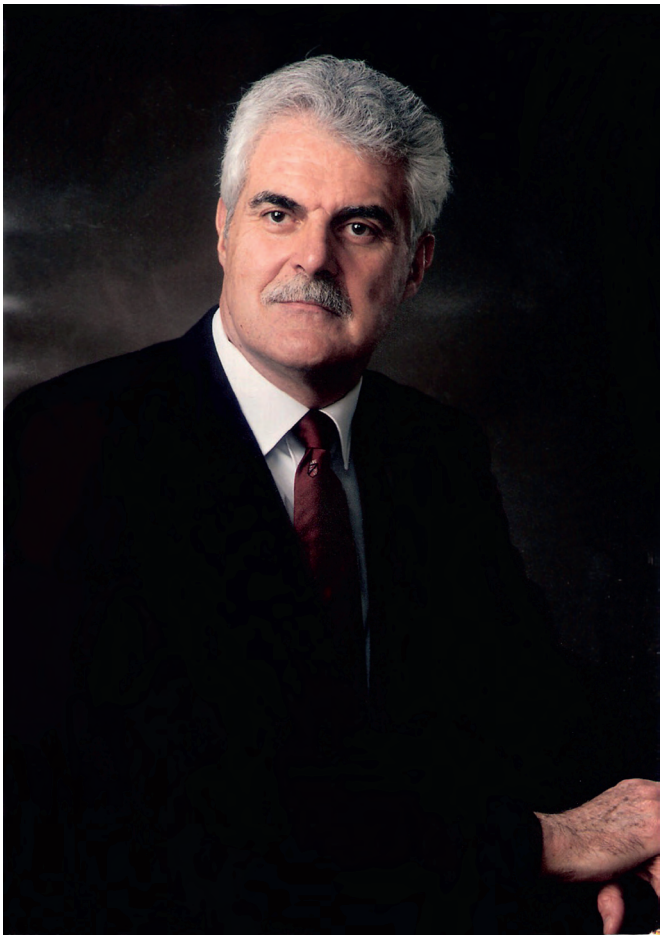
IN MEMORIAM

Robert B. Rutherford, MD, 1931-2013



Robert B. Rutherford, MD, the founding editor of this textbook, died on November 22, 2013, at the age of 82. The vascular surgery community is saddened by the loss of this extraordinary man, who created many opportunities for others and did so much to advance the care of patients with vascular disease.

Dr. Rutherford was born in Edmonton, Alberta, Canada. He received his BA (Phi Beta Kappa) in 1952 and his MD (Alpha Omega Alpha) in 1956, both from Johns Hopkins University. After internship at Johns Hopkins, he completed his general surgery residency at the University of Colorado in 1963. During residency, he did a clinical fellowship year as a Fulbright Scholar at Lund University in Malmo, Sweden. After residency he served 2 years in the military at the Walter Reed Army Institute of Research. He was then appointed to the surgical faculty at Johns Hopkins in 1965 before returning to the University of Colorado in 1970 where he spent the remainder of his professional career as Professor of Surgery and Chief of the Vascular Surgery Section.

In 1975, Dr. Rutherford was the first to recognize the need for a comprehensive textbook devoted exclusively to the new specialty of vascular surgery. He successfully recruited a group of peers to be associate editors, and in 1977 the first edition of *Vascular Surgery* was published. In the preface to the first edition, he stated in his usual humble manner that "our efforts will have been rewarded if the book proves helpful to any physician who has committed himself or herself to treating patients with vascular disease." Over the next 30 years, Dr. Rutherford shepherded his textbook through six editions, constantly updating authors, content, and associate editors, before assigning editorship to the Society for Vascular Surgery to ensure publication in perpetuity. Known colloquially as "Rutherford," this textbook, a reflection of his vision and commitment, has become the definitive source for all practitioners of vascular healthcare. It is his enduring contribution to our discipline for which he is owed a great debt of gratitude.

Dr. Rutherford had broad interests in vascular surgery, a scholarly command of the literature, and an outstanding memory. This led to the publication during his career of more than 400 scientific articles and book chapters, on a wide range of topics. Dr. Rutherford also recognized the need for regular updates of topics for practicing vascular surgeons, which led to his development and editing of "Seminars in Vascular Surgery" from 1988 to 2012. Given his knowledge base and editorial expertise, he was selected as senior editor of the *Journal of Vascular Surgery*, a position he held from 1996 to 2003. He was a natural editor who provided critical, but fair and balanced reviews, and was always prepared to help less experienced authors.

Dr. Rutherford was a member of many professional societies, and was president of four, most notably serving as the forty-third president of the International Society for Cardiovascular Surgery, North American Chapter (now the Society for Vascular Surgery). In his presidential address of 1995, he emphasized the importance of uniform disease-specific reporting standards for describing vascular interventions, their results, and complications. Dr. Rutherford organized the committees that developed the current reporting standards for the Society of Vascular Surgery (SVS), which was a major contribution to the advancement of our specialty. This initiative expanded globally when he co-chaired the first Transatlantic Consensus on Peripheral Arterial Occlusive Disease, in 2000.

In 2005, the SVS honored Dr. Rutherford with its Lifetime Achievement Award. This is the highest honor that the SVS bestows on one of its members. It recognizes an individual's outstanding and sustained contributions both to the profession of vascular surgery and to the Society, as well as exemplary professional practice and leadership.

Throughout his career, Dr. Rutherford traveled widely as an invited speaker. Despite his many accomplishments, he remained a humble, friendly person, who would always listen to colleagues and provide unselfish help in developing their careers. This tall vascular surgeon with a sparkle in his eye was recognized around the world and appreciated by all.

Bob Rutherford and his wife, Kay, enjoyed downhill and cross-country skiing in the Colorado mountains and sailing, windsurfing, tennis, and biking in Colorado and their summer home in Maine. In recent years, Bob enjoyed bird photography (especially in their winter home in North Padre Island), playing piano, fishing, and golf. His interest in new topics clearly extended to his recreational activities. He is survived by his wife of 58 years, their five children, and many grandchildren.

Robert B. Rutherford was a surgeon-scholar who will be remembered most because he was a "teacher's teacher" who conceived and edited the definitive vascular surgery textbook, lectured internationally, edited the *Journal of Vascular Surgery*, and stressed the importance of knowing outcomes through standard reporting. He made his scholarly mark on vascular surgery throughout the world through his enthusiastic work, friendships, mentoring of many colleagues, and tireless writing and editing. It was our distinct honor to have worked with Bob on many projects over the years, and to have become close personal friends. He is dearly missed by his many friends and colleagues in the global vascular community.

Jack L. Cronenwett, MD
K. Wayne Johnston, MD, FRCS(C)

RUTHERFORD'S

VASCULAR SURGERY

EIGHTH EDITION

Jack L. Cronenwett, MD

PROFESSOR OF SURGERY
GEISEL SCHOOL OF MEDICINE AT DARTMOUTH
DARTMOUTH-HITCHCOCK MEDICAL CENTER
LEBANON, NEW HAMPSHIRE

K. Wayne Johnston, MD, FRCS(C)

PROFESSOR OF SURGERY
UNIVERSITY OF TORONTO
TORONTO GENERAL HOSPITAL
TORONTO, ONTARIO
CANADA

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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VP, Global Content: Judith Fletcher
Content Development Specialist: Joanie Milnes
Publishing Services Manager: Anne Altepeter
Project Manager: Cindy Thoms
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This edition is dedicated to all of the students, residents, and fellows who have enriched our academic careers by their desire for new knowledge.

And to our early mentors, S. Martin Lindenauer, MD; James C. Stanley, MD; H. Edward Garrett, MD; Bernard Langer, MD; Ronald J. Baird, MD; and Donald R. Wilson, MD, who inspired and encouraged us to pursue an academic career.

And to our wives, Debra Cronenwett and Jean Johnston, who have provided strong support for all our academic endeavors.

And especially, to our founder, Robert B. Rutherford, MD, for his vision in creating this reference textbook for all providers of vascular healthcare. We miss our dear friend, whose name lives on in this important contribution—Rutherford's Vascular Surgery.

ASSOCIATE EDITORS

Peter Gloviczki, MD
Joe M. and Ruth Roberts Professor of Surgery
Mayo Clinic College of Medicine
Chairman Emeritus
Division of Vascular and Endovascular Surgery
Mayo Clinic
Rochester, Minnesota
Section 10—Venous Insufficiency and Occlusion
Section 11—Lymphedema

Heather L. Gornik, MD, MHS
Assistant Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Staff Physician and Medical Director
Noninvasive Vascular Laboratory
Cleveland Clinic
Cleveland, Ohio
Section 5—Atherosclerotic Risk Factors

Thomas S. Huber, MD, PhD
Professor and Chief
Division of Vascular and Endovascular Surgery
University of Florida College of Medicine
Gainesville, Florida
Section 13—Hemodialysis Access

Lois A. Killewich, MD, PhD
Leonard and Marie Louise Aronsfeld Rosoff Professor of Surgery
Assistant Dean for Continuing Education
University of Texas Medical Branch
Galveston, Texas
Section 14—Miscellaneous

Joseph L. Mills, Sr., MD
Professor and Chief
Division of Vascular and Endovascular Surgery
Co-Director, Southern Arizona Limb Salvage Alliance (SALSA)
Department of Surgery
University of Arizona Health Sciences Center
Tucson, Arizona
Section 18—Lower Extremity Arterial Disease

J. Gregory Modrall, MD
Professor of Surgery
Division of Vascular and Endovascular Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Section 27—Acute Ischemia

Marc L. Schermerhorn, MD
Chief, Division of Vascular and Endovascular Surgery
Beth Israel Deaconess Medical Center
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts
Section 25—Mesenteric Vascular Disease

Benjamin W. Starnes, MD
Chief, Division of Vascular Surgery
Department of Surgery
University of Washington
Seattle, Washington
Section 26—Vascular Trauma

W. Charles Sternbergh III, MD
Professor of Surgery
University of Queensland School of Medicine
Chief, Division of Vascular and Endovascular Surgery
Vice Chair for Research
Department of Surgery
Ochsner Clinic Foundation
New Orleans, Louisiana
Section 15—Technique

Carlos H. Timaran, MD
Chief, Endovascular Surgery
G. Patrick Clagett Professor in Vascular Surgery
Associate Professor of Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Section 23—Peripheral and Visceral Aneurysm

Gilbert R. Upchurch, Jr., MD
Muller Professor of Surgery and Physiology
Chief, Division of Vascular and Endovascular Surgery
University of Virginia
Charlottesville, Virginia
Section 22—Thoracic Aortic Aneurysms and Dissection

Fred A. Weaver, MD
Professor of Surgery
Chief, Division of Vascular Surgery and Endovascular Therapy
Keck School of Medicine at University of Southern California
Los Angeles, California
Section 7—Bleeding and Clotting

R. Eugene Zierler, MD
Medical Director, D.E. Strandness, Jr. Vascular Laboratory
University of Washington Medical Center
Harborview Medical Center
Professor of Surgery
University of Washington
Seattle, Washington
Section 2—Pathophysiology

CONTRIBUTORS

Ahmed M. Abou-Zamzam, Jr., MD
Chief, Division of Vascular Surgery
Associate Professor
Department of Cardiovascular and Thoracic Surgery
Loma Linda University Medical Center
Loma Linda, California
Lower Extremity Amputation: General Considerations

Christopher J. Abularrage, MD
Assistant Professor
Division of Vascular Surgery and Endovascular Therapy
The Johns Hopkins Hospital
Baltimore, Maryland
Takayasu's Disease

Ali F. AbuRahma, MD, RVT, RPVI
Professor of Surgery
Chief, Division of Vascular and Endovascular Surgery
Director, Vascular Surgery Fellowship and Residency Programs
Department of Surgery
Robert C. Byrd Health Sciences Center
West Virginia University
Medical Director, Vascular Laboratory
Co-Director, Vascular Center of Excellence
Charleston Area Medical Center
Charleston, West Virginia
Complex Regional Pain Syndrome

Charles W. Acher, MD
Professor of Surgery
Division of Vascular Surgery
University of Wisconsin
Madison, Wisconsin
Thoracic and Thoracoabdominal Aneurysms: Open Surgical Treatment

Stefan Acosta, MD, PhD
Associate Professor and Specialist in Vascular Surgery
Vascular Centre, Skåne University Hospital
Malmö, Sweden
Mesenteric Vascular Disease: Venous Thrombosis

Nathan Airhart, MD
Research Fellow in Vascular Surgery
Washington University School of Medicine
St. Louis, Missouri
Arterial Aneurysms

Ahmet Rüçhan Akar, MD, FRCS (C/Th)
Professor of Cardiovascular Surgery
Director, Ankara University Organ Transplantation Program
Deputy Director, Ankara University Stem Cell Institute
Heart Center, Ankara University School of Medicine
Dikimevi, Ankara, Turkey
Thromboangiitis Obliterans (Buerger's Disease)

Matthew J. Alef, MD
Fellow in Vascular and Endovascular Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Upper Extremity Arterial Disease: General Considerations

Yves S. Alimi, MD, PhD
Professor of Vascular Surgery
Chief, Department of Vascular Surgery
Université de la Méditerranée
University Hospital North
Marseille, France
Iliocaval Venous Obstruction: Surgical Treatment

Ahmad Alomari, MD, MSc, FSIR
Division of Vascular and Interventional Radiology
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts
Endovascular Therapy of Vascular Malformations

Juan I. Arcelus, MD, PhD
Professor of Surgery
Department of Surgery
Hospital Universitario Virgen de las Nieves
University of Granada
Granada, Spain
Acute Deep Venous Thrombosis: Prevention and Medical Management

Frank R. Arko III, MD
Director, Endovascular Surgery
Co-Director, Aortic Institute
Sanger Heart and Vascular Center
Carolinas Medical Center
Charlotte, North Carolina
Intravascular Ultrasound

David G. Armstrong, DPM, MD, PhD
Southern Arizona Limb Salvage Alliance
Department of Surgery
University of Arizona College of Medicine
Tucson, Arizona
Diabetic Foot Ulcers

Maggie Arnold, MD
Assistant Professor of Surgery
The Johns Hopkins University School of Medicine
Baltimore, Maryland
Carotid Artery: Endarterectomy

Zachary M. Arthurs, MD
Assistant Professor of Surgery
Uniformed Services University of Health Sciences
Chief, Vascular Surgery
San Antonio Military Medical Center
San Antonio, Texas
Vascular Trauma: Head and Neck

Marvin D. Atkins, MD
Assistant Professor of Surgery
Division of Vascular Surgery
Scott & White Hospital
Texas A&M University
Temple, Texas
Carotid Artery: Aneurysms

Robert Atnip, MD
Professor of Surgery
Penn State Heart and Vascular Institute
Penn State Milton S. Hershey Medical Center
Hershey, Pennsylvania
Local Complications: Nerve Injury

Faisal Aziz, MD
Vascular Surgery
Penn State Hershey Heart and Vascular Institute
Hershey, Pennsylvania
Acute Deep Venous Thrombosis: Surgical and Interventional Treatment

Ali Azizzadeh, MD, FACS
Associate Professor
Department of Cardiothoracic and Vascular Surgery
University of Texas Houston Medical School
Director of Endovascular Surgery
Memorial Hermann Heart and Vascular Institute
Houston, Texas
Vascular Trauma: Thoracic

Martin R. Back, MD, MS, FACS, PVI
Professor of Surgery
Division of Vascular and Endovascular Surgery
University of South Florida
Morsani School of Medicine
Tampa, Florida
Local Complications: Graft Infection

M. Shadman Baig, MD
Assistant Professor
Department of Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Upper Extremity Aneurysms

Jeffrey L. Ballard, MD
Staff Vascular Surgeon
St. Joseph Hospital
Orange, California
Operative Exposure for Spinal Reconstructive Surgery

John R. Bartholomew, MD
Section Head of Vascular Medicine
Director, Thrombosis Center
Sydell and Arnold Miller Family Heart and Vascular Institute
Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Cleveland, Ohio
Atheromatous Embolization

Ruediger G.H. Baumeister, MD
Doctor, Consultant in Lymphology
Chirurgische Klinik Muenchen Bogenhausen
Former Head
Department of Surgery
Division of Plastic, Hand, and Microsurgery, Lymphology
University Hospital Grosshadern
Muenchen, Bavaria, Germany
Lymphedema: Surgical Treatment

William Scott Beattie, MD, PhD
R. Fraser Elliot Chairman in Cardiac Anesthesia
Anesthesia and Pain Medicine
University Health Network
Professor
Department of Anesthesia
University of Toronto
Toronto, Canada
Systemic Complications: Cardiac

Carlos F. Bechara, MD
Division of Vascular and Endovascular Therapy
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Michael E. DeBakey VA Medical Center
Houston, Texas
Superior Vena Cava Occlusion: Surgical Treatment

Adam W. Beck, MD
Assistant Professor of Surgery
Division of Vascular Surgery and Endovascular Therapy
University of Florida College of Medicine
Gainesville, Florida
Infected Aneurysms

Joshua A. Beckman, MD, MS
Associate Professor of Medicine
Harvard Medical School
Director, Cardiovascular Fellowship Program
Cardiovascular Division
Brigham and Women's Hospital
Boston, Massachusetts
Atherosclerotic Risk Factors: Diabetes

Michael Belkin, MD
Chief, Division of Vascular and Endovascular Surgery
Brigham and Women's Hospital
Boston, Massachusetts
Aortoiliac: Direct Reconstruction

Simona Ben-Haim, MD, DSc
Department of Nuclear Medicine
Chaim Sheba Medical Center
Ramat-Gan, Israel
Institute of Nuclear Medicine
University College Hospitals NHS Trust
London, United Kingdom
Vascular PET/CT and SPECT/CT

Kyla M. Bennett, MD
Vascular Surgery Fellowship
Duke University
Durham, North Carolina
Coagulopathy and Hemorrhage

Scott A. Berceli, MD, PhD
Professor of Surgery
University of Florida College of Medicine
Malcom Randall VA Medical Center
Gainesville, Florida
Autogenous Grafts

Michael J. Bernas, MS
Associate Scientific Investigator
University of Arizona College of Medicine
Tucson, Arizona
Lymphatic Pathophysiology

Boback M. Berookhim, MD, MBA
Fellow
Sexual and Reproductive Medicine Program
Urology Service
Memorial Sloan-Kettering Cancer Center
New York, New York
Erectile Dysfunction

Christian Bianchi, MD, FACS
Chief, Division of Vascular Surgery
Loma Linda Veterans Affairs Healthcare System
Associate Professor
Cardiovascular Surgery
Loma Linda University
Loma Linda, California
Lower Extremity Amputation: General Considerations

Martin Björck, MD, PhD
Professor of Vascular Surgery
Uppsala University
Uppsala, Sweden
Mesenteric Vascular Disease: Venous Thrombosis

James H. Black III, MD, FACS
Bertram M. Bernheim MD Associate Professor of Surgery
Johns Hopkins School of Medicine
Baltimore, Maryland
Aneurysms Caused by Connective Tissue Abnormalities

Jan D. Blankensteijn, MD, PhD
Associate Professor of Vascular Surgery
VU University Medical Center
Amsterdam, The Netherlands
Computed Tomography

Thomas C. Bower, MD
Professor of Surgery
Mayo Clinic, College of Medicine
Chair, Division of Vascular and Endovascular Surgery
Mayo Clinic
Rochester, Minnesota
Venous Tumors

Kathleen E. Brummel-Ziedins, PhD
Associate Professor
Department of Biochemistry
University of Vermont
Burlington, Vermont
Normal Coagulation

Ruth L. Bush, MD, MPH
Professor of Surgery
Interim Vice Dean, Bryan/College Station
Texas A&M University
Vascular Surgeon, Division of Vascular Surgery
Central Texas Veterans Hospital
Temple, Texas
Carotid Artery: Aneurysms

John Byrne, MD
Chief, Division of Cardiac Surgery
Professor, Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts
Abdominal Aortic Aneurysms: Ruptured

Xzabia A. Caliste, MD
Vascular Surgery Residency Program
University of Rochester Medical Center
Rochester, New York
Venography

Keith D. Calligaro, MD
Chief, Division of Vascular Surgery
Pennsylvania Hospital
Philadelphia, Pennsylvania
Renovascular Disease: Aneurysms and Arteriovenous Fistulae

Richard P. Cambria, MD
Chief, Division of Vascular and Endovascular Surgery
Massachusetts General Hospital
Boston, Massachusetts
Aortic Dissection

Piergiorgio Cao, MD, FRCS
Professor of Vascular Surgery
University of Perugia, School of Medicine
Chief, Division of Vascular Surgery
S. Maria Misericordia Hospital
Perugia, Italy
Carotid Artery: Stenting

Joseph A. Caprini, MD, MS
Louis Biegler Chair of Surgery
Division of Vascular Surgery
North Shore University Health System
Evanston, Illinois
Clinical Professor of Surgery
Department of Surgery
Pritzker School of Medicine
University of Chicago
Chicago, Illinois
Acute Deep Venous Thrombosis: Prevention and Medical Management

Gregory D. Carlson, MD
Staff Orthopedic Surgeon
St. Joseph Hospital
Orange, California
Spinal Operative Exposure

Teresa L. Carman, MD
Director, Vascular Medicine
Medical Director, Coumadin Clinic
Medical Director, Center for Wound Care
University Hospitals Case Medical Center
Cleveland, Ohio
Atherosclerotic Risk Factors: Hyperlipidemia

Jeffrey P. Carpenter, MD
Professor and Chairman
Department of Surgery
Cooper Medical School
Rowan University
Camden, New Jersey
Magnetic Resonance Imaging

George P. Casale, PhD
Associate Professor of Surgery
University of Nebraska Medical Center
Omaha, Nebraska
Ischemia-Reperfusion

Neal S. Cayne, MD
Associate Professor of Surgery
Division of Vascular and Endovascular Surgery
Director of Endovascular Surgery
New York University Medical Center
New York, New York
Lower Extremity Aneurysms

Rabih A. Chaer, MD, MSc
Associate Professor of Surgery
Division of Vascular Surgery
The University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania
Carotid Artery: Dissection and Fibromuscular Dysplasia

Elliot L. Chaikof, MD, PhD
Johnson and Johnson Professor of Surgery
Harvard Medical School
Chairman
Roberta and Stephen R. Weiner Department of Surgery
Beth Israel Deaconess Medical Center
Associate Faculty
Wyss Institute of Biologically Inspired Engineering
Faculty
Harvard Stem Cell Institute
Boston, Massachusetts
Prosthetic Grafts

Stephen W.K. Cheng, MBBS, MS, FRCS(E), FRCS
Serena H.C. Yang Professor of Vascular Surgery
Chief, Division of Vascular Surgery
The University of Hong Kong
Hong Kong
Radiation Safety

Andrea L. Cheville, MD, MDCE
Associate Professor
Physical Medicine and Rehabilitation
Mayo Clinic
Rochester, Minnesota
Lymphedema: Nonoperative Treatment

Jason Chin, MD
Vascular Surgery
Yale—New Haven Hospital
New Haven, Connecticut
Vessel Wall Biology

Jayer Chung, MD
Assistant Professor
Division of Vascular and Endovascular Surgery
Chief
Division of Vascular and Endovascular Surgery
Parkland Memorial Hospital
University of Texas
Southwestern Medical Center
Dallas, Texas
Thoracic Outlet Syndrome: Arterial Compartment Syndrome

Daniel G. Clair, MD
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Chairman of Vascular Surgery
Cleveland Clinic
Cleveland, Ohio
Brachiocephalic Artery: Endovascular Treatment Diseases

W. Darrin Clouse, MD
Professor of Surgery
Uniformed Services University of Health Sciences
Bethesda, Maryland
University of California, Davis
Sacramento, California
Upper Extremity Arterial Disease: Amputation

Anthony J. Comerota, MD
Director
Jobst Vascular Institute
The Toledo Hospital
Toledo, Ohio
Adjunct Professor of Surgery
Department of Vascular Surgery
University of Michigan
Ann Arbor, Michigan
Acute Deep Venous Thrombosis: Surgical and Interventional Treatment
Superficial Thrombophlebitis

Mark F. Conrad, MD
Director of Clinical Research
Assistant Program Director
Division of Vascular and Endovascular Surgery
Massachusetts General Hospital
Institute for Heart, Vascular and Stroke Care
Boston, Massachusetts
Aortic Dissection

Christopher J. Cooper, MD
Chairman, Department of Medicine
Professor of Medicine
University of Toledo
Toledo, Ohio
Renovascular Disease: Endovascular Treatment

Leslie T. Cooper, Jr., MD
Director
Gonda Vascular Center
Professor of Medicine
Mayo Clinic
Rochester, Minnesota
Vasculitis and Other Uncommon Arteriopathies

Matthew A. Corriere, MD, MS
Assistant Professor
Department of Vascular and Endovascular Surgery
Wake Forest University School of Medicine
Winston Salem, North Carolina
Renovascular Disease: Acute Ischemia

David L. Cull, MD
Professor of Surgery
University of South Carolina
School of Medicine-Greenville
Vice-Chair of Academic Affairs
Department of Surgery
Greenville Health System
University Medical Center
Greenville, South Carolina
Hemodialysis Access: Complex

John A. Curci, MD
Associate Professor of Vascular Surgery
Washington University School of Medicine
Chief
Division of Vascular and Endovascular Surgery
Veterans Affairs St. Louis Healthcare System
St. Louis, Missouri
Arterial Aneurysms

Michael C. Dalsing, MD
E. Dale and Susan E. Habegger Professor of Surgery
Director of Vascular Surgery
Indiana University School of Medicine
Indianapolis, Indiana
Chronic Venous Insufficiency: Deep Vein Valve Reconstruction

Scott M. Damrauer, MD
Instructor in Surgery
University of Pennsylvania
Fellow
Division of Vascular Surgery and Endovascular Therapy
University of Pennsylvania Health System
Philadelphia, Pennsylvania
Abdominal Aortic Aneurysms: Open Surgical Treatment

Paola De Rango, MD, PhD
Staff Vascular Surgery
Vascular and Endovascular Surgery Unit
S. Maria Misericordia Hospital
University of Perugia
Perugia, Italy
Carotid Artery: Stenting

David H. Deaton, MD
Associate Professor of Surgery
Georgetown University School of Medicine
Chief, Division of Vascular and Endovascular Surgery
Georgetown University Hospital
Washington, District of Columbia
Arterial Aneurysms: General Considerations

Demetrios Demetriades, MD, PhD, FACS
Professor of Surgery
Director, Acute Care Surgery
Los Angeles County and University of Southern California Medical Center
Los Angeles, California
Vascular Trauma: Abdominal

Sapan S. Desai, MD
Department of Cardiothoracic and Vascular Surgery
University of Texas Medical School at Houston
Houston, Texas
Brachiocephalic Artery: Surgical Treatment

Paul J. DiMuzio, MD, FACS
William M. Measey Professor of Surgery
Director, Division of Vascular and Endovascular Surgery
Program Director, Fellowship in Vascular Surgery
Thomas Jefferson University
Philadelphia, Pennsylvania
Arteriogenesis and Angiogenesis

Hasan H. Dosluoglu, MD, FACS
Associate Professor of Surgery
State University of New York at Buffalo
School of Medicine and Biomedical Sciences
Chief, Department of Surgery and Division of Vascular Surgery
Veterans Affairs Western New York Healthcare System
Buffalo, New York
Lower Extremity Arterial Disease: General Considerations

Matthew J. Dougherty, MD
Associate Clinical Professor of Surgery
Pennsylvania Hospital
University of Pennsylvania
Philadelphia, Pennsylvania
Renovascular Disease: Aneurysms and Arteriovenous Fistulae

Audra A. Duncan, MD
Professor of Surgery
Mayo Clinic College of Medicine
Program Director
Vascular Surgery Residency and Fellowship
Division of Vascular and Endovascular Surgery
Rochester, Minnesota
Local Complications: Lymphatic

Serkan Durdu, MD, PhD
Associate Professor of Cardiovascular Surgery
Heart Center, Ankara University School of Medicine
Dikimevi, Ankara, Turkey
Thromboangiitis Obliterans (Buerger's Disease)

Matthew J. Eagleton, MD
Associate Professor
Vascular Surgery
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Staff
Vascular Surgery
Cleveland Clinic
Cleveland, Ohio
Preoperative Management

Jonothan J. Earnshaw, MBBS, DM, FRCS
Consultant Vascular Surgeon
Gloucestershire Royal Hospital
Gloucester, United Kingdom
Acute Ischemia: Evaluation and Decision Making

Robert T. Eberhardt, MD
Associate Professor of Medicine
Boston University School of Medicine
Director of Vascular Medicine
Department of Cardiovascular Medicine
Boston Medical Center
Boston, Massachusetts
Chronic Venous Disorders: General Considerations

Matthew S. Edwards, MD, MS, RVT, FACS
Associate Professor and Chairman
Department of Vascular and Endovascular Surgery
Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina
Renovascular Disease: Endovascular Treatment

John F. Eidt, MD
Professor of Surgery
University of South Carolina School of Medicine–Greenville
Greenville Health System
Greenville, South Carolina
Lower Extremity Amputation: Techniques and Results

Jonathan L. Eliason, MD
Lindenauer Professor of Surgery
University of Michigan
Ann Arbor, Michigan
Renovascular and Aortic Developmental Disorders

Eric D. Endean, MD
Professor of Surgery
University of Kentucky
Lexington, Kentucky
Embryology

Mark K. Eskandari, MD
James S.T. Yao, MD, PhD, Professor of Education in Vascular Surgery
Chief, Division of Vascular Surgery
Northwestern University Feinberg School of Medicine
Chicago, Illinois
Occupational Vascular Problems

Ronald M. Fairman, MD
Clyde F. Barker-William Maul Measey Professor in Surgery
University of Pennsylvania School of Medicine
Chief
Division of Vascular Surgery and Endovascular Therapy
University of Pennsylvania Health System
Philadelphia, Pennsylvania
Abdominal Aortic Aneurysms: Endovascular Treatment

Alik Farber, MD
Associate Professor of Surgery and Radiology
Boston University School of Medicine
Chief, Division of Vascular and Endovascular Surgery
Medical Director
Catheterization and Angiography Laboratories
Co-Director of the Noninvasive Vascular Laboratory
Boston Medical Center
Boston, Massachusetts
Biologic Grafts

Peter L. Faries, MD
Franz W. Sichel Professor of Surgery
Mount Sinai School of Medicine
Chief, Division of Vascular Surgery
Mount Sinai Medical Center
New York, New York
Infrainguinal Disease: Endovascular Treatment

Mark Fillinger, MD
Professor of Vascular Surgery
Dartmouth Medical School
Program Director of Vascular Surgery
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Technique: Managing Branches During Endovascular Aortic Aneurysm Repair

Steven J. Fishman, MD
Stuart and Jane Weitzman Family Chair in Surgery
Boston Children's Hospital
Professor of Surgery
Harvard Medical School
Boston, Massachusetts
Surgical Management of Vascular Malformations

Thomas L. Forbes, MD, FRCSC, FACS
Professor of Surgery
Western University
Chief, Division of Vascular Surgery
London Health Sciences Centre
London, Ontario, Canada
Nonatheromatous Popliteal Artery Disease

Charles J. Fox, MD
Assistant Professor of Surgery
Uniformed Services University of the Health Sciences
Bethesda, Maryland
Program Director of Vascular Surgery
Attending Vascular Surgeon
Walter Reed Army Medical Center
Washington, District of Columbia
Vascular Trauma: Military

Julie A. Freischlag, MD
The William Stewart Halsted Professor
Chair, Department of Surgery
Surgeon-in-Chief, The Johns Hopkins Hospital
Baltimore, Maryland
Thoracic Outlet Syndrome: General Considerations

Gail L. Gamble, MD
Cancer Rehabilitation Program
Rehabilitation Institute of Chicago
Department of PM&R
Northwestern University Feinberg School of Medicine
Chicago, Illinois
Lymphedema: Nonoperative Treatment

Randolph L. Geary, MD
Professor of Vascular and Endovascular Surgery
Wake Forest University School of Medicine
Winston-Salem, North Carolina
Renovascular Disease: General Considerations

David L. Gillespie, MD
Professor of Surgery
Chief and Program Director, Division of Vascular Surgery
University of Rochester School of Medicine and Dentistry
Rochester, New York
Venography

Natalia O. Glebova, MD, PhD
Fellow
Division of Vascular Surgery and Endovascular Therapy
The Johns Hopkins Hospital
Baltimore, Maryland
Takayasu's Disease

Peter Gloviczki, MD
Joe M. and Ruth Roberts Professor of Surgery
Mayo Clinic College of Medicine
Chairman Emeritus
Division of Vascular and Endovascular Surgery
Mayo Clinic
Rochester, Minnesota
Superior Vena Cava Obstruction: Surgical Treatment

Philip P. Goodney, MD, MS
Assistant Professor
Section of Vascular Surgery
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Patient Clinical Evaluation

Kapil Gopal, MD
Assistant Professor of Surgery
University of Maryland Medical Center
Baltimore, Maryland
Intraoperative Management

Heather L. Gornik, MD, MHS
Assistant Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Staff Physician and Medical Director
Noninvasive Vascular Laboratory
Cleveland Clinic
Cleveland, Ohio
Atherosclerotic Risk Factors: Smoking

Anders Gottsäter, MD, PhD
Associate Professor of Medicine
Lund University/Skåne University Hospital
Malmö, Sweden
Renovascular Disease: Fibrodysplasia

Roy K. Greenberg, MD[†]
Director, Endovascular Research
Department of Vascular Surgery
Cleveland Clinic
Associate Professor
Department of Surgery
Cleveland Clinic Learner College of Medicine
Associate Professor
Biomedical Engineering
Case School of Engineering
Case Western Reserve University
Cleveland, Ohio
Thoracic and Thoracoabdominal Aneurysms: Branched and Fenestrated Endograft Treatment

[†]Deceased

Arin K. Greene, MD, MMSc
Associate Professor of Surgery
Harvard Medical School
Children's Hospital Boston
Boston, Massachusetts
Vascular Tumors of Childhood

Carlos J. Guevara, MD
Instructor, Radiology
Washington University School of Medicine
St. Louis, Missouri
Endovascular Therapy of Vascular Malformations

Raul J. Guzman, MD
Associate Professor of Surgery
Vanderbilt University Medical Center
Nashville, Tennessee
Local Complications: Anastomotic Aneurysms

Allen Hamdan, MD
Vice-Chairman
Department of Surgery
Associate Professor of Surgery
Harvard Medical School
Department of Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Upper Extremity Arterial Disease: General Considerations

Kimberley J. Hansen, MD
Professor of Surgery
Department of Vascular and Endovascular Surgery
Wake Forest University School of Medicine
Winston-Salem, North Carolina
Renovascular Disease: Open Surgical Treatment

Linda M. Harris, MD
Associate Professor of Surgery
Chief, Division of Vascular Surgery
Program Director
Vascular Surgery Residency and Fellowship
University at Buffalo, SUNY
Buffalo, New York
Hemodialysis Access: Nonthrombotic Complications

Olivier Hartung, MD
Vascular Surgeon
Department of Vascular Surgery
Université de la Méditerranée
University Hospital North
Marseille, France
Iliocaval Venous Obstruction: Surgical Treatment

Stephen M. Hass, MD, JD
Assistant Professor of Surgery
Division of Vascular and Endovascular Surgery
West Virginia University
Charleston, West Virginia
Vascular Laboratory: Arterial Duplex Scanning

Peter K. Henke, MD
Leland Ira Doan Professor of Surgery
University of Michigan
Ann Arbor, Michigan
Venous Pathology

Ariane L. Herrick, MD, FRCP
Professor
Centre for Musculoskeletal Research
University of Manchester
Manchester Academic Health Science Centre
Salford Royal NHS Foundation Trust
Salford, United Kingdom
Raynaud's Phenomenon

Peter J. E. Holt, PhD, FRCS
Senior Lecturer and Consultant Vascular Surgeon
St. George's Vascular Institute
London, United Kingdom
Abdominal Aortic Aneurysms: Evaluation and Decision Making

Thomas S. Huber, MD, PhD
Professor and Chief
Division of Vascular and Endovascular Surgery
University of Florida College of Medicine
Gainesville, Florida
Hemodialysis Access: General Considerations

Justin B. Hurie, MD
Assistant Professor of Surgery
Department of Vascular and Endovascular Surgery
Wake Forest University School of Medicine
Winston-Salem, North Carolina
Renovascular Disease: Open Surgical Treatment

Mark D. Iafrati, MD
Chief, Division of Vascular Surgery
Tufts Medical Center
Boston, Massachusetts
Varicose Veins: Surgical Treatment

Kenji Inaba, MD, FRCSC, FACS
Program Director
Surgical Critical Care Fellowship
Medical Director-SICU
Associate Professor
Surgery and Emergency Medicine
University of Southern California
Keck School of Medicine
Los Angeles, California
Vascular Trauma: Abdominal

Arsalla Islam, MD
Assistant Professor of Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Renovascular Disease: General Considerations

Ora Israel, MD
Director, Department of Nuclear Medicine
Rambam Health Care Campus
Professor of Imaging
Rappaport School of Medicine, Technion
Haifa, Israel
Vascular PET CT and SPECT CT

Glenn Jacobowitz, MD
Vice-Chief, Division of Vascular Surgery
Associate Professor of Surgery, Division of Vascular Surgery
New York University Langone Medical Center
New York, New York
Lower Extremity Aneurysms

Iqbal H. Jaffer, BA (Hons), MBBS
Division of Cardiac Surgery
McMaster University
Hamilton, Ontario, Canada
Antithrombotic Therapy

Zhihua Jiang, PhD
Assistant Professor
Department of Surgery
University of Florida College of Medicine
Gainesville, Florida
Intimal Hyperplasia

William Jordan, MD
Professor of Surgery and Section Chief
Division of Vascular Surgery and Endovascular Therapy
University of Alabama School of Medicine at Birmingham
Attending Surgeon
University of Alabama Hospital
Birmingham, Alabama
Nonaortic Stents and Stent-Grafts

Lowell S. Kabnick, MD, RPhS, FACS, FACPh
Associate Professor of Surgery
Division of Vascular Surgery
Director, New York University Vein Center
New York University Langone Medical Center
New York, New York
Attending Surgeon
Morristown Hospital Center
Morristown, New Jersey
Varicose Veins: Endovenous Ablation and Sclerotherapy

John Kakisis, MD, FEBVS
Department of Vascular Surgery
Attikon University Hospital
Athens, Greece
Atherosclerotic Risk Factors: General Considerations

Venkat R. Kalapatapu, MD, FRCS (Edin), FACS
Assistant Professor of Vascular Surgery
University of Pennsylvania
Chief, Division of Vascular Surgery
Philadelphia Veterans Affairs Medical Center
Philadelphia, Pennsylvania
Lower Extremity Amputation: Techniques and Results

Jeffrey Kalish, MD
Assistant Professor of Surgery and Radiology
Boston University School of Medicine
Director of Endovascular Surgery
Boston Medical Center
Boston, Massachusetts
Biologic Grafts

Manju Kalra, MBBS
Associate Professor of Surgery
Vascular Surgery
Mayo Clinic
Rochester, Minnesota
Superior Vena Cava Obstruction: Surgical Treatment

Jeanwan Kang, MD
Vascular Surgeon
Department of Vascular Surgery
Sydell and Arnold Miller Family Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio
Preoperative Management

Vikram S. Kashyap, MD
Associate Professor
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Staff, Department of Vascular Surgery
Cleveland Clinic
Cleveland, Ohio
Splanchnic Artery Aneurysms

Paulo Kauffman, MD
Professor of Vascular Surgery
Department of Vascular Surgery
University of Sao Paulo School of Medicine
Sao Paulo, Brazil
Upper Extremity Sympathectomy

David S. Kauvar, MD
Vascular Surgeon
Department of Surgery
Dwight D. Eisenhower Army Medical Center
Fort Gordon, Georgia
Associate Professor of Surgery
Uniformed Services
University of the Health Sciences
Bethesda, Maryland
Vascular Trauma: Extremity

Lois A. Killewich, MD, PhD
Leonard and Marie Louise Aronsfeld Rosoff Professor of Surgery
Assistant Dean for Continuing Education
University of Texas Medical Branch
Galveston, Texas
Venous Physiology

Esther S. H. Kim, MD, MPH
Staff Physician
Sections of Vascular Medicine and Preventive Cardiology
Cleveland Clinic
Cleveland, Ohio
Atherosclerotic Risk Factors: Smoking

Melissa L. Kirkwood, MD
Division of Vascular and Endovascular Surgery
Department of Surgery
University of Texas Southwestern Medical Center
Dallas, Texa
Thoracic Outlet Syndrome: Arterial

Jordan P. Knepper, MD
Integrated Vascular Surgery Resident
Section of Vascular Surgery
University of Michigan
Ann Arbor, Michigan
Acute Deep Venous Thrombosis: Pathophysiology and Natural History

Ted R. Kohler, MD
Professor of Surgery
University of Washington
Chief, Division of Peripheral Vascular Surgery
Veterans Affairs Puget Sound Healthcare System
Seattle, Washington
Vascular Laboratory: Arterial Physiologic Assessment

Leo J. Schultze Kool, MD
Professor of Interventional Radiology
Radbound University Medical Centre
Nijmegen, The Netherlands
Computed Tomography

Larry W. Kraiss, MD
Professor and Chief
Division of Vascular Surgery
University of Utah
Salt Lake City, Utah
Vascular Trauma: Extremity

Hari R. Kumar, MD
Fellow
Department of Vascular Surgery
Northwestern University
McGaw Medical Center
Chicago, Illinois
Occupational Vascular Problems

Christopher J. Kwolek, MD
Chief, Vascular and Endovascular Surgery
Director
Vascular and Endovascular Training Program
Newton Wellesley Hospital
Boston, Massachusetts
Acute Ischemia: Treatment

Nicos Labropoulos, PhD, DIC, RVT
Professor of Surgery and Radiology
Director, Vascular Laboratory
Department of Surgery
Stony Brook University Medical Center
Stony Brook, New York
Vascular Laboratory: Venous Duplex Scanning

Ryan O. Lakin, MD
General Surgery
Lakewood, Ohio
Splanchnic Artery Aneurysms

Brajesh K. Lal, MD, FACS
Professor
Department of Surgery
University of Maryland School of Medicine
Associate Professor
Department of Bioengineering
University of Maryland
Chief, Division of Vascular Surgery
Veterans Affairs Medical Center
Baltimore, Maryland
Vascular Laboratory: Venous Physiologic Assessment

Kathleen M. Lamb, MD
Surgical Resident, Research Resident
Department of Surgery
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania
Arteriogenesis and Angiogenesis

Glenn M. LaMuraglia, MD
Visiting Surgeon
Division of Vascular and Endovascular Surgery
Massachusetts General Hospital
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts
Carotid Artery: Carotid Body Tumors and Other Disorders

Giora Landesberg, MD, DSc
Professor
Department of Anesthesia and Critical Care Medicine
Head of Cardiovascular Anesthesia Center
Hadassah Medical Centre
Hebrew University
Jerusalem, Israel
Systemic Complications: Cardiac

Jeffrey H. Lawson, MD, PhD
Associate Professor of Surgery
Assistant Professor of Pathology
Duke University School of Medicine
Director of Vascular Surgery Research Laboratory and Clinical Trials for Vascular Surgery
Duke University Medical Center
Durham, North Carolina
Coagulopathy and Hemorrhage

Jason T. Lee, MD
Associate Professor of Surgery
Division of Vascular Surgery
Stanford University Medical Center
Stanford, California
Thoracic Outlet Syndrome: Neurogenic

Luis R. León, Jr., MD
Agave Surgical Associates
Tucson, Arizona
Vascular Laboratory: Venous Duplex Scanning

Wesley K. Lew, MD
Vascular Surgeon
Kaiser Sunset
Los Angeles, California
Thrombolytic Agents

Christos Liapis, MD, FACS
Professor of Vascular Surgery
University of Athens Medical School
Chairman of Department of Vascular Surgery
Attikon Hospital
Athens, Greece
Atherosclerotic Risk Factors: General Considerations

Howard A. Liebman, MD
Professor of Medicine and Pathology
Jane Anne Nohl Division of Hematology
Keck School of Medicine
University of Southern California
Los Angeles, California
Hypercoagulable States

Michael P. Lilly, MD
Professor of Surgery
Division of Vascular Surgery
University of Maryland School of Medicine
Baltimore, Maryland
Intraoperative Management

Peter H. Lin, MD
Professor of Surgery
Chief, Division of Vascular Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Texas
Superior Vena Cava Occlusion: Endovascular Treatment

Bengt Lindblad, MD, PhD
Associate Professor of Vascular Surgery
Lund University/Skåne University Hospital
Malmö, Sweden
Renovascular Disease: Fibrodysplasia

Pamela A. Lipsett, MD, MHPE
Warfield M. Firror Endowed Professorship in Surgery
Professor
Surgery, Anesthesiology, Critical Care, and Nursing
Program Director
General Surgery Residency Program
Johns Hopkins University
Schools of Medicine and Nursing
Co-Director, Surgical Intensive Care Units
Johns Hopkins Medical Institutions
Baltimore, Maryland
Systemic Complications: Respiratory

Harold Litt, MD, PhD
Associate Professor of Radiology and Medicine
Chief, Cardiovascular Imaging Section
Department of Radiology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania
Magnetic Resonance Imaging

Ruby C. Lo, MD
Research Fellow in Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Mesenteric Vascular Disease: General Considerations

William B. Long, MD
Trauma Medical Director
Department of Surgery
Legacy Emanuel Medical Center
Professor of Surgery
Oregon Health Sciences University
Portland, Oregon
Vascular Trauma: Epidemiology and Natural History

Ying Wei Lum, MD
Assistant Professor
Division of Vascular Surgery and Endovascular Therapy
The Johns Hopkins Hospital
Baltimore, Maryland
Section Director for Anatomy
Perdana University Graduate School of Medicine
Serdang, Selangor, Malaysia
Thoracic Outlet Syndrome: General Considerations

Fedor Lurie, MD, PhD, RPVI, RVT
Associate Director
Jobst Vascular Institute
ProMedica
Toledo, Ohio
Acute Deep Venous Thrombosis: Clinical and Diagnostic Evaluation
Chronic Venous Insufficiency: Treatment of Perforator Vein Incompetence

Sean P. Lyden, MD
Associate Professor
Department of Vascular Surgery
Cleveland Clinic Foundation
Cleveland, Ohio
Technique: Endovascular Diagnostic

Michel S. Makaroun, MD
Co-Director, UPMC Heart and Vascular Institute
Professor and Chair, Division of Vascular Surgery
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania
Thoracic and Thoracoabdominal Aneurysms: Endovascular Treatment

Thomas S. Maldonado, MD
Associate Professor
Service Chief at NYUHC
New York University Langone Medical Center
New York, New York
Cerebrovascular Disease: General Considerations

Bruce E. Maley, PhD
Associate Professor
Department of Anatomy and Neurobiology
University of Kentucky Medical Center
Lexington, Kentucky
Embryology

Kenneth G. Mann, PhD
Emeritus Professor, Biochemistry and Medicine
University of Vermont College of Medicine
Colchester, Vermont
Normal Coagulation

George Markose, MD
Assistant Professor, Radiology
Juravinski Hospital and Cancer Centre
McMaster University
Hamilton, Ontario, Canada
Cerebrovascular Disease: Diagnostic Evaluation

William A. Marston, MD
Professor and Chief, Division of Vascular Surgery
University of North Carolina School of Medicine
Chapel Hill, North Carolina
Wound Care

Matthew J. Martin, MD
Trauma Medical Director
Madigan Army Medical Center
Tacoma, Washington
Director of Trauma Informatics
Department of Surgery
Legacy Emanuel Medical Center
Portland, Oregon
Vascular Trauma: Epidemiology and Natural History

Michelle C. Martin, MD
Fellow in Vascular and Endovascular Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Mesenteric Vascular Disease: Acute Ischemia

Tara M. Mastracci, MD
Department of Vascular Surgery
Sydell and Arnold Miller Family Heart and Vascular Institute
Assistant Professor of Surgery
Cleveland Clinic
Lerner College of Medicine
Case Western Reserve University
Cleveland, Ohio
Thoracic and Thoracoabdominal Aneurysms: Branched and Fenestrated Endograft Treatment

Jon S. Matsumura, MD
Professor of Surgery and Chairman
Division of Vascular Surgery
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
Aortic Stents and Stent-Grafts

Kathleen O'Malley Maxfield, MD
Neurology
University of New Mexico Hospital
Albuquerque, New Mexico
Local Complications: Anastomotic Aneurysms

James F. McKinsey, MD, FACS
Associate Professor of Surgery
Weill Medical College at Cornell University
Ithaca, New York
Site Chief, New York-Presbyterian Medical Center
New York, New York
Local Complications: Endovascular

Robert B. McLafferty, MD
Professor of Surgery
Division of Vascular Surgery
Southern Illinois University School of Medicine
Springfield, Illinois
Arteriography

Manish Mehta, MD, MPH
Professor of Surgery
Albany Medical Center
Albany, New York
Abdominal Aortic Aneurysms: Ruptured

George H. Meier, MD
Professor, Chief, and Program Director, Vascular Division
University of Cincinnati
Cincinnati, Ohio
Hemodialysis Access: Failing and Thrombosed

Matthew T. Menard, MD
Instructor in Surgery
Harvard Medical School
Associate Surgeon
Brigham and Women's Hospital
Boston, Massachusetts
Aortoiliac Disease: Direct Reconstruction

Louis M. Messina, MD
Professor and Chief
Division of Vascular and Endovascular Surgery
Vice Chair
Department of Surgery
University of Massachusetts
Worcester, Massachusetts
Thoracic Outlet Syndrome: Venous

Joseph L. Mills, Sr., MD
Professor and Chief
Division of Vascular and Endovascular Surgery
Co-Director, Southern Arizona Limb Salvage Alliance
Department of Surgery
University of Arizona Health Sciences Center
Tucson, Arizona
Infrainguinal Disease: Surgical Treatment

Ross Milner, MD
Associate Professor of Surgery
Director, Center for Aortic Diseases
Pritzker School of Medicine
University of Chicago
Chicago, Illinois
Local Complications: Aortoenteric Fistula

Samantha Minc, MD
Fellow
Division of Vascular Surgery
University of Chicago Medical Center
Chicago, Illinois
Local Complications: Aortoenteric Fistula

J. Gregory Modrall, MD
Professor of Surgery
Division of Vascular and Endovascular Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Compartment Syndrome

Emile R. Mohler III, MD
Professor of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania
Atherosclerotic Risk Factors: Hypertension

Mark D. Morasch, MD, FACS
Vascular Surgeon
St. Vincent Healthcare Heart and Vascular
Billings, Montana
Vertebral Artery Disease

Lindsay Muir, MB, MChOrth, FRCS(Orth)
Consultant Hand Surgeon
Salford Royal Hospital
Salford, United Kingdom
Raynaud's Phenomenon

John P. Mulhall, MD, MSc, FECSM, FACS
Director
Sexual and Reproductive Medicine Program
Urology Service
Memorial Sloan-Kettering Cancer Center
New York, New York
Erectile Dysfunction

John B. Mulliken, MD
Co-director, Vascular Anomalies Center
Department of Plastic and Oral Surgery
Professor of Surgery
Harvard Medical School
Boston, Massachusetts
Classification and Natural History of Vascular Anomalies

Daniel J. Myers, MD
General Surgery
Iola, Kansas
Systemic Complications: Renal

Stuart I. Myers, MD, FACS
Lincoln, Nebraska
Systemic Complications: Renal

A. Ross Naylor, MBChB, MD, FRCSEd, FRCSEng
Professor of Vascular Surgery
Leicester Royal Infirmary
Leicester, United Kingdom
Cerebrovascular Disease: Diagnostic Evaluation

Matthew G. Nayor, MD
Clinical Fellow in Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts
Atherosclerotic Risk Factors: Diabetes

Peter Neglén, MD, PhD
Vascular Surgeon
SP Vascular Center
Trimiklini, Cyprus
Iliocaval Obstruction: Endovascular Treatment

Richard F. Neville, MD, FACS
Chief, Division of Vascular Surgery
Professor of Surgery
The George Washington University
Washington, DC
Technique: Open Surgical

Louis L. Nguyen, MD, MBA, MPH
Associate Professor of Surgery
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts
Epidemiology and Clinical Analysis

Aksone Nouvong, DPM, FACFAS
Assistant Professor
College of Podatric Medicine
Western University of Health Sciences
Oakland, California
Diabetic Foot Ulcers

Thomas F. O'Donnell, Jr., MD
Director
Dedham Medical Associate's Venous Center
Atrius Health
Norwood, Massachusetts
Varicose Veins: Surgical Treatment

Gustavo S. Oderich, MD
Associate Professor of Surgery
Division of Vascular and Endovascular Surgery
Mayo Clinic College of Medicine
Director of Endovascular Therapy
Division of Vascular and Endovascular Surgery
Mayo Clinic
Rochester, Minnesota
Mesenteric Vascular Disease: Chronic Ischemia

W. Andrew Oldenburg, MD
Associate Professor of Surgery
Division of Vascular Surgery
Mayo Clinic Florida
Jacksonville, Florida
Arterial Tumors

Jeffrey W. Olin, DO
Professor of Medicine (Cardiology)
Director
Vascular Medicine and Vascular Diagnostic Laboratory
Zena and Michael A. Wiener Cardiovascular Institute
Marie-Josée and Henry R. Kravis Center for Cardiovascular Health
Ichan School of Medicine at Mount Sinai
New York, New York
Atheromatous Embolization

Carl Orringer, MD
Associate Professor, Medicine
Case Western Reserve University
School of Medicine
Cleveland, Ohio
Atherosclerotic Risk Factors: Hyperlipidemia

Geoffrey O. Ouma, DO, MSc, RPVI
Cardiovascular Medicine Nocturnist
Division of Cardiovascular Medicine
Penn Presbyterian Medical Center
Philadelphia, Pennsylvania
Atherosclerotic Risk Factors: Hypertension

Christopher D. Owens, MD, MSc
Associate Professor of Surgery
Division of Vascular and Endovascular Surgery
University of California San Francisco
San Francisco, California
Atherosclerosis

C. Keith Ozaki, MD
Associate Professor of Surgery
Department of Surgery
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts
Intimal Hyperplasia

David Paolini, MD
Vascular Physician
Jobst Vascular Institute
ProMedica
Toledo, Ohio
Acute Deep Venous Thrombosis: Clinical and Diagnostic Evaluation

Giuseppe Papia, MD
Assistant Professor of Surgery
University of Toronto School of Medicine
Physician Lead in Cardiovascular Intensive Care Unit
Vascular and Endovascular Surgery
Critical Care Medicine
Sunnybrook Health Sciences Centre
Toronto, Ontario, Canada
Postoperative Management

Luigi Pascarella, MD
Clinical Assistant Professor of Surgery—Vascular Surgery
University of Iowa
Carver College of Medicine
Iowa City, Iowa
Chronic Venous Disorders: Nonoperative Treatment

Marc A. Passman, MD
Professor
Section of Vascular Surgery and Endovascular Therapy
University of Alabama at Birmingham
Birmingham, Alabama
Vena Cava Interruption and Pulmonary Embolism

Virendra I. Patel, MD
Associate Program Director
General Surgery
Vascular and Endovascular Surgery
Massachusetts General Hospital
Boston, Massachusetts
Carotid Artery: Carotid Body Tumors and Other Disorders

Philip Paty, MD
Chief of Vascular Surgery
St. Peters Hospital
Albany Vascular Group
Albany, New York
Upper Extremity Arterial Disease: Revascularization

Benjamin Pearce, MD
Assistant Professor of Surgery
Division of Vascular Surgery and Endovascular Therapy
University of Alabama School of Medicine at Birmingham
Attending Surgeon
University of Alabama Hospital
Birmingham, Alabama
Nonaortic Stents and Stent-Grafts

Bruce A. Perler, MD, MBA
Julius H. Jacobson II Professor
Department of Surgery
The Johns Hopkins University School of Medicine
Chief, Division of Vascular Surgery and Endovascular Therapy
The Johns Hopkins Hospital
Baltimore, Maryland
Carotid Artery: Endarterectomy

Iraklis I. Pipinos, MD, PhD
Professor of Surgery
University of Nebraska Medical Center
Chief, Division of Vascular Surgery
Veterans Affairs Nebraska and Western Iowa Medical Center
Omaha, Nebraska
Ischemia-Reperfusion

Lori L. Pounds, MD
Assistant Professor, Clinical
University of Texas Health Science Center
San Antonio, Texas
Venous Physiology

Richard J. Powell, MD
Professor of Surgery and Radiology
Geisel School of Medicine at Dartmouth
Section Chief Vascular Surgery
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Aortoiliac Disease: Endovascular Treatment

Alessandra Puggioni, MD
Vascular Surgery
Scottsdale Vascular Services
Scottsdale, Arizona
Chronic Venous Insufficiency: Treatment of Perforator Vein Incompetence

Zheng Qu, MD
Harvard Medical School
Department of Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Prosthetic Grafts

Joseph D. Raffetto, MD, MS
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts
Chief, Division of Vascular Surgery
Veterans Affairs Boston Healthcare System
West Roxbury, Massachusetts
Brigham and Women's Hospital
Boston, Massachusetts
Chronic Venous Disorders: General Considerations

Seshadri Raju, MD
Emeritus Professor and Honorary Surgeon
University of Mississippi Medical Center
Jackson, Mississippi
River Oaks Hospital
Flowood, Mississippi
Iliocaval Obstruction: Endovascular Treatment

Todd E. Rasmussen, MD
Professor of Surgery
Uniformed Services University
Bethesda, Maryland
Deputy Director
US Combat Casualty Care Research Program
Fort Detrick, Maryland
Vascular Trauma: Military

Suman Rathbun, MD, MS, RVT
Professor of Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma
Superficial Thrombophlebitis

Reid A. Ravin
Resident in Vascular Surgery
Mount Sinai School of Medicine
New York, New York
Infrainguinal Disease: Endovascular Treatment

Donald B. Reid, MD
Wishaw General Hospital
Wishaw, Scotland
Intravascular Ultrasound

Kristy L. Rialon, MD
Surgeon
Duke University
Durham, North Carolina
Surgical Management of Vascular Malformations

John J. Ricotta, MD
Harold H. Hawfield Chairman
Department of Surgery
Washington Hospital Center
Professor of Surgery
Georgetown University School of Medicine
Washington, District of Columbia
Carotid Artery Disease: Decision Making Including Medical Therapy

Joseph J. Ricotta, MD, MS, FACS
Chair
Department of Vascular Surgery and Endovascular Therapy
Director, Heart and Vascular Institute
Northside Hospital
Atlanta, Georgia
Carotid Artery Disease: Decision Making Including Medical Therapy

Addi Z. Rizvi, MD, FACS
Vascular and Endovascular Surgery
Minneapolis Heart Institute at Abbott Northwestern Hospital
Clinical Assistant Professor of Surgery
University of Minnesota
Minneapolis, Minnesota
Technique: Endovascular Therapeutic

Caron B. Rockman, MD, FACS, RVT
Associate Professor of Surgery
Director of Clinical Research
Division of Vascular Surgery
New York University Medical Center
New York, New York
Cerebrovascular Disease: General Considerations

Stanley G. Rockson, MD
Allan and Tina Neill Professor of Lymphatic Research and Medicine
Division of Cardiovascular Medicine
Stanford University School of Medicine
Stanford, California
Lymphedema: Evaluation and Decision Making

Sean P. Roddy, MD
Associate Professor of Surgery
Albany Medical College
Albany, New York
Upper Extremity Arterial Disease: Revascularization

Carolyn R. Rogers, MD
Instructor in Surgery
Department of Plastic and Oral Surgery
Harvard Medical School
Boston, Massachusetts
Classification and Natural History of Vascular Anomalies

Vincent L. Rowe, MD
Associate Professor of Surgery
Keck School of Medicine at University of Southern California
Los Angeles, California
Hemodialysis Access: Dialysis Catheters

Eva M. Rzucidlo, MD
Associate Professor of Surgery
Department of Vascular Surgery
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Aortoiliac Disease: Endovascular Treatment

Mikel Sadek, MD
Assistant Professor of Surgery
Division of Vascular Surgery
New York University Langone Medical Center
New York, New York
Varicose Veins: Endovenous Ablation and Sclerotherapy

Hazim J. Safi, MD, FACS, FRCS
Professor and Chairman
Department of Cardiothoracic and Vascular Surgery
The University of Texas Health Science Center at Houston
Houston, Texas
Brachiocephalic Artery: Surgical Treatment

Elliot B. Sambol, MD
Department of Surgery
New York Presbyterian Hospital
Weill Medical College of Cornell University
Columbia University College of Physicians and Surgeons
New York, New York
Local Complications: Endovascular

Andres Schanzer, MD
Associate Professor of Surgery
Division of Vascular and Endovascular Surgery
University of Massachusetts Medical School
Worcester, Massachusetts
Lower Extremity Arterial Disease: Decision Making and Medical Treatment

Marc L. Schermerhorn, MD
Chief, Division of Vascular and Endovascular Surgery
Beth Israel Deaconess Medical Center
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts
Mesenteric Vascular Disease: General Considerations

Joseph R. Schneider, MD, PhD
Professor of Surgery
Feinberg School of Medicine
Northwestern University
Chicago, Illinois
Vascular Surgeon, Vascular and Interventional Program
Cadence Physician Group and Cadence Health
Winfield, Illinois
Aortoiliac: Extra-Anatomic Bypass

Peter A. Schneider, MD
Chief, Division of Vascular Therapy
Kaiser Foundation Hospital
Honolulu, Hawaii
Carotid Artery: Dissection and Fibromuscular Dysplasia

Sharene Shalhub, MD, MPH
Assistant Professor of Vascular Surgery
University of Washington
Spokane, Washington
Vascular Trauma: Thoracic

Cynthia Shortell, MD
Professor and Chief of Vascular Surgery
Department of Surgery
Duke University Medical Center
Durham, North Carolina
Chronic Venous Disorders: Nonoperative Treatment

Fahad Shuja, MD
Division of Vascular and Endovascular Surgery
Massachusetts General Hospital
Boston, Massachusetts
Acute Ischemia: Treatment

Anton N. Sidawy, MD, MPH
Professor and Chairman
Department of Surgery
George Washington University
Washington, District of Columbia
Technique: Open Surgical

Jessica P. Simons, MD, MPH
Assistant Professor of Surgery
Division of Vascular and Endovascular Surgery
University of Massachusetts Medical School
Worcester, Massachusetts
Lower Extremity Arterial Disease: Decision Making and Medical Treatment

Michael J. Singh, MD, FACS, RPVI
Associate Professor of Surgery
Division of Vascular Surgery
University of Pittsburgh Medical Center
Director of Aortic Center
University of Pittsburgh Medical Center
Heart and Vascular Institute
Pittsburgh, Pennsylvania
Thoracic and Thoracoabdominal Aneurysms: Endovascular Treatment

Niten N. Singh, MD
Associate Professor of Surgery
Division of Vascular Surgery
University of Washington
Seattle, Washington
Upper Extremity Arterial Disease: Amputation

Leigh Ann Slater, MD
Interim Visiting Assistant Professor of Surgery
University of Maryland
Baltimore, Maryland
Systemic Complications: Respiratory

Ann DeBord Smith, MD
General Surgery Resident
Brigham and Women's Hospital
Boston, Massachusetts
Epidemiology and Clinical Analysis

James C. Stanley, MD
Handleman Professor of Surgery
Director, Cardiovascular Center
University of Michigan
Ann Arbor, Michigan
Renovascular and Aortic Developmental Disorders

Benjamin W. Starnes, MD
Chief, Division of Vascular Surgery
Department of Surgery
University of Washington
Seattle, Washington
Vascular Trauma: Head and Neck

W. Charles Sternbergh III, MD
Professor of Surgery
University of Queensland School of Medicine
Chief
Division of Vascular and Endovascular Surgery
Vice Chair for Research
Department of Surgery
Ochsner Clinic Foundation
New Orleans, Louisiana
Technique: Endovascular Aneurysm Repair

David H. Stone, MD
Assistant Professor of Surgery
Section of Vascular Surgery
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Local Complications: Graft Thrombosis

Patrick A. Stone, MD
Associate Professor of Surgery
Division of Vascular and Endovascular Surgery
West Virginia University
Charleston, West Virginia
Vascular Laboratory: Arterial Duplex Scanning

Timothy M. Sullivan, MD
Clinical Professor of Surgery
University of Minnesota
Chairman, Vascular and Endovascular Surgery
Minneapolis Heart Institute
Abbott Northwestern Hospital
Minneapolis, Minnesota
Technique: Endovascular Therapeutic

David S. Sumner, MD[†]
Distinguished Professor of Surgery, Emeritus
Southern Illinois University
School of Medicine
Springfield, Illinois
Arterial Physiology
Vascular Laboratory: Arterial Physiologic Assessment

Bauer Sumpio, MD, PhD
Professor of Surgery and Radiology
Yale University School of Medicine
Chief, Division of Vascular Surgery
Yale-New Haven Hospital
Director, Vascular Center
Program Director, Vascular Surgery
Yale-New Haven Medical Center
New Haven, Connecticut
Vessel Wall Biology

[†]Deceased

Girma Tefera, MD
Professor of Surgery
University of Wisconsin School of Medicine and Public Health
Vice Chair Division of Vascular Surgery
Chief of Vascular
William S. Middleton VA Hospital
Madison, Wisconsin
Aortic Stents and Stent-Grafts

Matt M. Thompson, MD
Professor
University of London
Professor of Vascular Surgery
St. George's Vascular Institute
London, United Kingdom
Abdominal Aortic Aneurysms: Evaluation and Decision Making

Carlos H. Timaran, MD
Associate Professor of Surgery
The University of Texas Southwestern Medical School
G. Patrick Clagett Professor in Vascular Surgery
Chief, Division of Endovascular Surgery
Dallas, Texas
Upper Extremity Aneurysms

Jessica M. Titus, MD
Fellow
Department of Vascular Surgery
Cleveland Clinic Foundation
Cleveland, Ohio
Brachiocephalic Artery: Endovascular Treatment Diseases

Cameron C. Trenor III, MD
Dana Farber/Boston Children's Cancer and Blood Disorders
Boston Children's Hospital
Boston, Massachusetts
Vascular Tumors of Childhood

Eric J. Turney, MD
Staff Surgeon
Department of Vascular Surgery
Mike O'Callaghan Federal Medical Center
Las Vegas, Nevada
Technique: Endovascular Diagnostic

Gilbert R. Upchurch, Jr., MD
Muller Professor of Surgery and Physiology
Chief, Division of Vascular and Endovascular Surgery
University of Virginia
Charlottesville, Virginia
Thoracic and Thoracoabdominal Aneurysms: Evaluation and Decision Making

R. James Valentine, MD
Professor and Chairman
Division of Vascular Surgery
Alvin Baldwin, Jr., Chair in Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Thoracic Outlet Syndrome: Arterial

Omaida Velazquez, MD
Chief, Division of Vascular and Endovascular Surgery
Executive Dean for Research and Research Training
Director, Vascular Laboratory
University of Miami Miller School of Medicine
Professor of Surgery
Vice Chairman for Research
Department of Surgery
University of Miami Jackson Memorial Medical Center
Miami, Florida
Cells of the Vascular System

Gabriela Velazquez-Ramirez, MD
Vascular Surgery Fellow
Division of Vascular Surgery and Endovascular Therapy
University of Florida College of Medicine
Gainesville, Florida
Infected Aneurysms

Thomas W. Wakefield, MD
Stanley Professor of Surgery
Head, Section of Vascular Surgery
University of Michigan
Ann Arbor, Michigan
Acute Deep Venous Thrombosis: Pathophysiology and Natural History

Daniel B. Walsh, MD
Professor of Surgery
Dartmouth Medical School
Hanover, New Hampshire
Local Complications: Graft Thrombosis

Bo Wang, MD
Post-Doctoral Research Fellow
Division of Vascular Surgery and Endovascular Surgery
University of Miami Miller School of Medicine
Miami, Florida
Cells of the Vascular System

Grace J. Wang, MD
Assistant Professor of Surgery
Division of Vascular Surgery and Endovascular Therapy
University of Pennsylvania
Philadelphia, Pennsylvania
Abdominal Aortic Aneurysms: Endovascular Treatment

Kenneth J. Warrington, MD
Associate Professor of Medicine
Gonda Vascular Center
Mayo Clinic
Rochester, Minnesota
Vasculitis and Other Uncommon Arteriopathies

Fred A. Weaver, MD
Professor of Surgery
Chief, Division of Vascular Surgery and Endovascular Therapy
Keck School of Medicine at University of Southern California
Los Angeles, California
Thrombolytic Agents

Ilene Ceil Weitz, MD
Associate Professor of Clinical Medicine
Jane Anne Nohl Division of Hematology
Keck School of Medicine at University of Southern California
Los Angeles, California
Hypercoagulable States

Jeffrey I. Weitz, MD, FRCP(C), FACP
Professor of Medicine and Biochemistry
McMaster University
Executive Director
Thrombosis and Atherosclerosis Research Institute
Hamilton General Hospital Campus
Hamilton, Ontario, Canada
Antithrombotic Therapy

Marlys H. Witte, MD
Professor of Surgery
University of Arizona College of Medicine
Attending Physician in Surgery
University Medical Center
Tucson, Arizona
Lymphatic Pathophysiology

Nelson Wolosker, MD, PhD
Associate Professor
Department of Vascular and Endovascular Surgery
University of Sao Paulo
Vice-President
Albert Einstein Hospital
Sao Paulo, Brazil
Upper Extremity Sympathectomy

Edward Y. Woo, MD
Associate Professor of Surgery
University of Pennsylvania
Vice-Chief and Program Director
Division of Vascular Surgery and Endovascular Therapy
Director, Vascular Laboratory
University of Pennsylvania Health System
Philadelphia, Pennsylvania
Abdominal Aortic Aneurysms: Open Surgical Treatment

Karen Woo, MD
Assistant Professor of Surgery
Division of Vascular Surgery and Endovascular Therapy
Keck School of Medicine
University of Southern California
Los Angeles, California
Hemodialysis Access: Dialysis Catheters

Mark C. Wyers, MD
Assistant Professor of Surgery
Harvard Medical School
Division of Vascular and Endovascular Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Mesenteric Vascular Disease: Acute Ischemia

Mimi Wynn, MD
Associate Professor
Department of Anesthesia
University of Wisconsin
Madison, Wisconsin
Thoracic and Thoracoabdominal Aneurysms: Open Surgical Treatment

Wei Zhou, MD
Professor of Surgery
Stanford University
Stanford, California
Chief, Division of Vascular Surgery
Veterans Affairs Palo Alto Health Care System
Palo Alto, California
Acquired Arteriovenous Fistulae

R. Eugene Zierler, MD
Medical Director, D.E. Strandness, Jr. Vascular Laboratory
University of Washington Medical Center
Harborview Medical Center
Professor of Surgery
University of Washington
Seattle, Washington
Arterial Physiology

PREFACE

As we complete our work as editors of the eighth edition of *Rutherford's Vascular Surgery,* we are grateful on many levels.

We appreciate the insight and hard work of the founding editor, Robert B. Rutherford, MD, who toiled through six editions of this textbook. Bob was a giant in many ways, but none more clearly than his enduring contribution of an encyclopedic reference that has elevated the quality of vascular health care since 1976. He was truly a "teacher's teacher."

We have been honored to serve as editors of the seventh and eighth editions and appreciate the opportunity afforded to us by the Society of Vascular Surgery, which has assumed responsibility for continued publication of this textbook. This will be our last edition as editors, in part to establish a tradition that will provide opportunity for many skilled members of our specialty to participate as editors.

We appreciate the great work done by our section editors Ali AbuRhama, Jan Blankensteijn, Richard Cambria, W. Darrin Clouse, Anthony Comerota, Alan Dardik, John Eidt, Ronald Fairman, Alik Farber, Steven Fishman, Tom Forbes, Julie Freischlag, Randy Geary, Peter Gloviczki, Heather Gornik, Thomas Huber, Lois Killewich, Joseph Mills, Greg Modrall, Marc Schermerhorn, Benjamin Starnes, Charles Sternbergh, Carlos Timaran, Gilbert Upchurch, Fred Weaver, and Eugene Zierler. In the eighth edition, we purposely expanded the number of section editors in order to distribute this large amount of work among more people. Each section editor participated in author selection and developed the content outline for his or her section. The most work, of course, was done by the individual authors, who were carefully selected for their expertise and scientific accomplishments. We recognize that they worked many hours without compensation to produce this educational material for the benefit of their colleagues and patients. We are especially grateful to each of them for this effort.

Finally, we are grateful for having been part of the evolution and revolutions in vascular surgery over our careers. Comparing the first and eighth editions of "Rutherford," which span nearly 40 years, one is immediately struck by the tremendous changes that have occurred and continue to occur in vascular surgery. The predominant treatment of vascular disease has become interventional, rather than open surgery, and vascular surgeons have embraced and developed these techniques. The current vascular specialist has an increasingly diverse armamentarium of investigational techniques and management options, thus augmenting the complexity of decision making, as reflected in this textbook.

We are especially excited that the eighth edition of *Rutherford's Vascular Surgery* is available in an advanced electronic format both online and for e-readers. Accessible by computer, tablet, or smart phone, this format provides text, images, videos, web-linked references, self-study questions, and bloglike interaction with authors and other readers. Most importantly the electronic format allows continuous modification of the text over time, thus creating a "living" textbook. For example, articles published in the *Journal of Vascular Surgery* and the *European Journal of Vascular and Endovascular Surgery* will be added as new references to relevant chapters each month. As editors, we have found it very gratifying to participate in the development of these valuable features, which are now part of the most modern publishing standards. We hope that readers enjoy this textbook as much as we have enjoyed assembling it.

In closing, we acknowledge the excellent work of the production team at Elsevier, who have worked especially hard to produce this edition in record time and to incorporate its many new features—Judy Fletcher, Vice President of Global Content; Joanie Milnes, Content Development Specialist; Stacy Matusik, Content Development Specialist; and Cindy Thoms, Project Manager.

Jack L. Cronenwett, MD
K. Wayne Johnston, MD, FRCS(C)

VIDEO CONTENTS

CHAPTER 1

Epidemiology and Clinical Analysis

LOUIS L. NGUYEN / ANN DEBORD SMITH

The goal of this chapter is to introduce the vascular surgeon to the principles that underlie the design, conduct, and interpretation of clinical research. Disease-specific outcomes otherwise detailed in subsequent chapters will not be covered here. Rather, this chapter discusses the historical context, current methodology, and future developments in epidemiology, clinical research, and outcomes analysis. This chapter serves as a foundation for clinicians to better interpret clinical results and as a guide for researchers to further expand clinical analysis.

EPIDEMIOLOGY

Epidemiology is derived from the Greek terms for "upon" (epi), "the people" (demos), and "study" (logos), and can be translated into "the study of what is upon the people." It exists to answer the four major questions of medicine: diagnosis, etiology, treatment, and prognosis.

Brief History

Hippocrates is considered to be among the earliest recorded epidemiologists because he treated disease as both a group event and an individual occurrence. His greatest contribution to epidemiology was the linkage of external factors (climate, diet, and living conditions) with explanations for disease. Before widespread adoption of the scientific method, early physicians inferred disease causality through careful observation. For example, they observed the geographic distribution of cases or common factors shared by diseased versus healthy persons. John Snow is recognized for ameliorating the cholera epidemic in the Soho district of London in 1854 by identifying the cause of the outbreak through mapping the location of known cases of cholera in the district. Based on the density and geographic distribution of cases, he concluded that the public water pump was the source and had the pump handle removed.[1]

Modern Developments

Modern epidemiology and clinical analysis seek to establish causation through study design and statistical analysis. Carefully designed studies and analyses can minimize the risk of false conclusions and maximize the opportunity to find causation when it is present. In other areas of biology, causation can be demonstrated by fulfilling criteria, such as Koch's postulates for establishing the relationship between microbe and disease. In epidemiology, the study design that would offer ideal proof of causation would be comparison of people with themselves in both the exposed and the unexposed state. This impossible and unethical experiment would control for everything, except the exposure, and thus, establish the causality between exposure and disease. Because this condition cannot exist, it is referred to as counterfactual. Because the ideal study is impossible to conduct, alternative study designs have developed with different risks and benefits. The crossover experimental design, for example, approaches the counterfactual ideal by exposing patients to both treatment groups in sequence. However, the influence of time and previous exposure to the other treatment assignment may still affect the outcome (also known as the carryover effect). Other study designs exist that include techniques such as randomization or prospective data gathering to minimize bias. Appropriate study design must be selected based upon a study's objectives. After a study is complete, conclusions can be drawn from a carefully crafted statistical analysis. Modern epidemiology includes applied mathematical methods to quantify observations and draw inferences about their relationships.

Evidence-based medicine is a relatively modern approach to the practice of medicine that aims to qualify and encourage the use of currently available clinical evidence to support a particular treatment paradigm. This practice encourages the integration of an individual practitioner's clinical expertise with the best currently available recommendations from clinical research studies.[2] Relying on personal experience alone could lead to biased decisions, whereas relying solely on results from clinical research studies could lead to inflexible policies. Evidence-based medicine stratifies the strength of the evidence from clinical research studies based on study design and statistical findings (Table 1-1). The criteria differ when the evidence is sufficient to support a specific therapeutic approach, prognosis, diagnosis, or other health services research. Criteria also differ among research institutions,

Table 1-1 Levels of Evidence for Therapeutics

Level	Evidence
1a	Systematic reviews of RCT studies with homogeneity
1b	Individual RCT with narrow confidence intervals
1c	"All or none" trials*
2a	Systematic reviews of cohort studies with homogeneity
2b	Individual cohort studies
2c	Clinical outcomes studies
3a	Systemic reviews of case-control studies with homogeneity
3b	Individual case-control studies
4	Case-series studies
5	Expert opinion without critical appraisal or based on bench research

Adapted from Oxford Centre for Evidence-based Medicine (2001).
RCT, Randomized controlled trial.
*In which *all* patients died before the therapeutic became available, but some now survive with it, or in which some patients survived before the therapeutic became available, but now *none* die with it.

including the U.S. Preventive Services Task Force and the U.K. National Health Service. However, common themes can be seen among the different fields. Systematic reviews with homogeneity are preferred over single reports, whereas randomized controlled trials (RCTs) are preferred over cohort and case-control studies. Even within similar study design groupings, the statistical strength of each study is evaluated, with preference for studies with large numbers, complete and thorough follow-up, and results with small confidence intervals. Clinical recommendations are then based on the available evidence and are further graded according to their strengths (Table 1-2).

Clinical Research Methods

Although measuring the incidence and prevalence of disease is useful in the initial understanding of a disease process, additional techniques must be used to identify risk factors and test treatments for disease. The choice of study design and statistical analysis technique depends on the available data, the hypothesis being tested, and patient safety and/or ethical concerns.

Table 1-2 Grades of Recommendation

Grade	Recommendation	Basis
A	Strong evidence to support practice	Consistent level 1 studies
B	Fair evidence to support practice	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Evidence too close to make a general recommendation	Level 4 studies or extrapolation from level 2 or 3 studies
D	Evidence insufficient or conflicting to make a general recommendation	Level 5 evidence or inconsistent studies of any level

Adapted from U.S. Preventive Services Task Force Ratings (2003) and Oxford Centre for Evidence-based Medicine (2001).

Study Design

Clinical research can be broadly divided into observational studies and experimental studies. Observational studies are characterized by the absence of a study-directed intervention, whereas experimental studies involve testing a treatment, be it a drug, a device, or a clinical pathway. Observational studies can follow ongoing treatments but cannot influence choices made in the treatment of a patient. Observational studies can be executed in a prospective or retrospective fashion, whereas experimental studies can be performed only prospectively.

Two factors that affect choice of study design include prevalence and incidence of disease. The prevalence of disease is the ratio of persons affected for the population at risk and reflects the frequency of the disease at the measured time point, regardless of the time of disease development. In contrast, the incidence is the ratio of persons in whom the disease develops within a specified period for the population at risk. For diseases with short duration or high mortality, prevalence may not accurately reflect the impact of disease because the single time point of measurement does not capture resolved disease or patients who died of the disease. Prevalence is a more useful parameter when discussing diseases of longer duration, whereas incidence is more useful for diseases of shorter duration.

Observational Studies

There are two main types of observational studies: cohort and case-control studies. A cohort is a designated group of individuals that is followed over a period of time. *Cohort studies* seek to identify a population at risk for the disease of interest. After a period of observation, patients in whom the disease develops are compared with the population of patients who are free of the disease. Cohort studies are most often associated with epidemiology because they comprise many of the most prominent studies in the modern era. The classic example is the Framingham Heart Study (FHS), in which 5209 residents of Framingham, Massachusetts, were monitored prospectively, starting in 1948.[3] Much of our epidemiologic knowledge regarding risk factors for heart disease comes from the FHS.[4] Although the FHS was initially intended to last 20 years, the study has subsequently been extended and now involves the third generation of participants. Cohort studies also seek to identify potential risk factors for development of the disease of interest. For example, if cigarette smoking is suspected in the development of peripheral arterial disease (PAD), smokers are assessed for the development of PAD from the beginning of the observation period to the end of the observation period. Because PAD does not develop in all smokers, and conversely, not all PAD patients are smokers, a relative risk (RR) is calculated as the ratio of the incidence of PAD in smokers versus the incidence of PAD in nonsmokers.

For diseases with low frequency, it is not cost effective to use a cohort study design. Instead, a case series seeks to prospectively follow or to retrospectively report findings of patients known to have the disease. This method is also commonly used to identify patients with a yet unknown disease by linking common risk factors or disease manifestations. Most often, findings from a case series are compared with findings in patients without the disease (control group) in a case-control study. Case-control studies are less costly and time consuming because the existence of the disease is the starting point. Risk factors correlated with disease can be deduced by comparisons between the two groups. In this retrospective design, an odds ratio (OR) is calculated from the ratio of patients exposed to patients not exposed to the risk factor. This differs from RR, in that the starting cohort is estimated only in case-control studies. The use of ORs reflects Bayesian inference, in which observations are used to infer the likelihood of a hypothesis. Bayesians describe probabilities conditional on observations and with degrees of uncertainty. In contrast, the alternative *probability theory* of Frequentists relies only on actual observations gained from experimentation.

The main challenge in case-control studies is to identify an appropriate control group with characteristics similar to those of the general population at risk for the disease. Inappropriate selection of the control group may lead to the introduction of additional confounding and bias. For example, matched case-control studies aim to identify a control group "matched" for factors found in the exposure group. Unfortunately, by matching even basic demographic factors, such as gender and the prevalence of comorbid conditions, unknown co-associated factors can also be included in the control group and may affect the relationship of the primary factor to the outcome. Appropriate selection of the control group can be achieved by using broad criteria, such as time, treatment at the same institution, age boundaries, and gender when the exposure group consists of only one gender.

Experimental Studies

Experimental studies differ from observational studies in that the former expose patients to a treatment being tested. Many experimental trials involve randomization of patients to the treatment group or appropriate control group. Although randomization ensures that known factors are evenly distributed between the exposure and control groups, the importance of RCTs lies in the even distribution of unknown factors. Thus, a well-designed RCT will result in more simplified endpoint analyses because complex statistical models are not necessary to control for confounding factors.

Randomization can be accomplished by complete randomization of the entire study population, by block randomization, or by adaptive randomization. For complete randomization, each new patient is randomized without prior influence on previously enrolled patients. The expected outcome at the completion of the trial is an equal distribution of patients within each treatment group, although unequal distribution may occur by chance, especially in small trials. Block randomization creates repeated blocks of patients in which equal distribution between treatment groups is enforced within each block. Block randomization ensures better end randomization and periodic randomization during the trial. End randomization is important in studies with long enrollment times or in multi-institutional studies that may have different local populations. Because the assignment of early patients within each block influences the assignment of later patients, block randomization should occur in a blinded fashion to avoid bias. Intrablock correlation must also be tested in the final analysis of the data. Adaptive randomization seeks to achieve balance of assignment of randomization for a prespecified factor (e.g., gender or previous treatment) suspected of affecting the treatment outcome. In theory, randomization controls for these factors, but unique situations may require stricter balance.

RCTs can be classified according to knowledge of the randomization assignment by the treating clinicians and their patients. In open trials, the clinician and patients know the full details of the treatment assignment. This leaves the potential for bias in interpretation of results and may also influence study patients to drop out if they are randomized to a treatment group that they perceive to be unfavorable. Open trials are often conducted for surgical patients, where it is not possible or ethical to conceal the treatment assignment from the patient or the provider. In single-blinded trials, the clinician is aware of the treatment assignment, but the patient is not. These studies have more effective controls, but are still subject to clinician bias. Double-blinded trials are conducted so that both clinicians and patients are unaware of the treatment assignment. Often, a separate research group is responsible for the randomization allocation and has minimal or no contact with the clinicians and patients.

Experimental studies face stricter ethical and patient safety requirements than their observational counterparts. To expose patients to randomization of treatment, clinical equipoise must exist. The principle of equipoise relies on a situation in which clinical experts professionally disagree on the preferred treatment method.[5] Thus, randomization of study patients to different treatments is justified to gain clinical information. Ideally, the patients being tested or their population counterparts would benefit from any medical knowledge gained from the study. It is worth noting that although the field may have equipoise, individual health care providers or patients may have bias for one treatment. In such a case, enrollment in an RCT may be difficult because the patients or their providers are not willing to be subject to randomization.

Although RCTs represent the pinnacle in clinical design, there are many situations in which RCTs are impractical or impossible. Clinical equipoise may not exist, or common sense may prevent randomization of well-established practices, such as the use of parachutes.[6] RCTs are also costly to conduct and must generate a new control group with each trial. For this reason, some studies are single-arm trials that use historical controls similar to the case-control design. In

addition, patient enrollment for RCTs is more difficult than for other trial designs because some patients and clinicians are uneasy with the randomization of treatment. They may have preconceived notions of treatment efficacy or may have an inherent aversion to being randomized, even when they know that equipoise exists. This risk aversion may be greatest for more life-threatening conditions, although patients in whom conventional treatment has been unsuccessful may be accepting of greater risk to obtain access to novel treatments otherwise not available outside the clinical trial. RCTs can also have methodological and interpretative limitations. For example, study patients are analyzed by their assigned randomization grouping (intent to treat). Studies with asymmetric or numerous overall dropout and/or crossover rates will not reflect actual treatment effects. RCTs are often conducted in high-volume specialty centers; as a result, enrollment and treatment of study patients may not reflect the general population with the disease. Finally, RCTs are often designed and powered to test one hypothesis. A statistically nonsignificant result may be influenced by inaccurate assumptions made in the initial power calculations.

Special Techniques: Meta-Analysis

Meta-analysis is a statistical technique that combines the results of several related studies to address a common hypothesis. The first use of meta-analysis in medicine is attributed to Smith and Glass in their review of the efficacy of psychotherapy in 1977.[7] By combining results from several smaller studies, researchers may decrease sampling error, increase statistical power, and thereby help clarify disparate results among different studies.

The related studies must share a common dependent variable along with the effect size specific to each study. The effect sizes are not merely averaged among the studies, but are weighted to account for the variance in each study. Because studies may differ in patient selection and their associated independent variables, a test for heterogeneity should also be performed. Where no heterogeneity exists ($P > .5$), a fixed-effects meta-analysis model is used to incorporate the within-study variance for the studies included, whereas a random-effects model is used when concern for between-study variance exists ($.5 > P > .05$). When heterogeneity among studies is found, the OR should not be pooled, and further investigation for the source of heterogeneity may then exclude outlying studies.

The weighted composite dependent variable is visually displayed in a forest plot along with the results from each study included. Each result is displayed as a point estimate with a horizontal bar representing the 95% confidence interval for the effect. The symbol used to mark the point estimate is usually sized proportional to other studies to reflect the relative weight of the estimate as it contributes to the composite result (Fig. 1-1). Classically, meta-analyses have included only RCTs, but observational studies can also be used.[8,9] Inclusion of observational studies can result in greater heterogeneity through uncontrolled studies or controlled studies with selection bias.

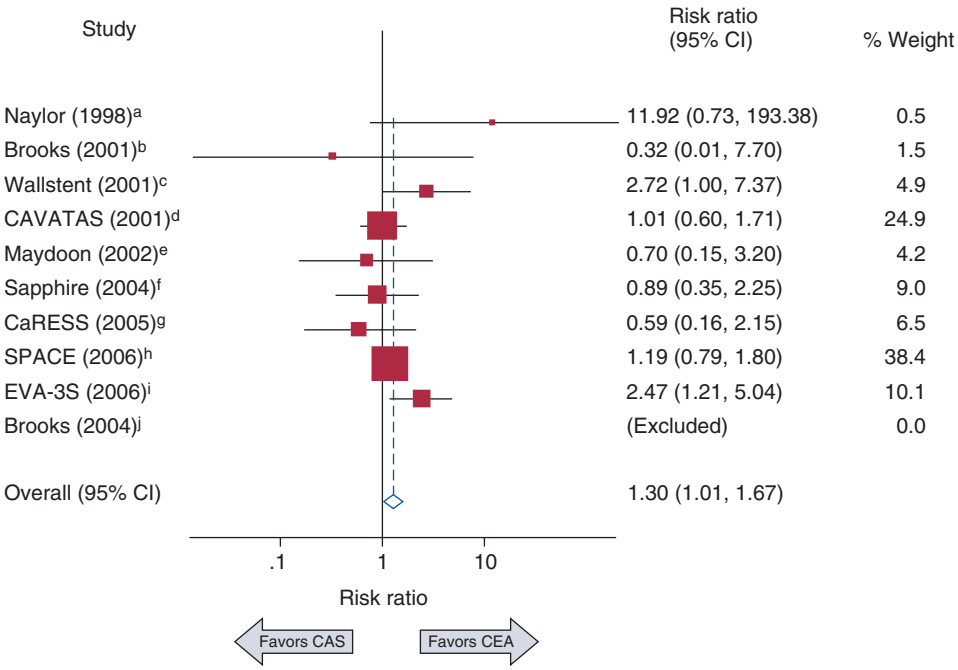
The strength of a meta-analysis comes from the strength of the studies that make up the composite variable. Furthermore, if available, the results of unpublished studies can also potentially influence the composite variable, because presumably many studies with nonsignificant results are not published. Therefore, an assessment of publication bias should be included with every meta-analysis. Publication bias can be assessed graphically by creating a funnel plot in which the effect size is compared with the sample size or other measure of variance. If no bias is present, the effect sizes should be balanced around the population mean effect size and decrease in variance with increasing sample size. If publication bias exists, part of the funnel plot will be sparse or empty of studies. Begg's test for publication bias is a statistical test that represents the funnel plot's graphic test.[10] The variance of the effect estimate is divided by its standard error to give adjusted effect estimates with similar variance. Correlation is then tested between the adjusted effect size and the meta-analysis weight. An alternative method is Egger's test, in which the study's effect size divided by its standard error is regressed on 1/standard error.[11] The intercept of this regression should equal zero, and testing for the statistical significance of nonzero intercepts should indicate publication bias.

Bias in Study Design

Clinical analysis is an attempt to estimate the "true" effects of a disease or its potential treatments. Because the true effects cannot be known with certainty, analytic results carry potential for error. All studies can be affected by two broadly defined types of error: random error and systematic error. Random error in clinical analysis comes from natural variation and can be handled with the statistical techniques covered later in this chapter. Systematic error, also known as bias, affects the results in one unintended direction and can threaten the validity of the study. Bias can be further categorized into three main groupings: selection bias, information bias, and confounding.

Selection bias occurs when the effect being tested differs among patients who participate in the study as opposed to those who do not. Because actual study participation involves a researcher's determination of which patients are eligible for a study and then the patient's agreement to participate in the study, the decision points can be affected by bias. One common form of selection bias is self-selection, in which patients who are healthier or sicker are more likely to participate in the study because of perceived self-benefit. Selection bias can also occur at the level of the researchers when they perceive potential study patients as being too sick and preferentially recruit healthy patients.

Information bias exists when the information collected in the study is erroneous. One example is the categorization of variables into discrete bins, as in the case of cigarette smoking. If smoking is categorized as only a yes or no variable, former smokers and current smokers with varying amounts of consumption will not be accurately categorized. Recall bias is another form of information bias that can occur particularly



[a] Naylor AR, et al: Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg* 28:326-334, 1998.

[b] Brooks WH, et al: Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol* 38:1589-1595, 2001.

[c] Alberts MJ: Results of a multicenter prospective randomized trial of carotid artery stenting vs carotid endarterectomy. *Stroke* 32:325, 2001.

[d] Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 357:1729-1737, 2001.

[e] Madyoon H, et al: Unprotected carotid artery stenting compared to carotid endarterectomy in a community setting. *J Endovasc Ther* 9:803-809, 2002.

[f] Yadav JS, et al: Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 351:1493-1501, 2004.

[g] Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. *J Vasc Surg* 42:213-219, 2005.

[h] SPACE Collaborative Group, et al: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 368:1239-1247, 2006.

[i] Mas JL, et al: Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 355:1660-1671, 2006.

[j] Brooks WH, et al: Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis a randomized trial in a community hospital. *Neurosurgery* 54:318-324, discussion 324-325, 2004.

Figure 1-1 Example of a forest plot from a meta-analysis of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) to determine 30-day risk for stroke and death. *CI,* Confidence interval. (Redrawn from Brahmanandam S, et al: Clinical results of carotid artery stenting compared with endarterectomy. *J Vasc Surg* 47:343-349, 2008.)

in case-control studies. For example, patients with abdominal aortic aneurysms may seemingly recall possible environmental factors that put them at risk for the disease. However, patients without aneurysms may not have a comparable imperative to stimulate memory of the same exposure.

Confounding is a significant factor in epidemiology and clinical analysis. Confounding exists when a second spurious variable (e.g., race/ethnicity) correlates with a primary independent variable (e.g., type 2 diabetes) and its associated dependent variable (e.g., critical limb ischemia). Researchers can conclude that patients in certain race/ethnicity groups are at greater risk for critical limb ischemia when diabetes is actually the stronger predictor. Confounding by indication is especially relevant in observational studies. This can occur when, without randomization, patients being treated with a drug can show worse clinical results than untreated counterparts because treated patients were presumably sicker at baseline and required the drug a priori. Confounding can be addressed by several methods: assigning confounders equally to the treatment and control groups (for case-control studies); matching confounders equally (for cohort studies); stratifying the results according to confounding groups; and multivariate analysis.

Outcomes Analysis

As physicians, we can usually see the natural progression of disease or the clinical outcome of treatment. Although these observations can be made for individual patients, general inferences about causation and broad application to all

patients cannot be made without further analysis. Clinical analysis attempts to answer these questions by either observing or testing patients and their treatments. Because clinical analysis can be performed only on a subset or sample of the relevant entire population, a level of uncertainty will always exist in clinical analysis. Statistical methods are an integral aspect of clinical analysis because they help the researcher understand and accommodate the inherent uncertainty in a sample in comparison to the ideal population. In the following sections, common clinical analytic methods are reviewed so that the reader can better interpret clinical analysis and also have foundations to initiate an analysis. Reference to biostatistical and econometric texts is recommended for detailed derivation of the methods discussed.

Statistical Methods

At the beginning of most clinical analyses, descriptive statistics are used to quantify the study sample and its relevant clinical variables. Continuous variables (such as weight or age) are expressed as means or medians; categorical variables (such as the Trans-Atlantic Society Consensus [TASC] Classification: A, B, C, or D) are expressed as numbers or percentages of the total. Study sample characteristics and their relative distribution of comorbid conditions help determine whether the sample is consistent with known population characteristics, and hence, addresses the issue of generalizability of the clinical results to the overall population.

The next step in clinical analysis is hypothesis testing, in which the factor or treatment of interest is tested against a control group. The statistical methods used in hypothesis testing depend on the research question and characteristics of the data under comparison (Box 1-1). At its core, hypothesis testing asks whether the observable differences between groups represent a true difference or an apparent difference attributable to random error. A variety of statistical tests are available to accommodate the types of data being analyzed.

One major distinguishing characteristic of data is whether it fits a normal (or Gaussian) distribution, where the distribution of continuous values is symmetric and has a mean of 0 and a variance of 1. Gaussian distributions are one example of parametric data in which the form of the distribution is known. In contrast, nonparametric data are not symmetric around a mean, and the distribution of the data is not well known. Nonparametric statistical methods are thus used because fewer assumptions about the shape of the distribution are made. In general, nonparametric methods can be used for parametric data to increase robustness, but at a cost of statistical power. However, the use of parametric methods for nonparametric data or data containing small samples can lead to misleading results.

Regression Analysis

Among the statistical tests available, a few deserve special mention because of their common application to the clinical analysis of studies of vascular patients. Regression analysis is a mathematical technique in which the relationship between a dependent (or response) variable is modeled as a function of one or more independent variables, an intercept, and an error term. General linear models take the form $Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n + e$, although the model can take quadratic and higher functions of x and still be considered in the linear family. The coefficients (β_1, β_2, etc.) are model parameters calculated to "fit" the data, as commonly done with the least-squares method. They describe the magnitude of effect that each independent variable (x) has on the dependent variable (Y). The goodness of fit for the model is tested by using the R^2 value and analysis of residuals. R^2 is the proportion of variability that is accounted for by the model and has a range of 0 to 1. Although higher R^2 values imply better fit, there is no defined threshold for goodness of fit, because R^2 can be unintentionally increased by adding more variables to the model. For binary dependent variables, a logistic (logit) regression is used, whereas for continuous dependent variables, linear regression is used (Box 1-1).

BOX 1-1

CHOOSING STATISTICAL TESTS BASED ON RESEARCH QUESTION AND DATA CHARACTERISTICS

IS THERE A DIFFERENCE BETWEEN MEANS, MEDIANS, AND PROPORTIONS?

One Group

- Parametric data: one sample *t*-test
- Nonparametric data: sign test, Wilcoxon signed rank test, transform data for *t*-test
- Proportions: exact binomial test, z approximation to exact test

Two Independent Groups

- Parametric data: *t*-test
- Nonparametric data: Wilcoxon rank-sum test
- Proportions: χ^2 or Fisher's exact test

Two Related Groups

- Parametric data: paired *t*-test
- Nonparametric data: sign test, Wilcoxon signed rank test
- Proportions: McNemar test or κ statistic

Three or More Independent Groups

- Parametric data: analysis of variance (ANOVA)
- Nonparametric data: Kruskal-Wallis test
- Proportions: χ^2 or Fisher's exact test

Three or More Related Groups

- Parametric data: repeated-measures ANOVA
- Nonparametric: ANOVA by ranks

IS THERE AN ASSOCIATION?

Two Comparable Variables

- Nominal data: relative risk
- Ordinal data: Spearman's rank correlation test
- Continuous data: linear regression

One Dependent Variable and Two or More Independent Variables

- Binary dependent variable: logistic regression
- Categorical dependent variable: analysis of covariance (ANCOVA)
- Continuous dependent variable: multiple linear regression
- Censored observations: Cox proportional hazards (CPH) model
- Clustered or hierarchic parametric data: linear mixed models
- Clustered or hierarchic semi-parametric data: generalized estimating equations (GEE)

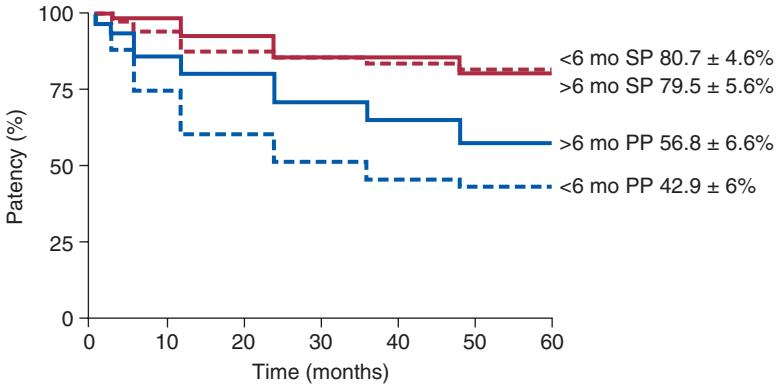


Figure 1-2 Example of life-table analysis of primary patency (PP) and secondary patency (SP) of bypass grafts after being revised before or after 6 months from the index operation. (Redrawn from Nguyen LL, et al: Infrainguinal vein bypass graft revision: factors affecting long-term outcome. *J Vasc Surg* 40:916-923, 2004.)

Survival Analysis

Survival analysis is a statistical method used to evaluate death or failure as related to time. Key variables needed for analysis include event status (e.g., graft patency or failure, patient living or dead) and the timing of that status measurement. Survival analysis also incorporates censorship, in which data about the event of interest are unknown because of withdrawal of the patient from the study. Traditionally, in clinical analysis, "death" is the event variable, and "loss to follow-up" is the censorship variable. In vascular surgery, where graft patency is more often the endpoint of interest, "graft patency" is treated as the event variable and "death or study withdrawal" is treated as the combined censoring variable. This assumes that censorship (death) is not due to the event (loss of graft patency); however, this assumption cannot be held true in other fields, such as oncology (death attributable to failure of cancer treatment) or cardiac surgery (death caused by loss of coronary artery bypass graft patency).

In essence, survival analysis accounts for event status between fixed periods of measurement. For example, in traditional methods, if graft patency is measured only after 1 year, a graft that fails at 30 days is statistically treated the same as a graft that fails on day 364. Similarly, a graft that was patent at 360 days but was lost to follow-up is treated the same as a graft that was patent but lost to follow-up at 60 days. In contrast, life-tables measure events at fixed intervals (e.g., every 30 days), so occurrences before 365 days are accounted for (Fig. 1-2).[12] Such analysis allows greater precision of events, but resolution is still limited to fixed time points. In the Kaplan-Meier (KM) method, each event is recorded at the time of occurrence, without the need for fixed time frames (Fig. 1-3).[13] Although the KM method allows more precise analysis of events and censorship, life-tables are still appropriate when only predetermined periodic measurement of events is available or when arbitrary important milestones are of interest, such as 1-year graft patency or patient survival.

The strength of survival analysis really lies in the ability to statistically account for censored data. The KM estimator (also known as the product-limit estimator) is the nonparametric maximum likelihood estimator of the survival function, which is based on the probability of an event conditional on reaching the time point of the previous event. The life-table method (or actuarial method) treats censored events as though they occurred at the midpoint of the time period. Most commonly, the Greenwood formula is used to calculate the standard error of the KM and life-table estimator for independent events.

Several tests are commonly used to test for differences between survival functions. The log-rank test adds observed and expected events within each group and sums them across all time points containing events. The log-rank statistic serves as the basis for the proportional hazard model

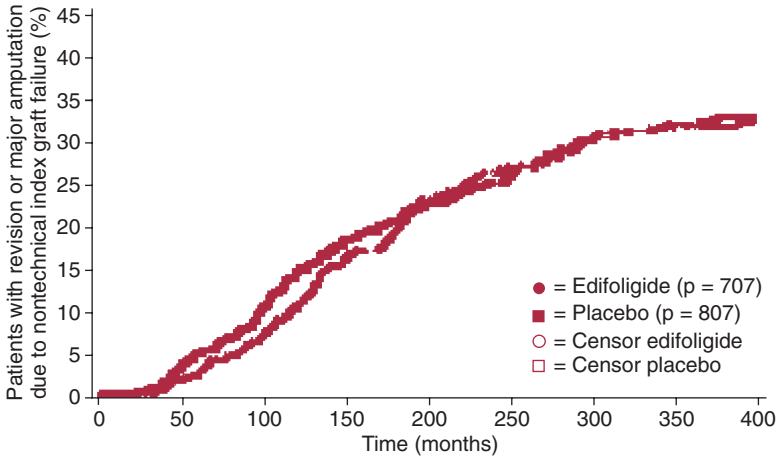


Figure 1-3 Example of Kaplan-Meier analysis of the effect of edifoligide on nontechnical graft failure. Each mark represents an event (graft failure) or censor (death or dropout). (Redrawn from Conte MS, et al: Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. *J Vasc Surg* 43:742-751, discussion 751, 2006.)

(discussed later). In contrast, the Wilcoxon test is the log-rank test weighted by the number of patients at risk for each time point. Mathematically, the Wilcoxon test gives more weight to early time points and is thus less sensitive than the log-rank test to differences between groups that occur at later time points. Unlike the parametric log-rank and Wilcoxon tests, Cox proportional hazard models assume that the underlying hazard (risk) function is proportional over time, so that parameters can be estimated without compete knowledge of the hazard function. Other hazard models, such as the exponential, Weibull, or Gompertz distributions, instead assume knowledge of the hazard function. The Cox proportional hazard assumption allows the application of survival analysis techniques to multivariable models because individual hazards do not have to be specified for each independent variable in the model.

Propensity Scoring

Propensity scoring is a statistical method that seeks to control for confounding. It is used most often to control for confounding by indication, where patients have already been assigned a treatment based on unspecified reasons. For each patient, a propensity score is generated to reflect the conditional probability of being in a treatment group based on known variables. In essence, this balances the treatment groups to allow testing of the treatment effect and is analogous to randomization. Two common methods of obtaining balanced groups are available: trimming and reweighting. In trimming, patients at the extremes of the propensity score are eliminated from the analysis so that the remaining cohorts are more comparable matches. In reweighting, all patients are kept in the analysis, but their characteristics are reweighed to provide equivalency between groups.

Limitations of propensity methods include an inability to control for unknown confounders (a feat that RCTs manage). Furthermore, the variables used to create the propensity score must be carefully chosen to reflect potential predictors of *treatment* assignment, but not *outcomes* of assignment. Despite these drawbacks, when an RCT is not possible or practical, propensity scoring methods are useful for providing some insight in comparing treatment groups. Propensity score methods have also been used for other purposes, including nesting covariates for multivariable regression models and generation of reweighted estimating equations to rebalance weights from missing data.

Errors in Hypothesis Testing

The null hypothesis is the default position of no difference between two or more groups. Because the null hypothesis can never be proven, hypothesis testing can only reject or fail to reject the null hypothesis. Two types of errors can be made in hypothesis testing. A type I error is rejection of the null hypothesis when the null hypothesis is true. Alpha (α) is the probability of making a type I error. The P value is calculated from statistical testing and represents the probability of obtaining a result as extreme or more extreme than the results observed. Commonly, α is set at .05, and a P value less than α would reject the null hypothesis. Because $\alpha = .05$ is an arbitrary setting, many will report actual P values to more precisely communicate statistical significance. Stricter α can be used when concern for a type I error is heightened, as in the testing of a large number of independent variables. For example, if 20 variables are tested, 1 variable (on average) is expected to be falsely positive with an α of .05. Accordingly, a stricter α of .01 or less may be required to reduce type I error. Conversely, a more relaxed α (typically .20) can be used in building stepwise regression models to be more inclusive of borderline variables.

A type II error is failure to reject the null hypothesis when the null hypothesis is false. Beta (β) is the probability of making a type II error. Power is defined as the probability of rejecting the null hypothesis when it is false (or concluding that the alternative hypothesis is true when it is true). In other words, power is the ability of a study to detect a true difference. Power is calculated as $1 - \beta$ and is closely related to sample size. Power analysis can be performed before or after data collection. A priori power analysis is used to determine the sample size needed to achieve adequate power for a study. Post hoc power analysis is used to determine the actual power of the study. Power analysis requires specification of several parameters, including α (usually .05), the level of power desired (usually 80%), expected effect size, and variance. Variance is simply estimated from previous measurements of related outcomes. However, the expected effect size is a parameter most susceptible to unintended influence. Setting the expected effect size too small decreases type I error, but also decreases power and results in the necessity of enrolling larger numbers of patients. Setting the expected effect size too large allows lower enrollment numbers, but at the cost of type I error. The actual calculation for necessary sample size depends on the expected statistical test for the data and can be performed by using "power calculators" available at statistics websites or with statistical software packages.

Statistical and Database Software

Before the widespread use of computers, statistics were calculated by hand through tedious procedures. Statistical software and computing power have greatly improved the ability and efficiency of statisticians and clinical researchers. Even the rapid advancements in desktop computing ability in the last decade have resulted in faster analysis of larger amounts of data via more complex modeling. At its core, statistical software requires user coding of specific commands to perform data analysis and database manipulation. SAS (originally Statistical Analysis System) was created by Anthony Barr from his work as a graduate student at North Carolina State University in the early 1960s. He and other collaborators later created the SAS Institute in 1976 to commercialize the statistical package. SAS statistical software is widely used in clinical analysis of large trials, epidemiology, the insurance industry, and other business applications of data mining. Frequently, the development of new statistical techniques is included as new SAS commands or macros. Stata was created by Statacorp and is the other widely used statistical program,

especially in the social sciences and economics. Stata can open only one data set at a time and hold it in virtual memory, which can limit its use for very large data sets.

Both SAS and Stata also have graphics user interfaces (GUIs) that automate or facilitate statistical analysis without exposing the user to the complexities of coding, although most users of these packages prefer the native coding interface. Most other statistical packages, such as SPSS (originally Statistical Package for the Social Sciences), JMP, and Minitab, are promoted with GUIs and pulldown menus as the primary interface for performing statistical tests. Another statistical package that is rapidly gaining in popularity is R, particularly because it is both free and highly functional. It is available with only a very limited GUI. However, others have created more elaborate GUIs that are available for download. We do not recommend one product over another, but do recommend that clinical researchers be familiar with at least one of these widely used packages. The choice often depends on the preferences of the local institution or research field. For those so inclined, direct statistical coding allows greater flexibility and creativity in data analysis and modeling than GUIs can provide. Even when clinicians rely on full-time statisticians to perform the analysis, detailed interpretation of raw statistical output requires some basic knowledge of the statistical software used to generate the results.

Functional Studies

Traditionally, the ankle-brachial index (ABI) has been widely used to screen for peripheral vascular disease and to quantify its severity. ABI has also been correlated with walking ability, quality of life (QoL),[14] and cardiovascular comorbidity.[15] In addition, ABI has been used as a measure of success in PAD revascularization. Despite its utility, ABI does not directly measure PAD functional performance, namely, walking performance in claudication patients. Furthermore, traditional ABI measurements are obtained from patients at rest in the supine position rather than during activity, where tissue demand, increased cardiac output, and vasodilatation may alter ABI measurements. Treadmills were first used to diagnose and evaluate cardiopulmonary function, but have since been applied to walking performance as well. Patients are asked to walk on the treadmill, and their claudication pain distance and maximal walking distance are recorded. Constant-load exercise testing consists of a fixed speed and treadmill grade, whereas in graded treadmill testing, the slope is increased at each interval (e.g., 2% grade every 2 minutes). Graded testing has the advantage of a broader range of walking challenge to patients and increases the likelihood that they will reach their claudication pain distance and maximal walking distance within testing times. Because being in a walking program itself is associated with improved walking performance, frequent treadmill testing must have appropriate controls to better distinguish the treatment effect being studied.

Many elderly or disabled patients are uncomfortable or unable to walk on a treadmill where parameters such as speed and incline are predetermined. The 6-minute walking test was initially designed to test the functional capacity of patients with chronic congestive heart failure,[16] but it has now been extended to test patients with claudication[17] and other cardiopulmonary processes. Patients are asked to walk for 6 minutes at their own pace on level ground and with periodic resting if needed. This allows patients to control their walking speed and allows them to better demonstrate their real-life walking ability. Recently, global positioning satellite (GPS) monitors have been used to assess walking distance and speed during a dedicated outdoor walk.[18] This new technology allows remote testing of patients and may be a more realistic reflection of their walking capability.

Quality of Life

Quality of life is the degree of wellness felt by an individual. QoL is generally considered a composite of two broadly defined domains: physical and psychological. Although the components of each domain can be measured, each individual patient's overall QoL cannot be predicted because the effects are not necessarily similar among individuals. However, one can assume that for populations, higher physical and psychological domains generally lead to higher QoL. Health-related QoL (HRQoL) measures focus on health-related physical and psychological attributes, although it can be hard to isolate non–health-related factors influencing overall QoL.

Because QoL cannot be measured directly, surveys (also known as instruments) are used to obtain necessary information. When compared with other clinical methods, surveys have low cost and allow efficient collection of information from a large number of participants. However, surveys are susceptible to variability in response as a result of temporary motivational states, cultural and language differences, and other impairments affecting survey completion. Several instruments have been developed for both specific disease fields and for general applicability. Instruments cannot be developed to suit specific needs without undergoing validity and reliability testing. Validity is the degree to which an instrument measures what it was intended to measure. Validity has several aspects, including the ability of the instrument to support the causal effect being tested (internal validity), generalize the effect to the larger population from which the sample was drawn (statistical validity), support the intended interpretation of the effect (construct validity), and support the generalization of results to external populations (external validity). Reliability is the consistency of the instrument if it were to be repeated on the same participant under identical conditions. Reliability can be tested by multiple administration of the test to the same participant or by single administration of the test to a divided participant population. Reliability does not imply validity because an instrument can measure an effect consistently, but that effect may not be the causal effect being studied. Reliability is analogous to precision, whereas validity is analogous to accuracy.

Health-Related, Quality-of-Life Survey Instruments

Types of Survey Instruments. The Short Form (36 questions) Health Survey (SF-36) is perhaps the best known HRQoL instrument; it has been used in more than 4000 medical publications, applied to 200 different diseases and conditions, and translated for use in 22 different countries. The SF-36 consists of 36 questions that yield an eight-scale profile of functional healing and well-being.[19] The physical component summary is composed of physical functioning, role (physical), body pain, and general health, whereas the mental component summary is composed of vitality, social functioning, role (emotional), and mental health. In 1996, SF-36v2 was released with modifications in wording, layout, response scales, scoring, and expected norms. The SF-12 (and now the SF-12v2) is a subset of SF-36 that still measures the eight health domains. Its brevity is ideal for use in conjunction with longer disease-specific instruments. The SF-8 was designed to measure the eight health domains through single questions for each domain. It was created by using information from various questionnaires, including, but not limited to, SF-36. However, the SF-8 was calibrated with the same metric as the SF-36, and thus, the summary scores can be compared. The SF-36 was developed without utility measures (detailed in the next section), but algorithms have been developed to address this shortcoming.

The EQ-5D was developed by the European Quality of Life Group (EuroQol) as a non–disease-specific instrument for describing and valuing HRQoL.[20] It is designed to be cognitively simple, quick to complete, and easily self-administered. Currently, the EQ-5D is available in 160 languages. The EQ-5D consists of a descriptive system composed of five dimensions of health: mobility, self-care, usual activities, pain and/or discomfort, and anxiety and/or depression. A health state is generated from these dimensions and then converted into a weighted health state index by applying scores from the EQ-5D value sets generated from general population samples. The EQ-5D also has a visual analog scale component that records the patient's self-rated health status on a vertical graduated (0 to 100) scale. The visual analog scale serves as the utility measure that allows conversion of the results for use in decision and cost-effectiveness analysis.

The Walking Impairment Questionnaire (WIQ) is a four-component instrument designed to assess walking performance in claudicants.[21] A score is generated for each of the four components: walking distance, walking speed, stair climbing, and other symptoms that may limit walking. The WIQ has been correlated with treadmill walking time and validated in patients with and without PAD. It uses "blocks" as a measure of distance and "flight of stairs" as a measurement of stair climbing, measures that may not be applicable to some cultures. Furthermore, the lack of utility measures in WIQ limits its use in advanced QoL analysis. Nevertheless, as a survey instrument, the WIQ functions well as a gauge of walking performance in patients undergoing treatment for claudication.

The Vascular Quality of Life Questionnaire (VascuQol) was developed at King's College Hospital, London, to assess patients with chronic lower extremity ischemia rather than just claudication.[22] The questionnaire contains 25 questions divided into 5 domains: pain, symptoms, activity, social, and emotional. Validity and test-retest reliability were evaluated and found to be very high. Continued use of this relatively new instrument will provide additional confirmation of its role in QoL analysis.

Limitations of Survey Instruments. All surveys have unique concerns that need to be addressed by researchers. One of the biggest is incomplete surveys. Because surveys are usually administered before and after a treatment or observation period, the absence of a survey for some patients during follow-up periods is troublesome. Although many researchers simply include only patients with complete surveys, this strategy may introduce bias into the results. The most severe case of omission bias is due to the fact that dead study patients cannot complete surveys. For more subtle factors, complex regression analysis of patients with missing data can identify potential factors associated with survey incompletion and serve as a cautionary measure against over-interpretation of results. A second issue in surveys is the statistical challenge of repeated measures. Because patients serve as their own survey control, simple pooled statistical techniques can mask individual effects. Mean differences, ratios, or preferably, paired tests must be used. When surveys are administered at three or more time points, simple one-to-one point comparisons do not completely account for the relationships between all time points. Linear mixed-method regression modeling can be adapted for multiple repeated measures to control for missing data.[23]

Economic Analysis

The conduct of health care occurs in the context of perceived patient benefits and incurred societal costs. For example, bypass graft or stent patency is not the only endpoint in the care of claudication. Rather, it is an important contributor of the patient's ambulatory status, which, in turn, influences overall QoL. This care has a cost to society, but it can also result in benefit to society in the form of intellectual and labor contributions made by the treated patient. Therefore, analysis of clinical outcomes should be made in the framework of its impact on the patient, the health care system, and society.

Utility Measures

In economic analysis and decision analysis, patients are considered to be in distinct "states" that reflect defined medical diagnoses or symptoms (e.g., asymptomatic vs symptomatic carotid artery stenosis). QoL instruments capture health states, but generally do not capture preferences for a given state. Utility measures capture how a person values (or prefers) a state of health, not just the characteristics of that state. Utility measures also have mathematical properties that allow their use in decision trees and cost-effectiveness

analysis. The Health Utilities Index and the EQ-5D are two widely used utility measures. The simplest method of determining utility is to ask patients to value their own health or a hypothetical state of health by using a rating scale. This information is then transformed into a utility measure by using data from a reference population. Transformations of health states from descriptive instruments (e.g., SF-36) have also been created, although low correlations between descriptive and preference measures have been demonstrated. For transformations to be meaningful, the reference population itself has to be subject to utility assessment.

Direct assessment of utility can be performed by using the standard gamble, in which for a given health state, patients are asked whether they would choose to remain in that state or take a gamble between death and perfect health. The question is then repeated with varying gamble probabilities. The utility of the health state is then derived from the probability of achieving perfect health when the patient is at equilibrium (or indifferent between the choices) between taking the gamble or remaining in the known state of intermediate health. Another common direct utility assessment method is the time tradeoff, in which the patient is asked to choose between a length of life in a given compromised state and a shorter length of life in a perfect state. The utility of the health state is then derived from the ratio of the shorter to the longer life expectancy at the point of equilibrium.

Because these utility assessment methods are artificial and do not actually expose subjects to decisions with true implications, variations in utility values exist between the methods. Generally, standard gamble methods generate the highest utility values because most patients are unwilling to accept a significant risk of sudden death, even if the alternative health state is poor. Utility values from time tradeoff methods are lower, which is consistent with the theory that decreased life expectancy is an easier price to pay for a chance to improve health. Rating scales usually generate the lowest utility values because there is no perceived penalty for underrating, as there is with the other methods.

Decision Analysis

In the daily practice of surgery, many significant decisions involve tradeoffs between risk and benefit with uncertainties. Uncertainties can exist with diagnostic testing, the actual diagnosis, the natural history of the disease, and the treatment choices and their outcomes. Despite these uncertainties, a decision must be made. Decision analysis is the formal methodology of addressing decisions by defining the problem, considering alternative choices, modeling the consequences, and estimating their chances. The process not only reveals the best choices for a particular type of patient, but also demonstrates the critical factors that may alter that decision. Thus, for the practicing clinician, knowledge of relevant decision analyses may serve as a foundation from which to make decisions and as a resource with which to modify that decision based on patient specifics.

One of the primary tools used in decision analysis is the decision tree, where the relevant factors are represented in chronological relationship to each other from left to right. The alternative choices (diagnostic tests, natural history states, treatments, etc.) are visually represented on branches of the tree, and each branch point is a decision node (usually represented as a square) in which a choice is possible, or a chance node (usually represented as a circle) in which the probability of a consequence is conditional on the events that preceded it. The end of each branch has an outcome that is based on the choices made preceding it and their probabilities. Each outcome is then given a value, whether it is life expectancy, quality-adjusted life-years (QALYs), or cost. The expected value for each alternative is then calculated on the basis of cumulative probabilities and outcome values. The best decision is then chosen to optimize the outcome value, such as the lowest cost or highest QALYs.

The results from decision analysis are strongly influenced by the event probabilities and outcome values used. Ideally, these figures are derived from strong clinical studies in the field, although a consensus on precise figures and values can be difficult. Sensitivity and threshold analysis can then be performed to test the results of decision analysis under different probability and outcome assumptions. Sensitivity analysis is performed mathematically by setting the key probability as an unknown variable to be solved algebraically. This results in a probability value threshold around which the analysis can change to favor different decisions. If the threshold value (or probability) is within accepted estimated clinical probabilities for that event, researchers can have greater confidence in the applicability of the decision analysis results.

Markov Models and Monte Carlo Simulation

The decision trees discussed in the previous section work well for clinical situations in which one or a small number of decisions are made over a defined time frame. In reality, decision points may occur repeatedly, and the relevant factors influencing the outcome may also change over time. Markov models (named after the Russian mathematician Andrey Markov) assume that patients begin in one of a discrete number of possible mutually exclusive "states." For every cycle, each patient has a probability of remaining in the state or transitioning between one state and the next. Markov models also assume the Markov property, whereby future states are independent of past states. The model can then be analyzed by using matrixes, cohort simulation, or Monte Carlo simulation. Matrix solutions require matrix algebra techniques and can be used only when transition probabilities do not vary over time, and costs are not discounted. Cohort simulation begins with a hypothetical large cohort of patients and subjects them to the Markov transition probabilities. A table is then generated with the new cohort distribution among the states. The process is repeated for the next and subsequent cycles until there is equilibrium or all patients are in a state without an exit, called the absorbing state. Monte Carlo simulation is similar to cohort simulation, except that one patient at a time is simulated, rather than the entire cohort. The simulation continues until the patient arrives at the absorbing state, or the predetermined cycle is reached in

models without absorbing states. Simulation of individual patients allows researchers to measure the variance of outcomes in addition to the mean.

Cost Benefit and Cost-Effectiveness Analysis

At the heart of cost analysis is the assumption that resources are constrained. If unlimited resources are available, all testing and treatment would be offered, as long as they are not harmful. However, in an environment of limited resources, cost analysis helps policymakers and clinicians decide on the greatest utility of the resources available. Cost analysis is certainly not the only or necessarily the best criterion for making health policy decisions, but it is an objective, quantitative tool that yields important information about the efficacy of clinical practice, and thus, may serve as a key factor in the overall choice of health care decisions.

From an economic standpoint, tests or treatments can be measured in two parameters: health improvement and cost saving. Treatments that improve health and save cost are considered superior and should be adopted. Likewise, treatments that do not change (or worsen) health and increase cost should be abandoned. Treatments that improve health but also increase cost or do not change health but decrease cost need further investigation before implementation. Cost-effectiveness analysis (CEA) compares treatments based on a common measure of cost and health effectiveness. The measure of health effectiveness can be represented by the number of lives saved, cases cured, cases prevented, and preference-based utility measures such as QALYs. Cost-benefit analysis (CBA) seeks to quantify cost and health effectiveness in monetary terms, with positive CBA treatments being favored over those with negative CBA. CBA is useful for comparing very different choices of treatments or interventions. Because many involved in health care are uncomfortable with the monetary valuation of life and life-years, CEA is more commonly used in health-related analysis, whereas CBA is more prevalent in economic-oriented health care analysis.

The CEA measure is the ratio of cost to effectiveness, typically dollars per QALY gained. Comparative choices (treatments, programs, tests) are subsequently ranked in order of lowest cost-effectiveness ratio to highest. Funding is then given to the programs with lowest cost per efficacy measure until all available funding is spent. The cost-effectiveness ratio of the last funded program in this algorithm is defined as the permissible cost-effectiveness threshold for other programs to meet until new budgetary constraints are in effect. In the United Kingdom, the National Institute for Health and Clinical Excellence has adopted a cost-effectiveness threshold range of £20,000 to £30,000 ($39,400 to $59,100 U.S. dollars) per QALY gained. In the United States, no official threshold has been adopted, although many in practice have used the threshold of $60,000 per QALY. This figure is based on the calculated average cost of hemodialysis per person per year and Medicare's special coverage of renal failure patients, regardless of age.

The term cost is often misunderstood and misused. In economic analysis, cost is not limited to currency but can be applied to other valuable resources, such as time, personnel, space, and alternative choices. Opportunity cost is the loss or sacrifice incurred when one mutually exclusive option is chosen over another. Thus, if a plot of land is chosen to be developed into a hospital, the cost of that project includes the building cost, as well as the lost opportunity to build a different facility at that site. Cost must also be distinguished from "charges" by health care researchers because administrative accounting data often contain billing charges, which are based on the cost of materials and services, but probably also include indirect costs and a margin for profit. For most health care cost analyses, cost is stated from the perspective of the society. This utilitarian perspective differs from the perspective of the patient, provider, and institution. Although these other perspectives have validity, the societal perspective is more comprehensive and eliminates distortions, such as moral hazard and cost shifting.

Outcomes Translational Research

The practice of surgery has undergone several important transformations since its early beginnings. Initially, issues of anatomy, physiology, and anesthesia were the obstacles to overcome for advancement of the field. Adoption of technology and refinement of surgical technique helped define the growth of surgery in the last century. Most recently, study of clinical outcomes plus adherence to evidence-based medicine has increased the efficacy and safety of surgery. The proliferation of surgical care (and medicine as a whole) does come with a cost, however. In the United States, expenditure on health care for 2011 was $2.7 trillion, which corresponds to $8680 per person or 17.9% of the gross national product. Other developed countries spend less, but their expenditures are increasing.

Although the actual care of patients will continue to challenge us, the way we conduct and finance health care will also have a profound impact. Thus, health care is a continuum from advancements in basic sciences, to patient applications, to clinical outcomes, to efficacy analysis, and finally, to policy. Translational research has been coined to describe the connection between the basic sciences and patient care. Similarly, outcomes translational research can be thought of as the connection between clinical outcomes and health care policy. Policy decisions based on arbitrary expenditure caps may be an effective way to control health care costs, but the resulting distribution of resources may be inefficient. Rather, policy should be based on clinical evidence and efficacy so that limited resources are used optimally.

Outcomes translational research begins with careful analysis of clinical results. Such analysis should ideally incorporate carefully designed studies to understand the natural history of disease and compare treatment options. Even the outcome measure itself needs thoughtful selection. For example, in the surgical treatment of claudication, the classic measure of outcome was bypass graft patency. With the greater adoption

of percutaneous treatment methods, vessel patency has been adopted. However, vessel patency does not accurately reflect all outcomes. From the patient's perspective, improvement in walking function (and its effect on QoL) is the benchmark. Although vessel patency clearly influences walking function, a patent vessel does not confer improved walking if other comorbid conditions, such as severe arthritis or neuropathy, are limiting. Conversely, assessment of functional and QoL endpoints alone does not allow analysis of the components leading to patient-perceived improvements. Greater understanding of technical success, vessel patency, and treatment durability will allow further improvements in the treatments themselves. Therefore, measurement of clinical outcomes is a multimodality technique involving the use of integrated components that measure several aspects of success and failure.

There is no doubt that the results of clinical trials have had an impact on the care of surgical patients. However, these trials are costly and may not have comprehensive generalizability because most trials occur in large institutions with known expertise in the area of interest. The majority of vascular surgery occurs outside clinical trials, in institutions of varying size, and by practitioners of varying expertise. The outcomes of these "real-world" efforts are not well studied. Many have used large national or statewide administrative databases in an attempt to analyze care broadly, although these databases lack detailed information because they were not designed to be research tools. For example, most administrative databases do not distinguish the left from the right extremity. Thus, two vascular procedures performed on an extremity within 1 year can be a revision of the first procedure, or they can signify sequential bilateral procedures. Other surgical and medical specialties have comprehensive registries that allow broader inclusion of patients who receive care within specific diagnostic groups. In the field of vascular surgery, other countries have national registries with research and administrative objectives. In the United States, efforts are under way to extend statewide or regional databases to encompass a wider cohort. The cost of such endeavors is certainly a factor in achieving a nationwide database, although arguably, the cost of not knowing the outcomes and efficacy of health care may be greater.

The use of economic analysis is an important component of outcomes translational research because health care, like all human effort, requires resources. Economics has often been maligned as being "cold," and this quality is its strength, not its weakness. Few of us can hope to be without bias when making health care decisions for ourselves, our patients, or our relatives. By extension, each specialty group strives to increase resources that can be applied to their disease or cause. Economic analysis of health care allows assessment of outcomes as measured by a common comparable unit (cost). However, economics as a whole can shed light only on the tradeoffs between different alternatives and their impact. It is up to policymakers to assign value to these tradeoffs, and in the end, make decisions about allocation of health care resources. In some ethical and societal frameworks, additional value may be assigned to the treatment of specific disease groups (e.g., dialysis care) that is not captured by traditional analytic methods. Nevertheless, without clinical and economic analytic tools, such decisions are made while blinded to their impact on alternative decisions. Clinician researchers in outcomes translational research are well suited to contribute to the policies that affect health care because they can generate data to help formulate policy and also see the effect of policy on the individual patients they are treating.

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CHAPTER 2

Embryology

ERIC D. ENDEAN / BRUCE E. MALEY

Based on a chapter in the seventh edition by Geoffrey D. Guttmann and Eric Endean

The fundamental purpose of the vascular system is to supply the organism with oxygen and nutrients and to remove metabolic waste products. During the first 3 weeks of gestation, simple diffusion is sufficient to support the embryo; however, by the fourth week, a functional cardiovascular system must be in place to maintain the rapidly developing embryo. The cardiovascular system in the embryo is one of the first and earliest systems to appear and begin to function. Isolated blood vessels and blood components form in the yolk sac by day 17, while just a day later isolated blood vessels begin to appear in the embryo proper. The heart begins to beat by day 22 and is pumping blood by day 24. In the past, the development of the vascular system has been viewed as no more than the growth of arteries, veins, and lymphatic vessels from a basic set of tubes. In reality, the appearance, growth, and remodeling of the vascular system are orchestrated by a series of signaling molecules, receptor molecules, and transcription factors. Failure of proper development of the vascular system can result in the appearance of variations or abnormalities that can have clinical ramifications. Knowledge of the development of the vascular system enables the vascular surgeon to recognize vascular anomalies and understand how they may have developed.

Formation of Embryonic Blood Vessels

Molecular Signaling of Vasculogenesis and Angiogenesis

The process by which the vascular system develops involves a series of steps. The first step is the modification of splanchnic mesodermal cells into angioblasts that form vesicular aggregates in the splanchnic mesoderm of the embryo and extraembryonic regions, including the yolk sac, connecting stalk, and the chorion.[1] The angioblasts develop into flattened endothelial cells that form small vessel cords, which will, in turn, coalesce with one another to form vessels. This process, vasculogenesis, is under the control of signaling molecules secreted from underlying endoderm cells in each region. Vasculogenesis begins first in the yolk sac at day 17, where Indian hedgehog, bone morphogenic protein, and transforming growth factor β (TGF-β) induce the yolk sac's mesoderm to form hemangioblastic aggregates. These cellular aggregates are composed of an inner core of hematopoietic stem cells and an outer rim of endothelial cells.[2,3] The hematopoietic stem cells serve as the source of blood cells to the embryo until day 60, when the liver, spleen, thymus, and ultimately, the bone marrow become the source of the blood. Hemangioblastic aggregates also form in the connecting stalk and chorion at day 17. These aggregates coalesce to form the extraembryonic umbilical vessels that will act as the circulatory connection between the embryo and the maternal tissue. By day 18, the embryonic endoderm layer secretes bone morphogenic protein (BMP) and TGF-β to induce the splanchnic mesoderm to form vessels in a manner similar to what occurs in the yolk stalk. One of the first regions to develop a recognizable vascular system is at the cranial end of the embryo. Here, the splanchnic mesoderm forms a pair of endocardial tubes that are continuous with one another at their most rostral end as a horseshoe-shaped region called the cardiogenic area,[1] the region that is the precursor of the heart. At the same time, additional embryonic splanchnic mesoderm also forms aggregates of hemangioblastic tissue that eventually will coalesce to form the paired dorsal aortas and will connect to the rostral end of the endocardial tubes by day 20. Extraembryonic vascular blood islands in the yolk sac and the connecting stalk eventually fuse with the developing embryonic vessels.[1]

Once the endothelial cells are established as vascular elements, they begin to sprout and bud, forming simple capillary networks. These capillary networks will be remodeled into arterial, capillary, and venous systems based on the surrounding environment. Additionally, some of the presumptive vessels will undergo vascular intussusception to remodel and generate additional vessels. Much of this growth is under the influence of vascular endothelial growth factor (VEGF), which activates a series of molecular and cellular events that ultimately lead to a stable vascular network.[4] Angiogenic sprouting from existing vessels is facilitated by hypoxia, which upregulates a number of genes, including VEGF,

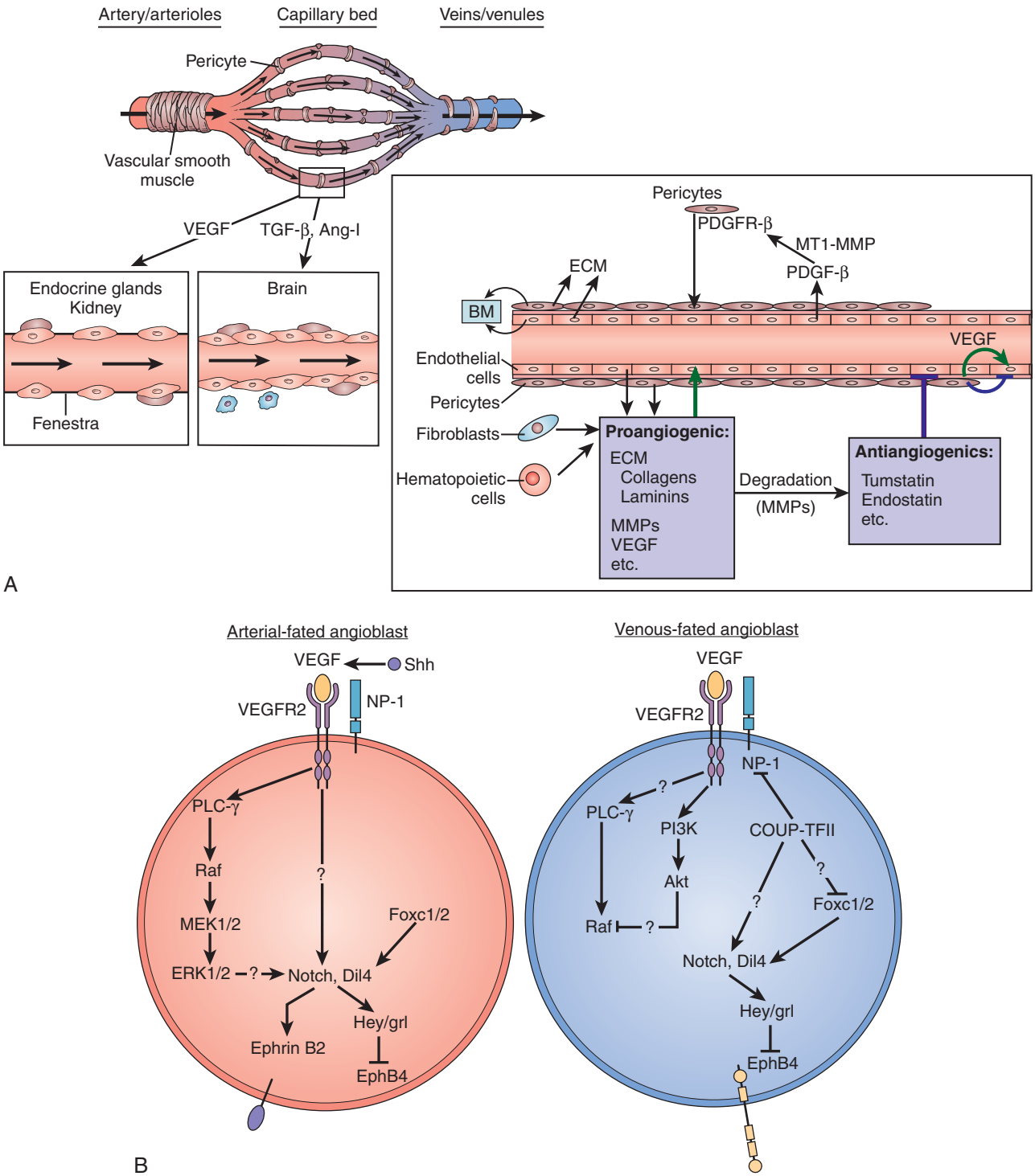

Figure 2-1 Initial development of vessels. **A,** Architectural features of the vasculature and their signaling molecules. **B,** Proposed molecular signaling pathways that determine the fate of angioblasts to become arterial or venous endothelial cells. *Ang-I*, Angiotensin I; *BM*, basement membrane; *COUP-TFII*, chicken ovalbumin upstream promotor transcription factor II; *ECM*, extracellular matrix; *ERK*, extracellular signal–regulated kinase; *MEK*, mitogen-activated protein kinase; *MMPs*, matrix metalloproteinases; *MT1-MMP*, membrane type 1 metalloproteinases; *NP-1*, neuropilin-1; *PDGFR*, platelet-derived growth factor receptor; *PI3K*, phosphatidyl-3′-kinase; *PLC*, phospholipase C; *TGF-β*, transforming growth factor-β; *VEGF*, vascular endothelial growth factor; *VEGFR*, vascular endothelial growth factor receptor.

angiopoietin-2, and nitric oxide synthase. Signaling molecules such as VEGF and angiopoietin-1 not only are proangiogenic factors, but also lead to endothelial specificity. VEGF expresses for a fenestrated endothelial layer within the capillaries of endocrine glands and the kidneys, whereas angiopoietin-1 expresses for tight junctions as seen in the capillaries of the brain (i.e., the blood-brain barrier) (Fig. 2-1A).[4,5] As vessels mature, components of the extracellular matrix and the associated basement membrane stabilize the developing vasculature by acting as a source for a number of

growth factors and proenzymes needed by the maturing vessels. The importance of the basement membrane in the maturation and maintenance of the vascular system is demonstrated by the number of vascular defects observed in animal models that have a deficiency of type IV collagen or laminins, key constituents of the basement membrane.[5]

Veins and arteries have been used to describe vessels whose blood flow direction is either to (veins) or from (arteries) the heart. Although there are morphologic differences in the walls of veins and arteries, it was not until recently that it was demonstrated that arteries and veins are also different with regard to their specific cell surface markers. Artery endothelial cells express ephrin B2 receptor, whereas vein endothelial cells express the EphB4 receptor. It is now known that angioblasts are fated to become either arterial or venous endothelial cells based on the attachment of VEGF either to the VEGF receptor 2 and neuropilin 1 (VEGFR2-NP-1) complex or simply to VEGFR2, respectively. The VEGFR2-NP-1 complex initiates a signaling cascade that leads to expression of the arterial cell surface marker ephrin B2. In angioblasts fated to be venous endothelial cells, VEGFR2 initiates a signaling cascade that leads to the inhibition of NP-1 by chicken ovalbumin upstream promotor transcription factor II (COUP-TFII) and finally to expression of the cell surface marker EphB4 (Fig. 2-1B).[4,5] Lymphatic vessels develop through the process of angiogenesis from existing veins in specific sites of the developing vascular system. Budding of the lymphatic system from veins is under the direction of the gene, Prospero-related homeobox-1 (Prox-1), which is first expressed in a specific subpopulation of endothelial cells associated with the anterior cardinal veins. These cells ultimately bud, divide, and migrate from this venous structure to form lymph sacs.[6] In embryos lacking the Prox-1 gene, the endothelial cells never acquire a lymphatic phenotype; rather, they keep a blood vascular phenotype. Other growth and transcription factors including VEGFR-3 and VEGFR-C have been shown to be critical for lymphatic endothelial sprouting and migration. The angiopoietin-2 gene is also critical for the correct patterning and integrity of lymphatic vessels; animals that lack angiopoietin-2 have lymphatics that are misshapen, leaky, and do not have the typical association of smooth muscle cells.[7]

Early Angiogenesis

As the major vascular structures including the heart, dorsal aortas, umbilical vessels, vitelline vessels, and cardinal veins are being formed by vasculogenesis, the embryo is already beginning to remodel this vascular system by the processes of angiogenesis and vascular intussusception. Other factors, especially related to the heart and dorsal aortas, have a profound effect on the definitive vascular system's configuration. By day 20, the growth of the neural tube forces the cardiogenic area ventrally and caudally to its final position in the thoracic region, whereas lateral folding of the embryo causes the two enodcardial tubes to fuse along the midline, resulting in a single endocardial tube with a more cranially placed outflow and a more caudally located inflow region. As the presumptive heart lengthens, a series of swellings in the developing heart become visible. Beginning at the inflow end, these include the sinus venosus with its right and left horns, primitive atrium, primitive left ventricle, bulbus cordis (future right ventricle), and truncus arteriosus. The aortic sac, the rostral dilation of the truncus arteriosus, connects the developing heart to the dorsal aortas. As the developing heart moves into its ventral position, the attached dorsal aortas are forced into a dorsoventral bend that forms the first aortic arch between days 22 and 24. The first aortic arch is contained in the thickened mesoderm of the developing first pharyngeal arch surrounding the pharynx. Aortic arches 2 to 6 form from mesenchyme within their own pharyngeal arches in a rostral to caudal sequence between days 26 and 30. Lateral folding of the embryo also forces the paired dorsal aortas beginning at the fourth thoracic somite to fuse with one another as a common aorta; however, rostral to this level, the dorsal aortas remain as separate vessels. By the beginning of the fourth week, intersegmental vessels between each somite arise from the dorsal aortas. Each intersegmental vessel has a dorsal branch, a lateral branch, and a ventral branch that supply the individual somite regions.

Aortic Arch

Normal Arch Development

The vascular system in humans is symmetric, with the exception of the adult aortic arch. The right common carotid and right subclavian arteries arise from the brachiocephalic (innominate) artery, whereas the left common carotid and left subclavian arteries originate as separate vessels from the aortic arch. These differences are a consequence of the changes in the connections of the aortic arches, the dorsal aortas, and the aortic sac. Diagrammatic representation of these changes would suggest that the aortic arches are all present at the same time, but in reality, the first arches are already regressing while the others are still developing.

The first two aortic arches appear and regress quickly and contribute very little to adult structures, whereas the fifth aortic arch never develops in humans (Fig. 2-2A). The third aortic arches become the common carotid arteries and proximal segments of the internal carotid arteries. The distal segments of the internal carotid arteries are derived from the dorsal aorta between the first and third arches. The external carotid arteries sprout from the common carotid arteries. The dorsal aorta on each side of the embryo between the third and fourth arches disappears, thus directing blood through the third aortic arch system to the head and neck regions (Fig. 2-2B). The fourth aortic arches are asymmetrical with regard to their fate. The left aortic arch forms that part of the adult aortic arch between the left common carotid and left subclavian arteries, whereas the right aortic arch becomes the proximal segment of the right subclavian artery. The remainder of the right subclavian artery is derived from the right dorsal aorta and its right seventh intersegmental artery. The