






The “Woundosome” Concept and Its Impact on Procedural Outcomes in Patients With Chronic Limb-Threatening Ischemia

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Lorenzo Patrone ¹, Edoardo Pasqui ², Michael S. Conte ³, Alik Farber ⁴, Roberto Ferraresi ⁵, Matthew Menard ⁶, Joseph L. Mills ⁷, John Rundback ⁸, Peter Schneider ⁹, August Ysa ¹⁰, Kumar Abhishek ¹¹, George L. Adams ¹², Naseer Ahmad ¹³, Irfan Ahmed ¹⁴, Vlad A. Alexandrescu ¹⁵, Max Amor ¹⁶, David Alper ¹⁷, Martin Andrassy ¹⁸, Christopher Attinger ¹⁹, Andy Baadh ²⁰, Hashem Barakat ²¹, Lukla Biasi ²², Theodosios Bisdas ²³, Zagum Bhatti ²⁴, Erwin Blessing ²⁵, Marc P Bonaca ²⁶, Stefano Bonvini ²⁷, Michel Bosiers ²⁸, Andrew W. Bradbury ²⁹, Robert Beasley ³⁰, Christian-Alexander Behrendt ³¹, Marianne Brodmann ³², Gonzalo Cabral ³³, Roberto Cancellieri ³⁴, Andrea Casini ⁵, Venita Chandra ³⁵, Emiliano Chisci ³⁶, Omar Chohan ³⁷, Edward T.C. Choke ³⁸, Patrick F.S. Chong ³⁹, Giacomo Clerici ⁴⁰, Raphael Coscas ⁴¹, Mary Costantino ⁴², Luca Dalla Paola ⁴³, Sabeen Dand ⁴⁴, Robert S.M. Davies ⁴⁵, Mario D’Oria ⁴⁶, Athanasios Diamantopoulos ¹⁴, Sebastian Debus ⁴⁷, Koen Deloose ⁴⁸, Costantino Del Giudice ⁴⁹, Gianmarco de Donato ², Brian De Rubertis ⁵⁰, Jean Paul De Vries ⁵¹, Nuno V Dias ⁵², Larry Diaz-Sandoval ⁵³, Florian Dick ⁵⁴, Konstantinos Donas ⁵⁵, Anahita Dua ⁵⁶, Fabrizio Fanelli ⁵⁷, Stefano Fazzini ⁵⁸, Mazin Foteh ⁵⁹, Roberto Gandini ⁶⁰, Mauro Gargiulo ⁶¹, Luca Garriboli ⁶², Elizabeth A. Genovese ⁶³, Edward Gifford ⁶⁴, Yann Goueffic ⁶⁵, Peter Goverde ⁶⁶, Prem Chand Gupta ⁶⁷, Robert Hinchliffe ⁶⁸, Andrew Holden ⁶⁹, Kim C. Houlind ⁷⁰, Dominic PJ Howard ⁷¹, Bella Huasen ⁷², Giacomo Isernia ⁷³, Konstantinos Katsanos ⁷⁴, Barry Katzen ⁷⁵, Philippe Kolh ⁷⁶, Igor Koncar ⁷⁷, Grigorios Korosoglou ⁷⁸, Prakash Krishnan ⁷⁹, Thomas Kroencke ⁸⁰, Miltiadis Krokidis ⁸¹, Arun Kumarasamy ⁸², Paul Hayes ⁸³, Osamu Iida ⁸⁴, Enrique Alejandro Lafont ⁸⁵, Ralf Langhoff ⁸⁶, Alexandre Lecis ⁸⁷, Mark Lessne ⁸⁸, Hady Lichaa ⁸⁹, Michael Lichtenberg ⁹⁰, Marta Lobato ¹⁰, Alice Lopes ⁹¹, Giorgio Loreni ⁹², Pierleone Lucatelli ⁹³, Sreekumar Madassery ⁹⁴, Lieven Maene ⁹⁵, Marco Manzi ⁹⁶, Martin Maresch ⁹⁷, Jay Santhosh Mathews ⁹⁸, James McCaslin ⁹⁹, Antonio Micari ¹⁰⁰, Stefano Michelagnoli ³⁶, Bruno Migliara ¹⁰¹, Robert Morgan ¹⁰², Luis Morelli ¹⁰³, Daniele Morosetti ⁵⁹, Nicolas Mouawad ¹⁰⁴, Paul Moxey ¹⁰⁵, Stefan Müller-Hülsbeck ¹⁰⁶, Jihad Mustapha ¹⁰⁷, Tatsuya Nakama ¹⁰⁸, Bahaa Nasr ¹⁰⁹, Zola N’dandu ¹¹⁰, Richard Neville ¹¹¹, Elias Noory ¹¹², Joakim Nordanstig ¹¹³, Katariina Noronen ¹¹⁴, Luis Mariano Palena ⁹⁵, Gianbattista Parlani ⁷², Ashish S. Patel ²², Parag Patel ¹¹⁵, Rafiuddin Patel ¹¹⁶, Sanjay Patel ²², Costantino Pena ¹¹⁷, Drazen Perkovic ¹¹⁸, Mark Portou ¹¹⁹, Giovanni Pratesi ¹²⁰, Christos Rammos ¹²¹, Jim Reekers ¹²², Vicente Rimbau ¹²³, Trisha Roy ¹²⁴, Kenneth Rosenfield ¹²⁵, Maria Antonella Ruffino ¹²⁶, Fadi Saab ¹²⁷, Athanasios Saratzis ¹²⁸, Paolo Sbarzaglia ¹²⁹, Andrej Schmidt ¹³⁰, Eric Secemsky ¹³¹, Michael Siah ¹³², Henrik Sillesen ¹³³, Gioele Simonte ⁷², Marc Sirvent ¹³⁴, Jill Sommerset ¹³⁵, Sabine Steiner ¹³⁰, Ahmed Sakr ¹³⁶, Dierk Scheinert ¹³⁰

Mehdi Shishebor¹³⁷, **Stavros Spiliopoulos**¹³⁸, **Alessio Spinelli**¹³⁹,
Konstantinos Stravoulakis¹⁴⁰, **Gergana Taneva**⁵⁴, **Desarom Teso**¹³⁵,
Joerg Tessarek¹⁴¹, **Selva Theivacumar**¹, **Anish Thomas**¹⁴², **Shannon Thomas**¹⁴³,
Narayan Thulasidasan¹⁴, **Giovanni Torsello**¹⁴⁴, **Ramesh Tripathi**¹⁴⁵, **Nicola Troisi**¹⁴⁶,
Srini Tummala¹⁴⁷, **Venkat Tummala**¹⁴⁸, **Christopher Twine**¹⁴⁹, **Raman Uberoi**¹⁵⁰,
Alessandro Ucci¹⁵¹, **Domenico Valenti**¹⁵², **Jos van den Berg**¹⁵³,
Daniel van den Heuvel¹⁵⁴, **Isabelle Van Herzele**¹⁵⁵, **Ramon Varcoe**¹⁴³,
Melina Vega de Ceniga¹⁵⁶, **Frank J. Veith**¹⁵⁷, **Maarit Venermo**¹⁵⁸, **Badri Vijaynagar**¹⁵⁹,
Sanjiv Virdee¹⁶⁰, **Conrad Von Stempel**¹⁶¹, **Michiel T Voûte**¹⁶², **Kak Khee Yeung**¹⁶³,
Thomas Zeller¹¹², **Hany Zayed**²², and **Miguel Montero Baker**¹⁶⁴

Clinical Relevance

This editorial assembles endovascular specialists from diverse clinical backgrounds and nationalities with a global call to address key challenges to enhance revascularization in chronic limb-threatening ischemia (CLTI) patients.

- Dedicated below-the-ankle (BTA) angiography and revascularization is underutilized in ischemic foot treatment. Existing guidelines do not address

comprehensive BTA vessel analysis. CLTI trials also often lack data on in-line arterial flow to the ischemic lesion and BTA vessel evaluation, hindering outcome assessment.

- Dedicated multi-planar angiographic evaluation of the distal microcirculation is key: Direct arterial flow or good-quality collaterals are crucial in influencing wound healing and need to be assessed diligently to the level of the distal ischemic wound territory, termed “woundosome.”

¹West London Vascular and Interventional Center, London North West University Healthcare NHS Trust, London, UK

²Vascular Surgery Unit, Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

³Division of Vascular and Endovascular Surgery, University of California, San Francisco, CA, USA

⁴Boston Medical Center, Boston University School of Medicine, Boston, MA

⁵Diabetic Foot Unit, Clinica San Carlo, Paderno Dugnano, Milan, Italy

⁶Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

⁷Baylor College of Medicine, Michael E. DeBakey Department of Surgery, Houston, Texas, USA

⁸Advanced Interventional and Vascular Services, LLP, Teaneck, New Jersey

⁹Division of Vascular and Endovascular Surgery, University of California San Francisco, San Francisco, CA, USA

¹⁰Department of Vascular Surgery, Hospital Universitario Cruces, Barakaldo, Spain

¹¹Department of Radiology, University Hospital, Newark, NJ

¹²UNC REX Healthcare, Raleigh, NC

¹³Manchester University NHS Foundation Trust, Manchester, United Kingdom

¹⁴Department of Interventional Radiology, Guys' and St. Thomas' NHS Foundation Trust, London, United Kingdom

¹⁵Department of Thoracic and Vascular Surgery, Princess Paola Hospital, Marche-Famenne, Belgium

¹⁶Department of Interventional Cardiology, U.C.C.I. Polyclinique d'Essey, Nancy, France

¹⁷KSU Foot & Ankle Clinic, Independence, OH

¹⁸Rkh FürstStirumKlinik, Bruchsal, Germany

¹⁹Department of Plastic and Reconstructive Surgery, MedStar Georgetown University Hospital, United States

²⁰Regions Hospital, Saint Paul, Minnesota, USA

²¹University Hospitals Plymouth NHS Trust; Plymouth; United Kingdom

²²Cardiovascular Division, Academic Department of Surgery, Guy's and St Thomas' Hospital NHS Trust, London, United Kingdom

²³Department of Vascular Surgery, Athens Medical Center, Athens, Greece

²⁴Texas Vein & Wellness Institute, Houston, TX

²⁵University Hospital Hamburg, Hamburg, Germany

²⁶Division of Cardiology, Department of Medicine, University of Colorado School of Medicine, Aurora, CO, United States

²⁷Department of Vascular Surgery, Santa Chiara Hospital, Trento, Italy

²⁸Department of Vascular Surgery, University Hospital of Bern, University of Bern, Bern, Switzerland

²⁹Department of Vascular Surgery, University of Birmingham, Birmingham, United Kingdom

³⁰Palm Vascular Centers, Miami Beach, FL, United States

³¹Center for Population Health Innovation (POINT), University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

³²Division of Angiology, Medical University Graz, Austria

³³Hospital Beatriz Angelo, Loures, Portugal

³⁴Interventional Radiology Unit, S. Eugenio Hospital, Rome, Italy

³⁵Stanford Health Care, Division of Vascular & Endovascular Surgery, Stanford, CA, United States

- ³⁶Vascular and Endovascular Surgery Unit, San Giovanni di Dio Hospital, Florence, Italy
- ³⁷Great Lakes Medical Imaging, Buffalo, NY, United States
- ³⁸Department of Vascular Surgery, Seng Kang General Hospital, Singapore
- ³⁹Frimley Park Hospital, Frimley, United Kingdom
- ⁴⁰San Carlo Clinic, Paderno Dugnano, Milano, Italy
- ⁴¹Department of Vascular Surgery, Ambroise Paré University Hospital, Assistance PubliqueHôpitaux de Paris, BoulogneBillancourt, France
- ⁴²Advanced Vascular Centers, Portland, Oregon, United States
- ⁴³Maria Cecilia Hospital, GVM Care and Research, Cotignola, Italy
- ⁴⁴Los Angeles Imaging and Interventional Consultants, PIH Health, Whittier, CA
- ⁴⁵Leicester Vascular Institute, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom
- ⁴⁶Division of Vascular and Endovascular Surgery, CardioThoracoVascular Department, University Hospital of Trieste ASUGI, Trieste, Italy
- ⁴⁷Department of Vascular Medicine, Vascular Surgery–Angiology–Endovascular Therapy, University Heart & Vascular Center, University of HamburgEppendorf, Hamburg, Germany
- ⁴⁸Department of Vascular Surgery, AZ Sint Blasius, Dendermonde, Belgium
- ⁴⁹Department of Radiology, Interventional Radiology, Institut Mutualiste Montsouris, Paris, France
- ⁵⁰New York Presbyterian Weill Cornell Medical Center, Mount Sinai Hospital, Columbia University Irving Medical Center and Columbia Vagelos College of Physicians and Surgeons, New York, United States
- ⁵¹Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
- ⁵²Department of Thoracic Surgery and Vascular Diseases, Vascular Center, Skåne University Hospital, Malmö, Sweden
- ⁵³Borgess Heart Institute, Kalamazoo, MI, United States
- ⁵⁴Kantonsspital St. Gallen, St. Gallen, and University of Bern, Bern, Switzerland
- ⁵⁵Department of Vascular Surgery, Asklepios Clinic Langen, University of Frankfurt, Langen, Germany
- ⁵⁶Division of Vascular Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States
- ⁵⁷Interventional Radiology Unit, Azienda OspedalieroUniversitaria Careggi, Florence, Italy
- ⁵⁸Division of Vascular Surgery, Tor Vergata University of Rome, Rome, Italy
- ⁵⁹Baylor Scott & White Heart Hospital, Plano, TX, United States
- ⁶⁰UOSD Radiologia Interventistica, University Hospital Policlinico Tor Vergata, Roma, Italy
- ⁶¹Vascular Surgery, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, IRCCS Sant’OrsolaMalpighi Hospital, Bologna, Italy
- ⁶²Vascular Surgery Divisoin, IRCCS Sacro Cuore Don Calabria” Negrar, Verona, Italy
- ⁶³Division of Vascular Surgery and Endovascular Therapy, University of Pennsylvania, Philadelphia, PA, United States
- ⁶⁴Division of Vascular Surgery, Hartford Hospital, Hartford, CT, United States
- ⁶⁵Vascular Center, Groupe Hospitalier Paris Saint Joseph, Paris, France
- ⁶⁶Department of Vascular Surgery, ZNA Stuivenberg, Antwerp, Belgium
- ⁶⁷Department of Vascular and Endovascular Surgery, Care Hospitals, Banjara Hills, Hyderabad, India
- ⁶⁸Department of Vascular Surgery, North Bristol NHS Trust, Bristol, United Kingdom
- ⁶⁹Auckland City Hospital, School of Medicine, University of Auckland, Auckland, New Zealand
- ⁷⁰Department of Vascular Surgery, Hospital Lillebaelt, University of Southern Denmark, Odense, Denmark
- ⁷¹Nuffield Department of Clinical Neurosciences, Centre for Prevention of Stroke and Dementia, University of Oxford, Oxford, United Kingdom
- ⁷²Department of Interventional Radiology, Lancashire University Teaching Hospitals, Lancashire Care NHS Foundation Trust, Preston, United Kingdom
- ⁷³Vascular and Endovascular Surgery Unit, S. Maria Della Misericordia University Hospital, Perugia, Italy
- ⁷⁴Department of Interventional Radiology, Patras University Hospital, Patras, Greece
- ⁷⁵Miami Cardiac and Vascular Institute, Baptist Health South Florida, Miami, FL, United States
- ⁷⁶Department of Biomedical and Preclinical Sciences, University of Liège, Liège, Belgium
- ⁷⁷Clinic for Vascular and Endovascular Surgery, Clinical Center of Serbia, Belgrade, Serbia
- ⁷⁸Departments of Cardiology, Vascular Medicine and Pneumology, GRN Academic Teaching Hospital Weinheim, Weinheim, Germany
- ⁷⁹The Zena and Michael A Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States
- ⁸⁰Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Augsburg, Augsburg, Germany
- ⁸¹National and Kapodistrian University of Athens, Areteion Hospital, Athens, Greece
- ⁸²European Vascular Centre AachenMaastricht, Department of Vascular Surgery, Medical Faculty, University Hospital RWTH Aachen, Aachen, Germany
- ⁸³St John’s Innovation Centre, Cambridge, United Kingdom
- ⁸⁴Cardiovascular Center, Kansai Rosai Hospital, Inabaso, Hyogo, Amagasaki, Japan
- ⁸⁵Department of Radiology, Kantonsspital St.Gallen, Switzerland
- ⁸⁶Department of Angiology, St. Gertrauden Hospital, Berlin, Germany
- ⁸⁷Centre Hospitalier de Troyes, Troyes, France
- ⁸⁸Vascular and Interventional Specialists, Charlotte Radiology, Charlotte, NC, United States
- ⁸⁹Ascension Saint Thomas Heart, Ascension Saint Thomas Rutherford, Murfreesboro, TN, United States
- ⁹⁰Clinic of Angiology, KarolinenHospital, Arnsberg, Germany
- ⁹¹Department of Vascular Surgery, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
- ⁹²UOC Radiologia Interventistica, ASL Roma 2, Ospedale S. Pertini, Rome, Italy
- ⁹³Vascular and Interventional Radiology Unit, Department of Radiological, Oncological, and AnatomicPathological Sciences, Sapienza University of Rome, Rome, Italy
- ⁹⁴Rush University Medical Center, Chicago, IL, United States

- ⁹⁵Department of Vascular and Thoracic Surgery, OnzeLieveVrouwziekenhuis Aalst, Aalst, Belgium
- ⁹⁶Policlinico Abano Terme, Padova, Italy
- ⁹⁷Department of Vascular and Endovascular Surgery, BDF Hospital Royal Medical Services, Bahrain
- ⁹⁸Bradenton Cardiology Center, Manatee Memorial Hospital, Bradenton, FL, United States
- ⁹⁹The Northern Vascular Centre, Freeman Hospital, Newcastle upon Tyne, United Kingdom
- ¹⁰⁰Department of Biomedical and Dental Sciences and Morphological and Functional Imaging, University of Messina, Messina, Italy
- ¹⁰¹Vascular and Endovascular Surgery Unit, Pederzoli Hospital, Peschiera del Garda, Italy
- ¹⁰²Diagnostic, Vascular & Interventional Radiology, St George's University Hospitals NHS Foundation Trust and St George's, University of London, United Kingdom
- ¹⁰³Diabetic Foot Unit and Limb Salvage, Hospital San Juan de Dios, San Jose, Costa Rica
- ¹⁰⁴Department of Surgery, McLaren Health System, Grand Blanc, MI, United States
- ¹⁰⁵St George's Vascular Institute, St George's University Hospital, London, United Kingdom
- ¹⁰⁶Academic Hospital ChristianAlbrechtsUniversity Kiel, Kiel, Germany
- ¹⁰⁷Advanced Cardiac and Vascular Centers for Amputation Prevention, Grand Rapids, MI, United States
- ¹⁰⁸Jikei University Hospital, Department of Surgery, Division of Vascular Surgery, Tokyo, Japan
- ¹⁰⁹CHU Cavale Blanche Brest, Vascular and Endovascular Surgery Department, Brest, France
- ¹¹⁰Oschner Health, Kenner, LA, United States
- ¹¹¹Inova Schar Heart and Vascular, Inova Fairfax Medical Campus, Falls Church, VA, United States
- ¹¹²Department of Cardiology and Angiology, Medical Center, University of Freiburg, Bad Krozingen, Germany
- ¹¹³Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg, Göteborg, Sweden
- ¹¹⁴Department of Vascular Surgery, Abdominal Center, Helsinki University Hospital, Helsinki, Finland
- ¹¹⁵Department of Radiology, Vascular and Interventional Radiology, Medical College of Wisconsin, Milwaukee, WI, United States
- ¹¹⁶Department of Interventional Radiology, Oxford University Hospitals NHS Foundation Trust, Headley Way, Oxford, United Kingdom
- ¹¹⁷Miami Cardiac and Vascular Institute, Miami, FL
- ¹¹⁸Department of Diagnostic and Interventional Radiology, University Hospital Centre Zagreb, Zagreb, Croatia
- ¹¹⁹Royal Free Vascular, Division of Surgery and Interventional Science, Royal Free Campus, UCL, London, UK
- ¹²⁰Unit of Vascular and Endovascular Surgery-IRCCS Ospedale Policlinico San Martino, Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy
- ¹²¹Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center, University of DuisburgEssen, Germany
- ¹²²Amsterdam UMC, University of Amsterdam, Meibergdreef 9, Amsterdam, Netherlands
- ¹²³Vascular Surgery Department, Hospital Clinic de Barcelona, Barcelona, Spain
- ¹²⁴DeBakey Heart and Vascular Center, Houston Methodist Hospital, Houston, TX, United States
- ¹²⁵Department of Cardiology, Massachusetts General Hospital, Boston, MA, United States
- ¹²⁶Department of Interventional Radiology, Ticino Vascular Center, Institute of Imaging of Southern Switzerland, Lugano Regional Hospital, Lugano, Switzerland
- ¹²⁷ACV Centers, Grand Rapids, MI, United States
- ¹²⁸University Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom
- ¹²⁹Interventional cardiology, Maria Cecilia Hospital, Ravenna, Italy
- ¹³⁰Department of Angiology, University Hospital Leipzig, Leipzig, Germany
- ¹³¹Smith Center for Cardiovascular Outcomes Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States
- ¹³²Division of Vascular and Endovascular Surgery, Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, United States
- ¹³³Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
- ¹³⁴Department General, University Hospital of Granollers, CIBERCV, ISCIII, Granollers, Spain
- ¹³⁵PeaceHealth, Vancouver, WA, United States
- ¹³⁶Saudi German Hospital, Jeddah, Saudi Arabia
- ¹³⁷University Hospitals Cleveland Medical Centre and Case Western Reserve University School of Medicine, Cleveland, OH, United States
- ¹³⁸2nd Department of Radiology, Interventional Radiology Unit, Medical School, National and Kapodistrian University of Athens, Attikon, University General Hospital, Athens, Greece
- ¹³⁹Interventional Radiology, Hospital S. Eugenio, Rome, Italy
- ¹⁴⁰Department of Vascular Surgery, Ludwig Maximilians University, Germany
- ¹⁴¹Department Vascular and Endovascular Surgery, Bonifatius Hospital, Lingen, Germany
- ¹⁴²Mercy Clinic Heart And Vascular LLC, Saint Louis, MO
- ¹⁴³Prince of Wales Hospital, Sydney, NSW, Australia
- ¹⁴⁴University Hospital Münster, Institute for Vascular Research, Franziskus Hospital, Münster, Germany
- ¹⁴⁵University of Queensland, Brisbane, QLD, Australia
- ¹⁴⁶Vascular Surgery Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
- ¹⁴⁷Department of Interventional Radiology, University of Miami Health System, UM Miller School of Medicine, Miami, FL, United States
- ¹⁴⁸Lakeland Vascular Institute, FL United States
- ¹⁴⁹Bath and Weston Vascular Network, Southmead Hospital, North Bristol NHS Trust, Bristol, United Kingdom
- ¹⁵⁰John Radcliffe Hospital, Oxford University Hospitals, Oxford, United Kingdom
- ¹⁵¹Unit of Vascular Surgery, Department of Medicine and Surgery, Azienda OspedalieroUniversitaria di Parma, Parma, Italy
- ¹⁵²Department of Vascular Surgery, King's College Hospital, London, United Kingdom
- ¹⁵³Universitätsinstitut für Diagnostische, Interventionelle und Pädiatrische Radiologie, Inselspital, Universitätsspital Bern, Bern, Switzerland
- ¹⁵⁴Department of Radiology, St. Antonius Ziekenhuis, Nieuwegein, Netherlands

- An important primary emphasis of future trials should be on validating technologies and strategies for assessing tissue perfusion before, during, and after revascularization undertaken to heal tissue loss in CLTI patients. This will allow determination of a potentially significant delta in tissue perfusion prior to and following intervention at the “woundosome” level. Once changes in arterial perfusion have been identified as positively correlated to wound healing, these could serve as a much-needed novel primary technical outcome measure for patients with tissue loss undergoing surgical, hybrid, or endovascular revascularization.

Background and Current Literature/ Guidelines

Chronic limb-threatening ischemia (CLTI) represents the most advanced stage of lower-extremity peripheral artery disease (PAD) and is a major global health concern with escalating prevalence and significant health-care costs.¹ Fortunately, technological advancements, evolving revascularization strategies, as well as refinement and expansion of the skill set of surgical and endovascular specialists have successfully reduced the number of patients previously deemed inappropriate for revascularization.

Despite mounting evidence on the value of below-the-ankle (BTA) recanalization in wound-healing and limb salvage,²⁻⁵ the role of BTA angiographic evaluation and potential revascularization is yet to become the mainstay of ischemic foot treatment in daily clinical practice.

The recent Global Vascular Guidelines on the management of CLTI⁶ acknowledge limitations about incorporating the terminal circulation into its algorithmic framework. The concept of the preferred target artery pathway (TAP) does not include a comprehensive analysis of BTA anatomy, nor does it address specific mechanisms for establishing suitable perfusion to the ischemic portion of the foot, whether through direct or indirect means. The TAP approach suggests that interventionalists should identify a

preferred primary target path through the least-diseased (or most suitable) crural artery, sharing some similarity with the surgical principle of bypassing to the highest quality vessel providing runoff to the foot. In addition, the currently proposed pedal modifier, part of the Global Limb Anatomic Staging System (GLASS) classification,⁶ also has limitations in assessing the actual flow to the wound area. Nevertheless, it marks a significant step forward when compared to the most recent expansion of the Trans-Atlantic inter-Society Consensus (TASC) lesion classification,⁷ which did not include any assessment of BTA vessel status or account for the presence of multi-level occlusive disease.

Recent pivotal randomized controlled trials (RCTs) investigating CLTI treatments^{8,9} were not designed to directly assess in-line arterial flow to the tissue loss territory during patient stratification, either before or after the index procedure. To illustrate, the Bypass versus Angioplasty for Severe Ischemia of the Leg (BASIL)-2 trial did not include data on the status of BTA arteries and foot arch patency.⁸ The Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) trial group has, to date, reported infrapopliteal disease as a single “tibio-pedal” disease cohort.⁹ While specifically designed to determine the best treatment for patients with CLTI, they did not provide explicit reports on angiographic data concerning pre- or post-interventional BTA artery status or the patency of the pedal arch. More specific analysis of each of the 21 anatomic segments, including the dorsalis pedis and pedal branches of the posterior tibial artery, and the association between anatomic patterns on presentation and clinical outcomes are eagerly awaited, with the hope that they will shed light on how in-line arterial flow to the wound was achieved and its potential impact on trial endpoints.

From the Angiosome to the “Woundosome”

In 2006, Attinger et al¹⁰ introduced the concept of 6 angiosomes in the foot and ankle, originating from the 3 main

¹⁵⁵Department of Thoracic and Vascular Surgery, Ghent University Hospital, Ghent, Belgium

¹⁵⁶Department of Angiology and Vascular Surgery, University Hospital of GaldakaoUsansolo, Bizkaia, Spain

¹⁵⁷New York University Medical Centre, New York, NY and The Cleveland Clinic, Cleveland, OH, United States

¹⁵⁸Department of Vascular Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

¹⁵⁹Glenfield Hospital, Leicester, United Kingdom

¹⁶⁰The University of Rochester Medical Faculty Group, NY, United States

¹⁶¹Department of Radiology, University College London Hospitals, London, United Kingdom

¹⁶²Department of Surgery, Prince of Wales Hospital, Sydney, Australia

¹⁶³Department of Vascular Surgery, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centres, Amsterdam, Netherlands

¹⁶⁴Hope Vascular & Podiatry Clinical Innovation Center, Houston, TX

Corresponding Author:

Lorenzo Patrone, West London Vascular and Interventional Center, London North West University Healthcare National Health Service Trust, London HA1 3UJ, UK.

Email: lorenzo.patrone@nhs.net

infrapopliteal arteries, as a dependable method to guide revascularization procedures and ensure direct blood flow to trophic lesions. However, doubts about the utility of the “angiosome” concept have emerged over time. One significant limitation lies in its reliance on standard anatomy, disregarding potential anatomical variations, possible collateralized vessel contributions, such as from peroneal artery branches supplying anterior and/or posterior circulation patterns, and the role of a patent and non-significantly diseased pedal arch. In addition, the frequent involvement of more than one angiosome in cases of larger wounds clouds its application. Consequently, despite 2 distinct meta-analyses indicating improved outcomes in terms of wound-healing time and limb salvage for angiosome-targeted revascularization procedures,^{11,12} this intriguing anatomy-based concept has not consistently translated into clinical effectiveness, as evidenced by various retrospective studies.^{13–18}

Existing literature focusing on CLTI patients with tissue loss has consistently indicated that the presence of direct arterial flow to the wound is associated with superior outcomes in terms of limb salvage and wound healing.^{19,20} Conversely, the presence and quality of foot collaterals following indirect revascularization procedures have also shown to be important in predicting clinical success, often yielding results comparable to direct revascularization.^{21,22} Unfortunately, recent reports frequently overlook the significance of true and choke collaterals, arterial connections, and the patency and quality of the foot arch when categorizing patients by disease severity.

Efforts have been made to develop various independent classification systems for BTA disease patterns. While the Kawarada pedal arch classification²³ is sometimes considered overly simplistic as it does not fully address the crucial aspect of peri-wound circulation, the specific classification of foot atherosclerotic disease originating from angiosomal source arteries by Alexandrescu et al²⁴ offers a more precise framework for defining patterns of BTA disease. This recently published classification system represents a potentially excellent tool for studying the often-complex anatomy of the infra-malleolar circulation and its implications in foot perfusion, although its applicability and clinical significance remain to be validated in large-cohort studies.

Despite numerous attempts by previous authors to establish an acute performance measure, validation and consensus have remained elusive. The primary focus of revascularization efforts and, consequently, the definition of technical success should be centered on achieving a significant increase in arterial perfusion within the three-dimensional zone containing the ischaemic lesion. In this context, we propose the validation of the “woundosome” concept. This area may extend beyond its angiosomal anatomical borders to encompass adjacent territories if connections are established by true and choke

collaterals²⁵ and/or if the foot arch exhibits non-significant disease.²⁶

Assessing the Woundosome

To perform a comprehensive evaluation of the small-caliber below-the-knee (BTK) outflow arteries, the preferred method is super-selective Digital Subtraction Angiography (DSA), via an antegrade ipsilateral femoral approach with the catheter/sheath positioned just above the infrapopliteal trifurcation, as the CLI Global Society highlighted in their recent Expert Recommendation Statement.²⁷ Furthermore, to optimally visualize pedal arteries, a catheter compatible with a 0.018-inch or smaller wire should be placed as distally as possible in the tibial arteries and/or the infra-malleolar vessels.

Performing high-resolution intraoperative angiography from various views and projections is essential toward this objective. To improve angiographic visualization, local intra-arterial injection of vasodilators (such as nitrates, papaverine, or calcium channel blockers) can be useful. These maneuvers allow operators to gain a comprehensive understanding of the feeding arteries to the wound bed, identify potential anatomical variations, pinpoint the specific territory requiring direct perfusion restoration, and assess collateral integrity, size, and flow.

Importantly, it is often necessary to conduct antero-posterior (dorso-plantar) and lateral angiograms of the foot to fully delineate perfusion to the ischemic penumbra.¹¹ Specifically, the former is crucial for revealing the source of flow for the metatarsal arteries and the specific woundosome from either BTK or BTA vessels. The importance of utilizing two orthogonal projections when examining the BTA vessels becomes particularly evident in cases involving an occluded foot arch (Figures 1–4). For example, when dealing with a necrotic lesion of the first toe, a thorough examination of both the dorsalis pedis and medial plantar artery is imperative for identifying a suitable target for revascularization; while theoretically supplying flow to different angiosomes, both vessels have the potential to directly nourish the wound bed.

Although the benefits of in-line flow to the foot in patients with advanced tissue loss have been well-documented,^{2–5,19,20} the selection of patients for aggressive revascularization attempts should be grounded in the assessment of microcirculation functionality²⁸ and clinically validated radiological findings, such as the medial arterial calcification (MAC) score.²⁹ The simplicity and generalizability of this metric provides us with a predictive tool for assessing the potential success of limb salvage revascularization strategies. Its application has revealed that in patients with compromised or non-functional ultra-distal microcirculation, conventional open or endovascular techniques do not always sufficiently improve local tissue oxygen perfusion or attain limb salvage, even if infrapopliteal revascularization proves successful.^{28,29}

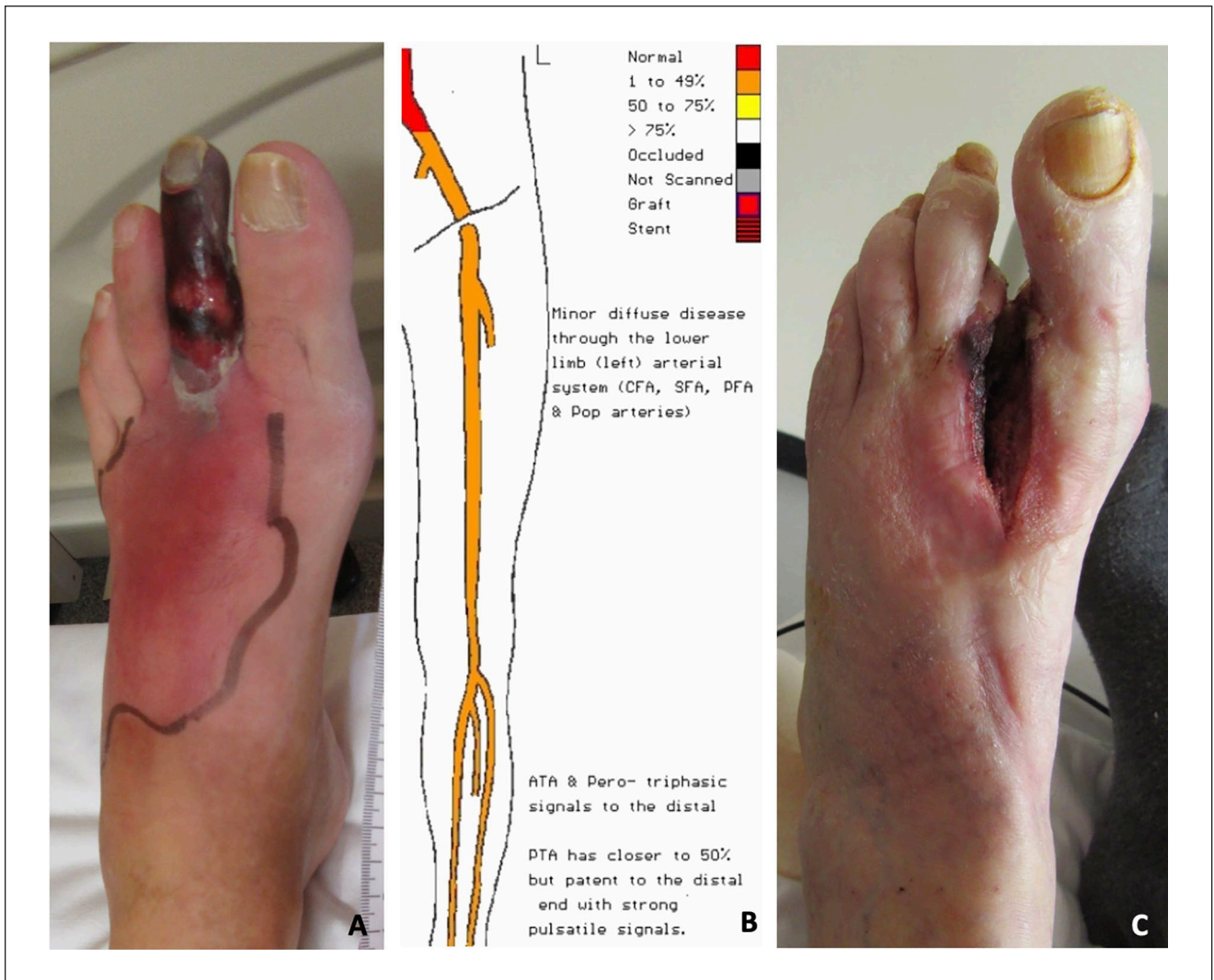


Figure 1. (A) Fifty-six-year-old man presenting with left diabetic foot attack, second toe necrosis, and clear signs of local infection. (B) Pictorial scheme of vascular duplex ultrasound highlighting triphasic signal in anterior tibial and peroneal arteries. The posterior tibial artery was found to be focally moderately stenotic but conserving strong pulsatile signals distally. (C) Static wound with no signs of granulation at the level of the second toe amputation site, despite best medical treatment and vacuum-assisted closure dressing applied. Abbreviations: CFA: Common Femoral Artery; SFA: Superficial Femoral Artery; DFA: Deep Femoral Artery.

Recognizing patterns of advanced infra-malleolar disease, which primarily affects the ultra-distal vessels, should prompt early referrals to centers experienced in alternative treatment modalities, such as deep vein arterialization (DVA). This is especially pertinent in cases where potential revascularization targets in the pedal vessels cannot be identified.

Current and Emerging Tools to Evaluate Foot Perfusion

Over the past 2 decades, various techniques have emerged to evaluate the pre- and post-revascularization grade of ischemia in CLTI patients with tissue loss. Among these,

the most utilized methods include Ankle-Brachial Pressure Index (ABI), Toe-Brachial Pressure Index (TBI), Transcutaneous Oxygen Pressure (TcPO₂), skin perfusion pressure (SPP), and pulse volume recording (PVR).^{12,13} However, a significant gap remains in standardized methods for quantifying arterial perfusion at the wound bed, crucially intra-procedurally,³⁰⁻³² and there is a growing awareness of the significant limitations of current assessment tools. The lack of reproducibility, standardization, and predictive utility in current evaluation modalities also highlights the clear need for established perfusion thresholds that reliably correlate with short- and long-term hemodynamic and clinical success. This benefit of improved evaluation and prognostic instruments will

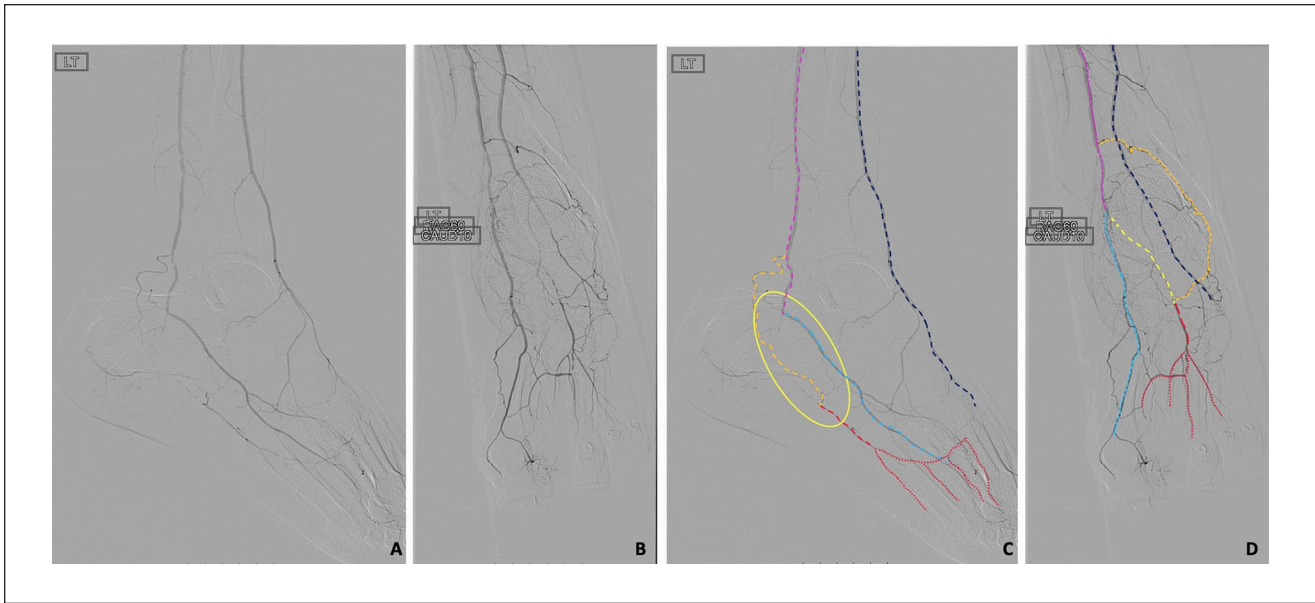


Figure 2. Preoperative angiographic views of the ankle and foot. (A and C) Latero-lateral projection. (B and D) Antero-posterior projection. Dark purple dashed line: anterior tibial artery and distally occluded dorsalis pedis artery (no connection with the deep plantar arch) and only lateral branches as ultra-distal outflow vessels; pink dashed line: posterior tibial artery; blue dashed line: medial plantar artery; dark yellow dashed line: threadlike collateral feeding the mid-lateral plantar artery; red dashed line: proximally occluded lateral plantar artery, providing flow to the deep plantar arch and to all the metatarsal arteries; light yellow dashed line (AP view): occluded segment of the lateral plantar artery, where the yellow circle indicates the target area of the revascularization procedure on the lateral view.

likely be most pronounced in the presence of advanced ischemia and the most challenging wounds, where the risk of limb loss is highest. Anatomically, this may frequently be in cases where single-vessel peroneal runoff feeds the posterior and/or anterior circulation or when flow to the “woundosome” is solely provided by collaterals.

More recently, several potential on-table Clinical Objective Performance tools have undergone evaluation, including implantable micro-oxygen sensors, perfusion angiography, diffuse speckle contrast analysis, and pedal acceleration time (PAT).³³ All these offer promising prospects as adjunctive tools for objectively measuring foot perfusion at baseline, during revascularization, and post-procedurally, with the potential to standardize assessments of normal and abnormal foot perfusion. This standardization can significantly contribute to the establishment of arterial flow threshold targets customized for wound healing.

- Micro-oxygen sensors (Profusa Inc, San Francisco, CA). Preliminary data³⁴ suggest a unique role in evaluating the acute success of revascularization, including the assessment of autonomic system integrity. Moreover, mathematical calculations based on preliminary data from the OMNIA (Oxygen Monitoring Near Ischemic Areas) study show high

sensitivity in predicting early success (or failure) of revascularisation efforts.

- Diffuse speckle contrast analysis (PedraTech Pte, Singapore) is a novel monitoring system that measures perfusion through the application of up to 4 radiolucent pads to the peri-wound tissue. This device offers continuous, quantifiable evidence of tissue perfusion to a depth of 8 mm by measuring the Blood Perfusion Index—a real-time indicator of blood cell movement in key microvascular spaces—before, during, and after revascularization. Although the only available data, derived from a preclinical study, demonstrate the device’s reliability and real-time responsiveness to changes in perfusion,³⁵ more robust data on CLTI patients with tissue loss are eagerly anticipated.
- Perfusion angiography (Philips, Eindhoven, The Netherlands) studies the time-density curve of contrast volume flow in the foot based on a dedicated post-processing software algorithm. Despite being an interesting technology, it needs yet to achieve full standardization. Factors such as movement artifacts, the need for specialized machines and software, and a lack of clearly defined perfusion thresholds linked to wound healing or limb salvage have presented significant challenges.³⁶

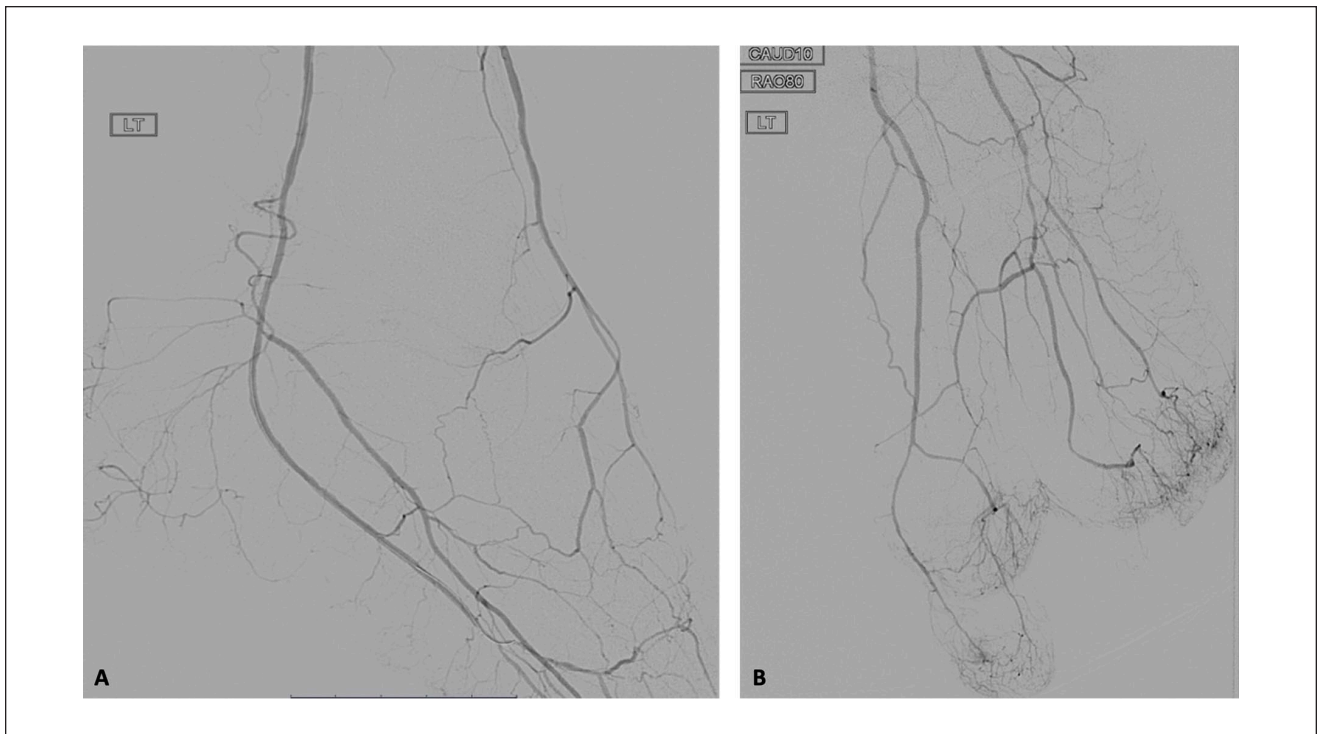


Figure 3. Final angiographies after successful revascularization. (A) Latero-lateral projection and (B) antero-posterior projection highlighting the successful revascularization of the previously occluded lateral plantar artery (2-mm angioplasty performed). Significant angiographic increase of blood perfusion at the level of the wound bed is noticed.



Figure 4. (A–C) Gradual improvement with complete wound healing after 5 months.

- In contrast, the latest addition, PAT, has swiftly gained global acceptance due to its non-invasive, reproducible, objective, and user-friendly attributes, coupled with its proven reliability.^{37,38} This innovative approach naturally aligns with the “woundosome” concept. Within the intraoperative setting, PAT offers a definitive endpoint—a novel metric previously lacking—for decisively determining when sufficient perfusion has been attained during the procedure.³³ Currently, a multicenter study correlating PAT with Toe-Brachial Index (TBI), Ankle-Brachial Index (ABI), and arterial duplex has been completed and is awaiting final data analysis and publication.³⁹ The limitation of this technique relies on operator’s ultrasound skills and the likely need for a dedicated specialized vascular technician in the room if the PAT needs to be measured intraoperatively.

Standardizing Classifications

Initial assessment and stratification of CLTI patients using the WIfI (Wound, Ischemia, and foot Infection) classification has demonstrated the high predictive value of baseline WIfI classification and limb clinical stage in estimating the risk of amputation within 1 year.^{40,41} The necessity for revascularization varies depending on the type of wound, its metabolic demands, and the possibly concomitant need for different types of BTA amputation. The centerpiece of the current unmet need related to ischemic ulcerations of the toes, forefoot, or heel is the lack of a clear understanding of the degree of perfusion required for successful healing or any reliable, easy-to-use tool to assess perfusion changes. Deep or infected wounds may necessitate direct revascularization to facilitate this process, while superficial, non-infected wounds may not always require this intervention, important in the setting of challenging BTA disease.⁴²

Second-look procedures, often referred to as “redo-interventions,” are often necessary to achieve durable resolution of presenting limb ischemia. As they reflect the recoil, restenotic, and intimal hyperplastic forces that are not uncommon following endovascular or surgical revascularization, they do not necessarily represent initial treatment failure. These procedures frequently unveil previously unnoticed hibernating targets that have become visible and highlight areas where recently recanalized vessels may be recoiling. Similarly, a combination of rigorous surveillance and revascularization, guided by imaging and clinical findings, is essential until the wounds have completely healed.

Patients affected by CLTI should be managed by a dedicated interdisciplinary specialty care team, possibly embedded in multi-specialty-driven “CLTI centers of excellence,” providing comprehensive imaging, clinical assessment, and treatment. In this setting, selective DSA should be considered the definitive “gold standard” imaging modality,

especially for distal occlusive disease associated with CLTI, as strongly indicated previously,^{27,43} but it could be augmented with intraprocedural perfusion monitoring.

Closing Thoughts

We firmly advocate for the systematic inclusion of angiographic and physiological evaluations of BTA vessels, along with their tributary flow to the wound, as critical parameters in patient stratification criteria for forthcoming CLTI trials. However, it should also be recognized that angiography itself possesses a few limitations. It provides only qualitative assessment of the distal vessels and requires subjective interpretation of the images, which in turn are affected by volume and flow rates of injected contrast. Flow improvement can only be assessed intermittently and requires boluses of contrast and radiation to do so. Finally, angiography only assesses visible vessels and not the extent or functionality of the microcirculation, where all actual oxygen and nutrient transfer takes place.³⁰

With ongoing evolution of multiple new perfusion measurement devices and techniques,⁴⁴ the primary emphasis of future studies and trials should be on validating these technologies and strategies for assessing tissue perfusion before, during, and after revascularization. Once changes in arterial perfusion have been identified as positively correlated to wound healing, these could serve as a much-needed novel primary technical outcome measure for patients with tissue loss undergoing surgical, hybrid, or endovascular revascularization.

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ORCID iDs

Lorenzo Patrone  <https://orcid.org/0000-0001-6586-8271>

Edoardo Pasqui  <https://orcid.org/0000-0001-6619-0159>

Roberto Ferraresi  <https://orcid.org/0000-0002-6185-6510>

Joseph L. Mills  <https://orcid.org/0000-0002-4955-4384>

Peter Schneider  <https://orcid.org/0000-0002-4498-5150>

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