Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017;377:2240-52. DOI: 10.1056/NEJMoa1615066

Supplementary Appendix

Table of Contents

List of Investigators and Staff

The study leadership wishes to acknowledge, and to express its deepest gratitude to, the following investigators who made important contributions to the success of the ATTRACT Trial:

Steering Committee

Samuel Z. Goldhaber, MD **(Chair)**	Harvard Medical School
David J. Cohen, MD, MSc	St. Luke's Mid America Heart Institute
Anthony J. Comerota, MD	University of Michigan
Heather L. Gornik, MD, MHS, RVT	Cleveland Clinic Heart & Vascular Institute
Michael R. Jaff, DO	Harvard Medical School
Jim Julian, MMath	McMaster University
Susan R. Kahn, MD, MSc	McGill University, Jewish General Hospital
Clive Kearon, MB, PhD	McMaster University
Stephen Kee, MD	UCLA Medical Center *(SIR Foundation representative)*
Andrei L. Kindzelski, MD, PhD	National Heart, Lung, and Blood Institute
Lawrence Lewis, MD	Washington University in St. Louis
Elizabeth Magnuson, ScD	St. Luke's Mid America Heart Institute
Mahmood K. Razavi, MD	St. Joseph's Vascular Institute
Timothy P. Murphy, MD	Brown University
Suresh Vedantham, MD	Washington University in St. Louis *(Principal Investigator)*

Operations Committee

Suresh Vedantham, MD **(Chair)**	Washington University in St. Louis
Samuel Z. Goldhaber, MD	Harvard Medical School
Clive Kearon, MB, PhD	McMaster University
Andrei L. Kindzelski, MD, PhD	National Heart, Lung, and Blood Institute
Timothy P. Murphy, MD	Brown University

Enrollment Committee

Suresh Vedantham, MD **(Co-Chair)**	Washington University in St. Louis
Lawrence Lewis, MD **(Co-Chair)**	Washington University in St. Louis
Anthony Comerota, MD	Jobst Vascular Center
Timothy P. Murphy, MD	Rhode Island Hospital
Gregory Soares, MD	Rhode Island Hospital
Mark Thoelke, MD	Washington University in St. Louis

Interventions Committee

Mahmood K. Razavi, MD **(Chair)**	St. Joseph's Hospital, Orange, CA
Mark Garcia, MD	Christiana Care Hospital, DE
Lawrence Hofmann, MD	Stanford University, CA
David W. Hunter, MD	University of Minnesota, MN
Robert Lookstein, MD	Mount Sinai Hospital, NY

Medical Therapy Committee

Heather L. Gornik, MD **(Chair)**	Cleveland Clinic, OH
Jerry Bartholomew, MD	Cleveland Clinic, OH
Anthony Comerota, MD	Jobst Vascular Center, OH
Charles Eby, MD	Washington University in St. Louis
Michael Militello, PharmD	Cleveland Clinic, OH

Society of Interventional Radiology Foundation

Stephen Kee, MD	Physician Representative
John Rundback, MD	Previous Physician Representative
Carolyn Strain	Executive Director
Keith Hume	Previous Executive Director
Kathleen Mercure	Staff Liaison

Inclinix

Robin Hosley and Donna Dail	Project Managers
Caroline Lambert and Dawn King	Enrollment Specialists
Christy Godwin and Britton Perko	Enrollment Specialists

Data Safety Monitoring Board

Jodi Segal, MD, MPH **(Chair)**	Johns Hopkins University
David Green, MD	Northwestern University
Anna Iltis, PhD	Saint Louis University
John W. Hirshfeld Jr, MD	University of Pennsylvania
Karim Valji, MD	University of Washington, Seattle
Susan Geyer, PhD	The Ohio State University
Robert Glynn, ScD	Harvard Medical School
Sameer Parpia, PhD	McMaster University, Reporting Statistician

Clinical Coordinating Center (Washington University)

Suresh Vedantham, MD	**Chair,** Clinical Coordinating Center
James R. Duncan, MD, PhD	Safety Officer
Patricia Nieters, RN, BSN	Clinical Research Nurse Coordinator
Mary Clare Derfler, RN, MSN	Clinical Research Nurse Coordinator
Daniel Santacruz	Financial Project Administrator
Kathy Taylor	Clinical Research Coordinator
Laura Todt, RN, BSN	Clinical Research Nurse Coordinator
Colleen Kilbourne-Glynn, MA	Financial Project Manager
Melissa Bellovich	Project Coordinator
Laura Carpenter, RN	Clinical Research Nurse Coordinator
Rochelle Williams	Staff Assistant
Yi Zhang, RN, JD	Administrative Director, Center for Clinical Studies
Bradley Evanoff, MD, MPH	Director, Institute for Clinical and Translational Sciences
Michelle Jenkerson, RN	Monitor - Center for Clinical Studies
Theresa Arb, RN	Monitor - Center for Clinical Studies
Phyllis Klein, RN	Monitor - Center for Clinical Studies
Sherry Banez-Muth, RN	Monitor - Center for Clinical Studies
Licia Rowe, MT	Core Laboratory for Clinical Studies
David Gibson, MD	Core Laboratory for Clinical Studies
Richard Ostland, MD	Core Laboratory for Clinical Studies
Kathryn Vehe, PharmD	Pharmacy
Charles Rathmann & Marcy Birner	Recruitment Enhancement Core
James Naes	Interventional Radiology Technical Supervisor

Data Coordinating Center (McMaster University)

Clive Kearon, MB, PhD	**Chair**, Data Coordinating Center
Susan R. Kahn, MD, MSc	**Chair**, Clinical Outcomes Committee (McGill University)
Jim Julian, MMath	Faculty Statistician *(**conducted the statistical analysis**)*
Chu-Shu Gu, PhD	Senior Statistician *(**conducted the statistical analysis**)*
Marc Filion, MSc	Study Coordinator
Erin McGean	Data Assistant
Luciana Spadafora	Adjudication Coordinator
Donna McCarty	Clinical Research Manager
Mark Levine, MD, MSc	**Chair**, Independent Central Adjudication Committee
Jeffrey Weitz, MD	Physician Adjudicator
James D. Douketis, MD	Physician Adjudicator
Sam Schulman, MD, PhD	Physician Adjudicator
Graham Thomson, MB	Physician Adjudicator

Vascular Ultrasound Core Laboratory (Massachusetts General Hospital)

Michael Jaff, DO	Original Director, VasCore
Ido Weinberg, MD	Director, VasCore
Gail Hadley, RN, RVT	Technical Director
Joshua Beckman, MD	Physician Reviewer
Victoria Sova, RN, RVT	Technical Reviewer
Sandra Croteau, RN, RVT	Technical Reviewer
Kathryn Lane, RVT	Technical Reviewer
Erin Lacey	Senior Administrative Coordinator
Meghna Lahiry	Administrative Coordinator
Justin McNeil	Project Team Leader
Kathryn McCullough	Administrative Director
Christopher Luongo	Administrative Assistant
Frances Veazy	Administrative Assistant
Lindsey St. Louis	Administrative Assistant
Dorina Cheung	Administrative Assistant
Sabina Dhami	Administrative Assistant
Justin Thompson	Administrative Assistant
Luis Cintron	Administrative Assistant
Ritu Shrestha	Administrative Assistant
Brian Chung	Administrative Assistant

Health Economic Core Laboratory (Mid America Heart Institute)

David J. Cohen, MD, MSc	St. Luke's Mid America Heart Institute
Elizabeth Magnuson, ScD	St. Luke's Mid America Heart Institute
Katherine Villain	Research Scientist and Data Coordinator Manager
Khaja Chinnakondepalli	Statistical Data Analyst II
Erin Notestein	Clinical Research Associate
Samantha King	Clinical Research Associate
Jamie Appelwick	Clinical Research Associate
Shawn Smitherman	Clinical Research Associate

ATTRACT Clinical Centers: Site Investigators

Adventist Midwest Health: Michael Sichlau – site PI, Athanasios Vlahos, Steven Smith, Quinn Thalheimer, Nisha Singh, Rekha Harting, John Gocke, Scott Guth, Neel Shah

Albert Einstein Medical Center: Paul Brady – site PI, Marvin Schatz, Mindy Horrow, Peyman Markazi, Leli Forouzan, Terence A.S. Matalon, David Hertzog

Allegheny General Hospital: Swapna Goday – site PI, Margaret Kennedy – previous site PI, Robert Kaplan, Thomas Campbell, Jamie Hartman, Elmer Nahum, Arvind Venkat

Ann Arbor VA Health Center: Venkataramu Krishnamurthy – site PI, John Rectenwald, Peter Henke, Jonathan Eliason, Jonathon Willatt, Guillermo Escobar

Baptist Cardiac and Vascular Institute: Shaun Samuels – site PI, Barry Katzen, James Benenati, Alex Powell, Constantino Pena, Howard Wallach, Ripal Gandhi

Central DuPage Hospital: Joseph Schneider – site PI, Stanley Kim, Farrah Hashemi, Joseph Boyle, Nilesh Patel, Michael Verta

Christiana Care Hospital: Daniel Leung – site PI, Marc Garcia – previous site PI, Phillip Blatt, Jamil Khatri, Dave Epstein, Randall Ryan, Tom Sweeny, Michael Stillabower, George Kimbiris, Tuhina Raman, Paul Sierzenski, Lelia Getto, Michael Dignazio, Paul Sierzenski, Mark Horvath

Cleveland Clinic Foundation: Heather Gornik – site PI, John Bartholomew, Mehdi Shishehbor, Frank Peacock, Douglas Joseph, Soo Hyum Kim, Natalia Fendrikova-Mahlay, Daniel Clair, Sean Lyden, Baljendra Kapoor, Gordon McLennon, Gregory Pierce, James Newman, James Spain, Amanjiit Gill, Aaron Hamilton, Anthony Rizzo, Woosup Park

Danbury Hospital: Alan Dietzek – site PI, Ira Galin, Dahlia Plummer, Richard Hsu, Patrick Broderick, Andrew Keller, Sameer Sayeed

Eastern Connecticut Hematology & Oncology Associates: Dennis Slater – site PI, Herb Lustberg, Jan Akus, Robert Sidman, Mandeep Dhami, Phillip Kohanski, Anca Bulgaru, Renuka Dulala, James Burch, Dinesh Kapur, Jie Yang

Florida Hospital: Mark Ranson – site PI, Alan Wladis, David Varnagy, Tarek Mekhail, Robert Winter, Manuel Perez-Izquierdo

Forsyth Medical Center: Stephen Motew – site PI, Robin Royd-Kranis, Raymond Workman, Scott Kribbs, Gerald Hogsette, Phillip Moore, Bradley Thomason, William Means, Richard Bonsall, John Stewart, Daniel Golwya

Gundersen Clinic, Ltd.: Ezana Azene – site PI, Wayne Bottner, William Bishop, Dave Clayton, Lincoln Gundersen, Jody Riherd, Irina Shakhnovich, Kurt Ziegelbein

Georgetown University: Thomas Chang – site PI, Karun Sharma – previous site PI, Sandra Allison, Fil Banovac, Emil Cohen, Brendan Furlong, Craig Kessler, Mike McCullough, Jim Spies

Henry Ford Health System: Judith Lin – site PI, Scott Kaatz, Todd Getzen, Joseph Miller, Scott Schwartz, Loay Kabbani, David McVinnie

Holy Name Medical Center: John Rundback – site PI, Joseph Manno, Richard Schwab, Randolph Cole, Kevin Herman, David Singh, Ravit Barkama, Amish Patel

Jobst Vascular Center: Anthony Comerota – site PI, John Pigott, Andrew Seiwert, Ralph Whalen, Todd Russell, Zakaria Assi, Sahira Kazanjian, Jonathan Yobbagy, Brian Kaminski, Allan Kaufman, Garett Begeman, Robert DiSalle, Subash Thakur

Maine Medical Center: Paul Kim – site PI, Marc Jacquet, Thomas Dykes, Joseph Gerding, Christopher Baker, Mark Debiasto, Derek Mittleider, George Higgins III, Steven Amberson, Roger Pezzuti, Thomas Gallagher PA-C

Massachusetts General Hospital: Robert Schainfeld – site PI, Stephan Wicky – previous site PI, Sanjeeva Kalva, Gregory Walker, Gloria Salazar, Benjamin Pomerantz, Virenda Patel, Christopher Kabrhel, Shams Iqbal, Suvranu Gangull, Rahmi Oklu, Scott Brannan

Mayo Clinic: Sanjay Misra – site PI, Haraldur Bjarnason – previous site PI, Aneel Ashrani, Michael Caccavale, Chad Fleming, **J**eremy Friese, John Heit, Manju Kalra, Thanila Macedo, Robert McBane, Michael McKusick, Andrew Stockland, David Woodrum, Waldemar Wysokinski

Mease Countyside Hospital: Adarsh Verma – site PI, Andrew Davis – previous site PI, Jerry Chung, David Nicker, Brian Anderson, Robert Stein, Michael Weiss

Medical College of Wisconsin/Froedtert Hospital & Clinics: Parag Patel – site PI, William Rilling, Sean Tutton, Robert Hieb, Eric Hohenwalter, M. Riccardo Colella, James Gosset, Sarah White, Brian Lewis, Kellie Brown, Peter Rossi, Gary Seabrook

Medical University of South Carolina: Marcelo Guimaraes – site PI, J. Bayne Selby, William McGary, Christopher Hannegan, Jacob Robison, Thomas Brothers, Bruce Elliott, Nitin Garg, M. Bret Anderson, Renan Uflacker, Claudio Schonholz, Laurence Raney, Charles Greenberg

Oregon Health & Science University: John Kaufman – site PI, Frederick Keller, Kenneth Kolbeck, Gregory Landry, Erica Mitchell, Robert Barton, Thomas DeLoughery, Norman Kalbfleisch, Renee Minjarez, Paul Lakin, Timothy Liem, Gregory Moneta, Khashayar Farsad, Ross Fleischman, Loren French

Pepin Heart Hospital and Dr. Kiran C. Patel Research Institute: Vasco Marques – site PI, Yasir Al-Hassani, Asad Sawar, Frank Taylor

Phoenix Heart & Cardiovascular: Rajul Patel – site PI, Rahul Malhotra – previous site PI, Stanley Kim, Farah Hashemi, Joseph Boyle, Nilesh Patel, Marvin Padnick , Melissa Gurley, Fred Cucher, Ronald Sterrenberg, G. Reshmaal Deepthi, Gomes Cumaranatunge

Riverside Methodist Hospital: Sumit Bhatla – site PI, Darick Jacobs, Eric Dolen, Pablo Gamboa, L. Mark Dean, Thomas Davis, John Lippert, Sanjeev Khanna, Brian Schirf, Jeffrey Silber, Donald Wood, J. Kevin McGraw, Lucy LaPerna, Paul Willette

Rhode Island Hospital: Timothy Murphy – site PI, Joselyn Cerezo, Rajoo Dhangana, Sun Ho Ahn, Gregory Dubel, Richard Haas, Bryan Jay, Ethan Prince, Gregory Soares, James Klinger, Robert Lambiase, Gregory Jay, Robert Tubbs, Michael Beland, Chris Hampson, Ryan O'Hara, Chad Thompson, Michael Beland, Aaron Frodsham, Fenwick Gardiner, Abdel Jaffan, Lawrence Keating, Abdul Zafar

Providence Sacred Heart Medical Center & Children's Hospital: Radica Alicic – site PI, Rodney Raabe – previous site PI, Jayson Brower, David McClellan, Thomas Pellow, Christopher Zylak, Joseph Davis, M. Kathleen Reilly, Kenneth Symington, Camerson Seibold, Ryan Nachreiner, Daniel Murray, Stephen Murray, Sandeep Saha, Gregory Luna

Southern Illinois University: Kim Hodgson – site PI, Robert McLafferty – previous site PI, Douglas Hood, Colleen Moore, David Griffen

St. Elizabeth Healthcare Edgewood (KY): Darren Hurst – site PI, David Lubbers, Daniel Kim, Brent Warren, Jeremy Engel, D. P. Suresh

St. Elizabeth Regional Medical Center (NE): Eric VanderWoude – site co-PI, Rahul Razdan – site co-PI, Mark Hutchins, Terry Rounsborg, Madhu Midathada, Daniel Moravec, Joni Tilford, Daniel Kim, Joni Beckman PA

St. Joseph Hospital: Mahmood Razavi – site PI, Kurt Openshaw, D. Preston Flanigan, Christopher Loh, Howard Dorne, Michael Chan

St. Luke's Hospital and Health Network: Jamie Thomas – site PI, Justin Psaila, Michael Ringold, Jay Fisher, Any Lipcomb, Timothy Oskin

St. Luke's Hospital: Brandt Wible – site PI, Brendan Coleman, David Elliott, Gary Gaddis, C. Doug Cochran

St. Vincent Medical Group: Kannan Natarajan – site PI, Stewart Bick, Jeffrey Cooke, Ann Hedderman, Anne Greist, Lorrie Miller, Brandon Martinez, Vincent Flanders, Mark Underhill

Stanford University Medical Center: Lawrence Hofmann – site PI, Daniel Sze, William Kuo, John Louie, Gloria Hwang, David Hovsepian, Nishita Kothary, Caroline Berube, Donald Schreiber, Brooke Jeffrey

Staten Island University Hospital: Jonathan Schor – site PI, Jonathan Deitch, Kuldeep Singh, Barry Hahn, Brahim Ardolic, Shilip Gupta

Temple University Hospital: Riyaz Bashir – site PI, Angara Koneti Rao, Manish Garg, Pravin Patil, Chad Zack, Gary Cohen, Frank Schmieder, Valdimir Lakhter

The Reading Hospital: David Sacks – site PI, Robert Guay, Mark Scott, Karekin Cunningham, Adam Sigal, Terrence Cescon, Nick Leasure, Thiruvenkatasamy Dhurairaj

TriHealth/Good Samaritan Hospital: Patrick Muck – site PI, Kurt Knochel, Joann Lohr, Jose Barreau, Matthew Recht, Jayapandia Bhaskaran, Ranga Brahmamdam, David Draper, Apurva Mehta, James Maher

University of Iowa: Melhem Sharafuddin – site PI, Steven Lentz, Andrew Nugent, William Sharp, Timothy Kresowik, Rachel Nicholson, Shiliang Sun, Fadi Youness, Luigi Pascarella

University of Illinois- Chicago: Charles Ray – site PI, Martha-Gracia Knuttinen – previous site PI, James Bui, Ron Gaba, Valerie Dobiesz, Ejaz Shamim, Sangeetha Nimmagadda, David Peace, Aarti Zain, Alison Palumto

University of Maryland: Ziv Haskal – site PI, Jon Mark Hirshon, Howard Richard, Avelino Verceles, Jade Wong-You-Chong, Bertrand Othee, Rahul Patel, Bogdan Iliescu

University of Michigan Hospitals and Health Centers: David Williams – site PI, Joseph Gemmete, Venkataramu Krishnamurthy, Wojciech Cwikiel, Kyung Cho, James Schields, Ranjith Vellody, Paula Novelli, Narasimham Dasika, Thomas Wakefield, John Rectenwald, Peter Henke, Jeffrey Desmond, James Froehlich, Minhajuddin Khaja

University of Minnesota: David Hunter – site PI, Jafar Golzarian, Erik Cressman, Yvonne Dotta, Nate Schmiechen

University of New Mexico: John Marek – site PI, David Garcia, Isaac Tawil, Mark Langsfeld

University of North Carolina: Stephan Moll – site PI, Matthew Mauro, Joseph Stavas, Charles Burke, Robert Dixon, Hyeon Yu, Blair Keagy, Kyuny Kim, Raj Kasthuri, Nigel Key

University of Pittsburgh: Rabih Chaer – site PI, Michael Makaroun, Robert Rhee, Jae-Sung Cho, Donald Baril, Luke Marone, Margaret Hseih, Kristian Feterik, Roy Smith, Geetha Jeyabalan, Jennifer Rogers

University of Utah Medical Center: Russel Vinik – site PI, Dan Kinikini, Larry Kraiss, Michelle Mueller, Robert Pendleton, Matthew Rondina, Mark Sarfati, Nathan Wanner, Stacy Johnson, Christy Hopkins, Daniel Ihnat

University of Virginia Health System: John Angle – site PI, Alan Matsumoto, Nancy Harthun, Ulku Turba, Wael Saad, Brian Uthlaut, Srikant Nannapaneni, David Ling, Saher Sabri, John Kern, B. Gail Macik, George Hoke, Auh Wahn Park, James Stone, Benjamin Sneed, Scott Syverud, Kelly Davidson, Aditya Sharma, Ziv Haskal, Luke Wilkins

Utah Valley Reginal Medical Center: Carl Black – site PI, Mark Asay, Daniel Hatch, Robert Smilanich, Craig Patten, S. Douglas Brown, Ryan Nielsen, William Alward, John Collins, Matthew Nokes

Wake Forest Baptist Health: Randolph Geary – site PI, Matthew Edwards, Christopher Godshall, Pavel Levy

Weill Cornell Medical College: Ronald Winokur – site PI, Akhilesh Sista – previous site PI, David Madoff, Kyungmouk Lee, Bradley Pua, Maria DeSancho, Raffaele Milizia, Jing Gao

Western Penn Allegheny Health System: Swapna Goday – site PI, Margaret Kennedy – previous site PI, Robert Kaplan, Thomas Campbell, Gordon McLean, Jamie Hartman, Elmer Nahum, Sanualah Khalid

Washington University in St. Louis: Suresh Vedantham – site PI, Larry Lewis, Nael Saad, Mark Thoelke, Robert Pallow, Seth Klein, Gregorio Sicard

ATTRACT Clinical Centers: Study Staff

Adventist Hospital: Kathleen Mansell, Kristen Koridek-Phillips, Elizabeth Cummings

Albert Einstein: Jenna Wald, Angelica Rugege, Alyssa Buggy, Alyson Singer. Ashley Smith

Allegheny General: Sue Ann Livingston, Sandra Brown, Holly Strausser, Rich Wonder

Ann Arbor VA Medical Center: Mary Burton, Carmela Lee, Eric Henricks

Baptist Cardiac and Vascular Institute: Susan Arp, Claudia Hodgson, Maria Ardid

Central DuPage: Stefanie Miller, Sarah Lidtke, Sarah Madia, Shanda Pool-Schneider

Christiana Care Health Systems: Angela DiSabatino, Catherine Wade, Jacqueline Huntley, Andrea Squire, Jacqueline Laucirica, Nancy Huebner, Krista Brazell, Desiree Hodges. Neanall Wells, Ann Marie LeNoir

Cleveland Clinic: Jackie McCluskey, Susan Hejl, Linda Kerchenski

Cornell: Jamie Stern, Miriam Abu, Ame Ng, Angela Hoang

CorVasc: Patrice Powell, Jamie Weidner, Nicole Toole, Daphne Johnson, Sara Gallagher, K Slopsema, Holly Spaulding

Danbury Hospital: Suzanne House, Judith Nagey, Laurie Noreika, Jo-Ann Russell, Zachary Gortler, Phyllis Brand

Eastern Connecticut Hematology and Oncology Assoc: Susan Johnson, Nancy Wilcox, Robin Millis

Florida Hospital: Sandra Houser, Virginia Cimas, Beverly Mansker, Delores Barnes, LeAnn Goodwin, Kim Mink, Kelly Behm

Forsyth Medical Center: Yvonne Whitley, Brian Coleman, Keishia Rodriguez, Jennifer Short,

Wendy Hobbs, Eugina Hutchinson

Georgetown University Hospital: Kimiknu Mentore, Maggie Infeld, Anna Argyris, Meredith Preziosi

Good Samaritan Hospital: Susan Reilly, Lori Reid, Carol Krabbe, Angela Hein, Aline Summe, Marien Bryson, Chris Scheuerman, Mary Lynn Hotel

Gundersen Clinic: Tracey Coleman, Ashley Quinnell, Sara Meyers, Vanessa Grams

Henry Ford: Crystal Bradley, Theresa Bailey, Chiquita Whitfield, Bonita Braxton, Andrei Rus, Sheryl Cummings

Holy Name Medical Center: Yitzchak David, Jennifer Leto, Shraddha Agarwal, Noman Majeed

Jobst Vascular: Regina Zoller, Susan Shuman, Joan Bick, Angela Link, Janeen Przysiecki-Hume, Linda Andrews, Kendra Mann

Maine Medical Center: Renee Daigle, Debra Burris

Massachusetts General Hospital: Connie Crittenden, Nuralima Grandison, Abdulah Hanifi, Deb O'Shaughnessy

Mayo Clinic: Connie Sathre, Shirley Johnson, Tiffany Macedo, Sandra Everson, Mary Jondal

Mease Countryside Hospital: Adrienne Turner, Teresa Jones, Danielle Ebers

Medical University of South Carolina: Tina Cooper, Debra Nelson, Corie Lynn

Oregon Health and Sciences University: Lori Watson

Pepin Heart Hospital: Juliet Bala, Elizabeth Szymanski, Gayle Coyle, Marjorie Posey J Dayton, Jesicca Norcihi, Gloria Stagi Coyle, Jadie Dayton, Diane Bashton

Phoenix Heart: Bijal Dave, Ashley Cunningham, Yvette Binns

The Reading Hospital: Brian Couch, Crystal Nagle, Caitlin Cammarano, Julie Sheidy, Catherine Gery, Natasha Peifer-Soder, Susan Swonger, Heather Close, Elizabeth Marks, Cynthia Stuhmeier

Rhode Island Hospital: Gait Jordan, Gregory McEnteggart, Joselyn Cerezo, Gregory Soares, Muhammad Naeem, Efaza Siddiqui

Riverside Methodist Hospital: Mindie Taylor, Cheryl Crabtree, William Metz, Teri Campbell, Jennifer Mull

Sacred Heart: Ruthie Franks, Beth Aaron, Truman Cantrell

St. Elizabeth Healthcare: Michelle Parker, Cynthia Mulcahy, Brian Burkhardt

St. Elizabeth Nebraska: Paul Edwards, Elizabeth Czirr

St. Luke's Hospital and Health Network: Denise Tarsi, Rosemarie Cabral, Eileen Taff, Marcie Taff, Katie Anderson, Ghada Suleian

St. Luke's of Kansas City: Mindy Epstein, Lisa Strand

St. Joseph Hospital: Gemma Miralles, Sandy Chung, Robin Uthus

Stanford University Medical Center: Risa Jiron, Krithika Rupnarayan, Fizaa Ahmed, Alison Holzer, Arjun Banerjee, Kamil Unver, Archana Verma

Staten Island: Gabriella Taflin, Maria Scibilia, Anne Giamar Noble

Southern Illinois University: Carol Buettner, Tiffany Whitaker, Amy Skeeters

Temple University: Jennie Wong, Francine McGonagle

University of Illinois at Chicago: Peggy Pocius, Alejandro Mercado

University of Iowa: Judith Pena-Quevedo, Tracy Peters, Lori Stout, Constance Shelsky, Emily Avgenackis, Maria Ana Canaya-Voskov

University of Maryland: Abigail Quish

University of Michigan: LaDonna Austin, Mary Burton

University of Minnesota: Karen Kowalik

University of New Mexico: Hadya Khawaja, Michele Spear, Lyra Sandre, Ericka Mardonado, Erika Griffith, Jacqueline Torrez, Mar Gallegos, Sarah Sanders, Jonathan Aregon, Cheri Wells

University of North Carolina: Cheryl Jeanneret, Karen Smith, Kavita Gupta, Shannon Yonkers, Will Simmons, Marcus Layer

University of Pittsburgh: Judith Brimmeier, Patricia Dragone, Susan Tamburro, Kevin Stiegler, Dana Lowers

University of Utah: Maria Maloney, Sara Mesley

University of Virginia Health Systems: Katie Rea, Doug Spauling, Diana Farrell, Kimberly Gahring, Jennifer Phillips, Sandra Burks, Brigitte Kelly, Carie Dallinger

Utah Valley Regional Medical Center: Shauna Hill, Diana Lloyd

Wake Forest: Rob Paris

Western Penn: Rich Wonder, Jean Goy, Bina Militello, Sandy Brown, Lori Stover, Chris Back, Helen Andreko

Inclusion and Exclusion Criteria

Inclusion Criterion

Symptomatic proximal DVT involving the iliac, common femoral, and/or femoral vein.

Exclusion Criteria

Subjects meeting any of these criteria will be excluded (all times are relative to screening date):

1. Age less than 16 years or greater than 75 years.
2. Symptom duration > 14 days for the DVT episode in the index leg (i.e. non-acute DVT).
3. In the index leg: established PTS, or previous symptomatic DVT within the last 2 years.
4. In the contralateral (non-index) leg: symptomatic acute DVT a) involving the iliac and/or common femoral vein; or b) for which thrombolysis is planned as part of initial therapy.
5. Limb-threatening circulatory compromise.
6. PE with hemodynamic compromise (i.e. hypotension).
7. Inability to tolerate PCDT procedure due to severe dyspnea or acute systemic illness.
8. Allergy, hypersensitivity, or thrombocytopenia from heparin, rt-PA, or iodinated contrast, except for mild-moderate contrast allergies for which steroid pre-medication can be used.
9. Hemoglobin < 9.0 mg/dl, INR > 1.6 before warfarin was started, or platelets < 100,000 /ml.
10. Moderate renal impairment in diabetic patients (estimated GFR < 60 ml/min) or severe renal impairment in non-diabetic patients (estimated GFR < 30 ml/min).
11. Active bleeding, recent (< 3 months) GI bleeding, severe liver dysfunction, bleeding diathesis.
12. Recent (< 3 months) internal eye surgery or hemorrhagic retinopathy; recent (< 10 days) major surgery, cataract surgery, trauma, CPR, obstetrical delivery, or other invasive procedure.
13. History of stroke or intracranial/intraspinal bleed, tumor, vascular malformation, aneurysm.
14. Active cancer (metastatic, progressive, or treated within the last 6 months). Exception: patients with non-melanoma primary skin cancers are eligible to participate in the study.
15. Severe hypertension on repeated readings (systolic > 180mmHg or diastolic > 105 mmHg).
16. Pregnant (positive pregnancy test, women of childbearing potential must be tested).
17. Recently (<1 month) had thrombolysis or is participating in another investigational drug study.
18. Use of a thienopryridine antiplatelet drug (except clopidogrel) in the last 5 days.
19. Life expectancy < 2 years or chronic non-ambulatory status.
20. Inability to provide informed consent or to comply with study assessments (e.g. due to cognitive impairment or geographic distance).

Details of PCDT Methods

In the ATTRACT Trial, PCDT was performed consistent with published guidelines by board-certified physicians whose credentials were approved by study leadership, as follows:

Phase 1 **Procedure Initiation:** Conscious sedation, local anesthesia, and strict sterile technique were used. Catheter access to the deep venous system (any lower extremity vein or internal jugular vein, per physician choice) was obtained with use of real-time ultrasound guidance (this was required), and the anatomic extent of the thrombus was defined via venography through a diagnostic catheter.

Phase 2 **Initial PCDT** involved the initial intrathrombus delivery and dispersion of recombinant tissue plasminogen activator (rt-PA) (alteplase, Activase®, Genentech, South San Francisco) through an FDA-approved device/catheter, by one of three methods. If the popliteal vein was occluded or the IVC was involved, physicians were required to use "infusion-first PCDT" which started with rt-PA infusion through a multi-sidehole catheter of the physician's choice for ≤ 30 hours. For the remaining patients, physicians were required to attempt single-session thrombus removal with rapid delivery of rt-PA through the AngioJet Rheolytic Thrombectomy System (Boston Scientific, Malborough, MA) or the Trellis Peripheral Infusion System (Covidien, Inc., Mansfield, MA [now Medtronic]). Each clinical center chose the single-session thrombus removal method it would use before starting the study. If complete thrombus removal was not achieved in a single session, rt-PA could be infused afterwards for up to 24 hours through a multi-sidehole catheter.

Required rt-PA dosing parameters were: (1) for infusions, 0.01 mg/kg/hr, maximum 1.0 mg/hr; (2) for AngioJet/Trellis delivery during single-session therapy, initial dose range 0.25 – 0.33 mg/cm thrombus length (estimated from the initial venogram), minimum 4 mg; (3) ≤25 mg during first session; (4) ≤5 mg during each follow-up session; and (5) ≤35 mg for all sessions and infusions combined. During PCDT, the physician could reduce the rt-PA dose or stop it entirely at his/her discretion if there were safety concerns. If serious bleeding occurred at the venous access site (uncontrolled by sheath upsizing or compression), rt-PA administration was stopped. If sheath upsizing and/or compression were effective in stopping the bleeding, rt-PA could be later re-started at a lower dose. If serious bleeding occurred in a distant location, or if a severe or life-threatening reaction occurred, administration of rt-PA were permanently stopped.

The INR had to be ≤ 1.6 at the start of PCDT. During PCDT, patients received twice daily subcutaneous low molecular weight heparin in therapeutic doses or unfractionated heparin infusions (reduced to 6-12 units/kg/hr [maximum 1000 units/hr] during rt-PA infusions). Additional on-table heparin boluses (up to 50 units/kg) were given at physician discretion.

After Initial PCDT, the measures that must be taken to achieve an open vein and prevent immediate re-thrombosis depend upon the amount and location of residual thrombus and/or venous stenosis, which vary widely among subjects. Hence, for Phases 3 and 4, investigators

were allowed the flexibility to tailor adjunctive therapy, aimed at eliminating residual thrombus and/or venous stenosis, to individual patient circumstances, pursuant to certain guidelines.

Phase 3 **Clean-Up of Residual Thrombus:** After initial PCDT (any method), physicians could use balloon maceration, catheter aspiration, AngioJet or Trellis thrombectomy, and/or additional rt-PA to clear residual thrombus.

Phase 4 **Treatment of Obstructive Lesions:** Stenting was encouraged for lesions in the iliac and/or common femoral vein with ≥ 50% diameter narrowing, robust collateral filling, and/or mean pressure gradient > 2 mmHg. Percutaneous transluminal balloon angioplasty was utilized to treat obstructive lesions in the femoral vein.

Phase 5 **Completion of PCDT Procedures:** Treatment was discontinued when there was ≥ 90% thrombus removal with restoration of flow, or a serious complication. When therapy was completed, the sheath could be removed at the physician's discretion, but no less than 1 hour after the last rt-PA dose or UFH bolus dose was given. Hemostasis was achieved via manual compression. The subject was to remain at bedrest with the treated leg immobile for 6 hours, after which he/she could ambulate as tolerated. Therapeutic-level anticoagulation was resumed within 2 hours after hemostasis was obtained. If UFH was used, a bolus dose was not given. Subjects receiving LMWH continued their previous regimen of scheduled injections. Warfarin was initiated on the same day as sheath removal. Warfarin intensity, duration of therapy, INR monitoring, overlap with heparin therapy, and hospital discharge were managed in the same way as in the Control Arm. However, PCDT subjects could not be discharged from the hospital until at least 12 hours after sheath removal.

Efficacy Outcome Measures

Post-Thrombotic Syndrome (PTS)

Villalta PTS Scale

The primary measure used to assess PTS in the ATTRACT Trial was the Villalta PTS Scale (1,2). The Villalta PTS Scale scores the severity of 5 patient-reported symptoms (pain, cramps, heaviness, paresthesia, pruritus) and 6 clinician-observed signs (pretibial edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression) of PTS on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe) for each leg. Clinical personnel performing the Villalta PTS signs assessment were blinded to subject treatment allocation.

For the assessment of PTS, the Villalta Scale was administered at 6, 12, 18, and 24 months post-randomization. The points for each of the 11 items were summed into a **PTS Total Score** ranging from 0 to 33 for each leg (higher is worse). If the assessor determined that the patient had a venous leg ulcer and the summed score was less than 15, a score of 15 was assigned.

The study's **primary outcome** was the presence of PTS, defined as a PTS Total Score of 5 or greater on the Villalta Scale in the leg with the index DVT, or an ulcer in that leg, at any time between the 6-month post randomization follow-up visit and the 24-month visit (inclusive). Patients were also counted as having PTS if they underwent an unplanned endovascular intervention (PCDT or another intervention) for the treatment of severe symptomatic venous disease in the index leg more than 6 months after randomization, and either a) they had a total score of 5 or more on the Villalta PTS Scale that was performed immediately preceding that intervention, or an ulcer; or b) the Villalta PTS Scale was not performed at that time.

The PTS Total Score was also reported for each of the above visits. For the assessment of PTS severity at each visit, the PTS Total Score was analyzed as a continuous variable. Finally, the PTS Total Score was also used to categorize subjects as having mild (score 5-9), moderate (score 10-14), or severe PTS (score ≥15) at each assessment (**PTS Class**). This categorization was subsequently used to derive the proportion of patients who had moderate or severe PTS.

Venous Clinical Severity Score (VCSS)

The VCSS was used as another measure of PTS severity. The VCSS is a venous severity scoring system, derived from selected elements of the CEAP (Clinical-Anatomic-Etiologic-Pathophysiologic) Classification system (3). The VCSS scores 8 clinical signs (varicose veins, venous edema, skin pigmentation, inflammation, induration, and number, duration and size of active ulcers) and one symptom (pain) of chronic venous disease on a 4-point scale (0=absent, 1=mild, moderate=2, severe=3) (4-6). The **VCSS Score** is the sum of these 9 ratings, and ranges from 0 to 27 (higher is worse). A tenth item that grades the extent of use of compression therapy is present in the VCSS and is sometimes used; however, since use of compression stockings was standardized in ATTRACT, the study excluded that item. Clinical personnel performing the Villalta PTS signs assessment were blinded to subject treatment allocation.

Administration of PTS Measures

Villalta's PTS Scale and the VCSS were administered to subjects at the 6, 12, 18, and 24 month

follow-up visits in uniform fashion across all centers. Prior to initial use, clinical assessors were required to complete a web-based training module on the proper administration. Standardization of clinical signs assessment was aided by distribution to the centers of a) a full color, plasticized graphic visual aid depicting the Villalta clinical signs; and b) published tables and descriptions that instruct examiners on how to grade the VCSS clinical signs. Examiners were blinded to treatment allocation. Patients were instructed to not wear their compression stockings that day and, when possible, were examined in the afternoon to allow PTS symptoms and signs to manifest. Patients were also instructed not to inform study staff which leg their DVT occurred in.

The patient was unclothed to mid-thigh level and was seated facing the examiner in a well-lit room. The patient first rated the presence and severity (mild, moderate, severe), in each leg (right then left), of the 5 PTS symptoms, and completed the Symptoms part of the PTS Form. Subsequently, and without access to the patient's rating of symptoms, the examiner assessed the clinical signs required for the Villalta and VCSS measures. The examiner completed the Clinical Signs part of the PTS Form and the VCSS Form, and then checked all completed forms to ensure that they were filled out correctly, to minimize the occurrence of missing data.

Health-Related Quality of Life

Venous Disease-Specific Quality of Life

Venous disease-specific quality of life (QOL) was measured using the VEINES instrument, a patient self-assessment questionnaire. It consists of 25 question items that measure venous symptoms, limitations in daily activities due to venous disease, psychological impact of venous disease, and change over the past year (7,8). Responses are rated on 2-point to 7-point Likert scales of intensity, frequency, or agreement. Scoring utilized established computer algorithms which include imputation of missing data. The **VEINES/QOL** summary score (normalized to the study cohort; 0-100 scale; mean=50; SD=10) was calculated based on all 25 questions.

Generic Quality of Life

Generic QOL was measured using the Short Form-36 Health Survey, Version 2 (**SF-36**v2), a validated, widely-used gold standard instrument (9). For the SF-36, summary scores (normalized to the US population; 0-100 scale; mean=50, standard deviation=10) were computed for the Physical (**PCS**) and Mental (**MCS**) Component Summary Scales.

Administration of QOL Measures

The SF-36 and VEINES measures were combined into a single 5-page questionnaire that takes 15-20 minutes for an average patient to complete. Following a standardized orientation, the patient completed the QOL questionnaire in a quiet office. When he/she was finished, the study team member checked for missing data and politely encouraged the patient to respond to all items. The measures were scored by using established computer-programmed scoring algorithms which include an algorithm for imputing missing data (10,11).

Treatment Failures that are Not PTS

A **major non-PTS treatment failure** was defined as an event meeting one or more of the following criteria during the 24 months post randomization:

(1) the patient underwent an unplanned endovascular or surgical intervention for the treatment of severe symptomatic venous disease in the index leg within the first 6 months after randomization, excluding a) PCDT Arm patients who underwent repeat PCDT within the first 3 months after randomization (considered part of randomized therapy), and b) Control Arm patients whose intervention occurred within 7 days after randomization and was performed for reasons other than acute limb threat (considered non-adherence to randomized therapy);

(2) the subject underwent an amputation in the index leg anytime within 24 months after randomization; or

(3) the subject developed venous gangrene in the index leg within the first 6 months after randomization.

Patients who either developed PTS or experienced a major non-PTS treatment failure within 24 months were counted as having a composite treatment failure ("any treatment failure")

Presenting DVT Symptoms

Leg Pain Severity

The severity of pain in each leg was assessed on a 7-point Likert scale at baseline and 10-day and 1-month follow-up (12). The patient was asked to "Please rate the overall intensity of "pain" or "discomfort" that you have felt in your leg during the past 24 hours by checking one response on the following scale" (1=No pain, 2=Very mild pain, 3=Mild pain, 4=Moderate pain, 5=Severe pain, 6=Very severe pain, 7=Extremely severe pain). That is, **Leg Pain Severity** was measured on a 1 to 7 scale (higher being worse).

Leg Swelling

At baseline, 10 days and 1 month follow-up, blinded clinicians assessed **Leg Swelling** by measuring calf circumference (in centimeters) at 10 cm below the tibial tuberosity in both legs.

Degree of Resolution of Thrombus with PCDT

Two sets of venograms were analyzed in each PCDT Arm subject: (a) the baseline venogram of the proximal veins (popliteal vein through infrarenal IVC) obtained after initial catheter insertion into the venous system and before PCDT; and (b) the final venogram of the proximal veins obtained after PCDT and any adjunctive procedures, and before sheath removal. Blinded physicians experienced with venogram adjudication in DVT trials, in standardized fashion and with the aid of a customized form showing a diagram of the deep veins of the leg, quantified clot burden using the elements of the Marder score (13) that describe the proximal veins (popliteal vein = 4; femoral vein = 10; common femoral vein = 4; iliac vein = 6; yielding a total score range 0-24, with 0 representing no thrombus and 24 representing complete thrombosis). The degree of thrombus elimination (% change in pre-PCDT and post-PCDT Marder score) was calculated.

Safety Outcome Measures

Bleeding

At the clinical centers, evaluation of clinically overt bleeding was targeted to the suspected bleeding site (e.g., head CT scan for suspected intracranial bleeding). Clinically overt bleeding was classified as "**major**" if it was associated with a fall in the hemoglobin level of at least 2.0 g/dl, transfusion of ≥ 2 units of red blood cells, or involvement of a critical site (e.g., intracranial, intraspinal) (14). Less severe clinically overt bleeding was classified as "**minor**". To distinguish clinically important hemorrhage from hemoglobinuria (which is routinely observed in subjects undergoing mechanical thrombectomy), discoloration of the urine during or after mechanical thrombectomy was not by itself considered to indicate the presence of clinically-overt bleeding. Major bleeding, minor bleeding, need for transfusion, and intracranial bleeding were assessed throughout the study period and reported from baseline to 10 days and 24 months.

Symptomatic Pulmonary Embolism (PE)

When PE was clinically suspected at a clinical center, spiral CT of the pulmonary arteries and/or ventilation-perfusion lung scan was obtained. If there was a new intraluminal filling defect of a segmental or more central pulmonary artery or a "high probability" perfusion defect, PE was diagnosed. PE was excluded if the spiral CT was normal or there were no perfusion defects. If the perfusion scan or CT scan was non-diagnostic, bilateral lower extremity ultrasound was performed and PE was diagnosed if there was new DVT (see next section). Ultrasound could be repeated after 7 ± 2 days if there was no new DVT. Pulmonary angiography could be performed if there were equivocal findings or serial ultrasound was considered unsafe – PE was diagnosed if there was a new intraluminal filling defect in a segmental or more central pulmonary artery.

Symptomatic Recurrent DVT

To increase the accuracy of diagnosing recurrent DVT, there was standardized recording of the extent of thrombus (diameters of the common femoral vein and popliteal vein and the thrombus' proximal and distal extent) on the baseline (strongly recommended when the exam was performed locally) and 1-month follow-up (required) ultrasound exams. When recurrent DVT was suspected during follow-up, compression ultrasound of the proximal veins (popliteal vein to common femoral vein) was performed. If a non-compressible proximal vein segment was seen and there was no DVT on the last ultrasound (or venogram) of the same leg, recurrent DVT was diagnosed. If a previous ultrasound or a follow-up venogram was available for comparison, recurrent DVT was diagnosed if one of the following criteria was met: (a) there was a new non-compressible common femoral, femoral, or popliteal vein; (b) there was ≥ 10 cm extension of thrombus margin (transition from not fully compressible to normal); or (c) there was a 4-mm increase in compressed thrombus diameter at the common femoral or popliteal vein (15-18).

If these criteria were not met, DVT was not diagnosed. If there was still uncertainty about the presence of recurrent DVT, the ultrasound could be repeated after 7 ± 2 days, and judged by the same criteria. If the second test was not diagnostic for recurrence, DVT was excluded. Venography or CT scan could be performed if, in the absence of diagnostic findings, clinical suspicion for recurrence was high or the ultrasound findings were equivocal.

Death

Cause of death was determined from medical records, autopsy data, and other information. Death was attributed to PE if unexplained and sudden or there was substantive supporting evidence. Deaths were reported throughout, and summarized at 10 day and 24 months.

Safety Outcome Event Adjudication

Data on suspected clinical events was reviewed by two blinded adjudicators who were expert clinicians with extensive experience in adjudicating clinical events for DVT trials, with use of an adjudication manual, and without knowledge of treatment allocation. If there was disagreement, a second adjudication occurred with three adjudicators to obtain consensus. If consensus was not obtained, two votes were sufficient to adjudicate the outcome. To further blind the adjudicators, unknown to them suspected events from ATTRACT were interspersed with suspected events from other studies being adjudicated at the data coordinating center.

Missed PTS Assessments and Sensitivity Analysis

If patients with missed assessments (due to death, failure to attend visits, administrative errors, refusals, withdrawal of consent) never had a Villalta score above 4 during the 6- to 24-month follow-up, they were assumed to not have developed PTS.

A sensitivity analysis of the primary efficacy outcome was performed where the missed assessments were addressed using multiple imputation (MI) under the missing-at-random assumption. The imputations were performed separately for each treatment arm. Twenty datasets with imputed data were generated using SAS Proc MI with the FCS (fully conditional specification) method. The following baseline variables were used in the imputation: age, sex, body-mass index, DVT extent, and the Villalta score at baseline. In addition, we used post-baseline Villalta scores (at 10 days, 30 days, and the maximum score observed between 6 months and 24 months) in the imputation. If any of these post-baseline scores were missing, they were also imputed based on the earlier scores using the predictive mean matching (PMM) method. Finally, the primary outcome of PTS (a binary outcome) was imputed using logistic regression with all of the auxiliary variables as covariates. At the final stage, the CMH adjusted analysis was run 20 times, and the resulting 20 log RRs and covariance estimators were averaged and then anti-logged to produce a summary estimate. SAS Proc MIANALYZE was used to combine the results. **See Table S4.**

The issue of deaths during follow-up was also addressed in the sensitivity analysis. Of the 15 deaths, 7 had experienced PTS prior to death (i.e. Villalta scores ≥ 5). The other 8 who died (3 PCDT, 5 Control) were “eligible” for imputation of a PTS outcome. When included in the imputation, the result was RR=0.89, 95% CI 0.77 to 1.02. If they were excluded from the imputation, the result did not change (RR=0.89, 95% CI 0.78 to 1.02).

Figure S1: Forest Plots of PTS within Subgroups

Baseline Factor	Subgroup	PCDT vs Control	P Interaction
Age	< 65	123/278 vs 144/292	0.038
	65+	34/58 vs 27/63	
Sex	Female	61/131 vs 60/134	0.51
	Male	96/205 vs 111/221	
Ethnicity	Hispanic	10/15 vs 13/26	0.26
	Non-Hispanic	147/321 vs 158/329	
Race	African American	25/61 vs 32/62	0.25
	White	126/266 vs 132/276	
	Other	6/9 vs 7/17	
BMI	< 25	19/50 vs 27/65	0.59
	25-29	36/101 vs 44/105	
	≥30	102/193 vs 98/181	
Leg Symptom Duration	< 1 week	82/184 vs 88/178	0.34
	≥1 week	75/152 vs 83/177	
DVT Extent	Iliofemoral	96/196 vs 100/195	0.85
	Femoropopliteal	61/140 vs 71/160	
Previous DVT	Ipsilateral	1/5 vs 8/14	0.14
	Other	156/331 vs 163/341	
Side of DVT	Left	97/207 vs 103/218	0.73
	Right	60/129 vs 68/137	
Major risk factor < 6 weeks	Yes	16/42 vs 31/59	0.17
	No	141/294 vs 140/296	
Villalta severity score	0-4	15/57 vs 22/69	0.068
	5-9	57/115 vs 50/124	
	10-14	48/98 vs 50/94	
	≥15	37/66 vs 49/66	

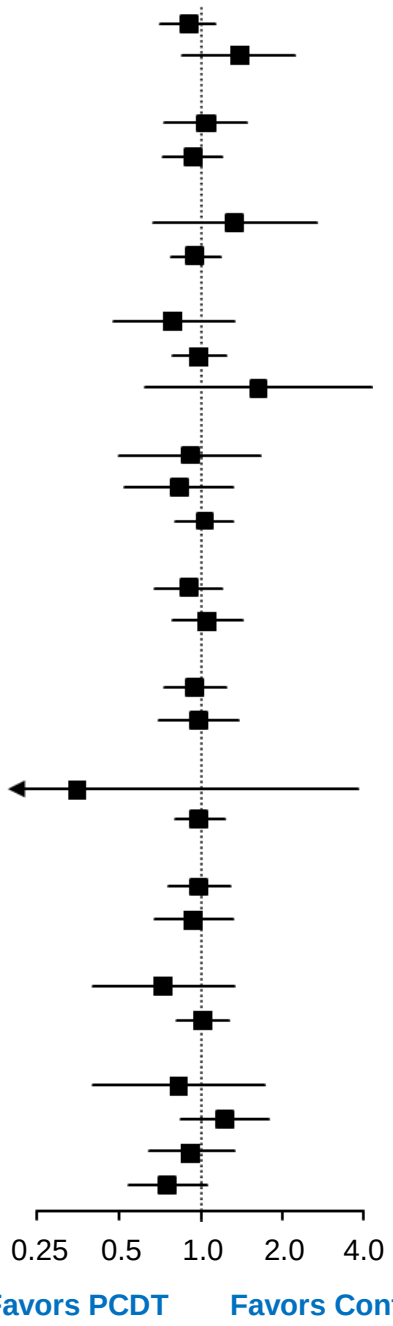

Table S1: Exclusion Criteria - Observed %

Exclusion #	Reason for Exclusion*	%
1	Age < 16 years, or Age > 75 years	**31%**
14	Active cancer…	**24%**
2	Symptom duration > 14 days…	**15%**
3	Index leg: established PTS…	**15%**
9	Hemoglobin < 9.0 mg/dl, INR > 1.6 before…	**14%**
20	Inability to provide informed consent…	**14%**
12	Recent (< 3m) internal eye surgery…	**12%**
13	History of stroke or intracranial/intraspinal bleed…	**11%**
10	Moderate renal impairment in diabetic patients…	**10%**
7	Inability to tolerate PCDT procedure due to…	**7%**
11	Active bleeding, recent (< 3m) GI bleeding…	**7%**
4	Contralateral leg: symptomatic acute DVT…	**5%**
19	Life expectancy < 2 years…	**5%**
6	PE with hemodynamic compromise…	**3%**
17	Recently (<1m) had thrombolysis…	**2%**
5	Limb-threatening circulatory compromise…	**1%**
8	Allergy, hypersensitivity, or thrombocytopenia…	**1%**
15	Severe hypertension…	**1%**
16	Pregnant…	**1%**
18	Use of a thienopryridine antiplatelet drug…	**1%**
16	Pregnant…	**<1%**

* Patients may fall into more than one category

Table S2: Baseline Characteristics by Treatment Group

Characteristic	PCDT n = 336	Control n = 355	Total N = 691
Age at Enrollment, years**:**			
mean (SD)	51 (14)	51 (13)	51 (13)
min, Q1, median, Q3, max	16, 41, 52, 62, 75	17, 43, 53, 62, 75	16, 42, 53, 62, 75
Age Group: *n (%)*			
< 45	109 (32)	95 (27)	204 (30)
45 – 54	79 (24)	92 (26)	171 (25)
55 – 64	90 (27)	104 (29)	194 (28)
65 – 75	58 (17)	63 (18)	121 (17)
Sex: *n (%)*			
Female	131 (39)	134 (38)	265 (38)
Male	205 (61)	221 (62)	426 (62)
Ethnicity: *n (%)*			
Hispanic/Latino	15 (4)	26 (7)	41 (6)
Not Hispanic/Latino	310 (92)	319 (90)	629 (91)
Not reported or refused	11 (3)	10 (3)	21 (3)
Race: *n (%)*			
American Indian/Alaska Native	1 (<1)	3 (1)	4 (1)
Asian	1 (<1)	4 (1)	5 (1)
Black/African-American	61 (18)	62 (17)	123 (18)
Native Hawaiian/Other Pacific Islander	0	0	0
White	265 (79)	276 (78)	541 (78)
Not reported or refused	8 (2)	10 (3)	18 (3)
Employment Status: *n (%)*			
Employed 35 or more hours/week	156 (46)	168 (47)	324 (47)
Employed < 35 hours/week	33 (10)	34 (10)	67 (10)
Homemaker/housewife	8 (2)	7 (2)	15 (2)
Not employed, disabled	36 (11)	39 (11)	75 (11)
Not employed, retired or other reason	103 (31)	105 (30)	208 (30)
Unknown	0	2 (1)	2 (<1)

Table S2: Baseline Characteristics by Treatment Group

Characteristic	PCDT n = 336	Control n = 355	Total N = 691
Medical History: *n (%)**			
Hypertension	143 (43)	139 (39)	282 (41)
Diabetes	59 (18)	54 (15)	113 (16)
High Cholesterol	97 (29)	105 (30)	202 (29)
Asthma	36 (11)	38 (11)	74 (11)
COPD	9 (3)	15 (4)	24 (3)
Angina/MI	13 (4)	15 (4)	28 (4)
Congestive Heart Failure	13 (4)	19 (5)	32 (5)
Other active conditions	197 (59)	207 (58)	404 (58)
Height, cm**:**			
mean (SD)	174 (11)	174 (10)	174 (11)
min, Q1, median, Q3, max	150, 165, 173, 183, 218	147, 168, 175, 183, 201	147, 165, 175, 183, 218
Weight, kg**:**			
mean (SD)	97 (25)	96 (24)	97 (24)
min, Q1, median, Q3, max	52, 81, 95, 111, 200	47, 79, 92, 110, 179	47, 80, 93, 110, 200
BMI, kg/m^2**:**			
mean (SD)	32 (7.5)	31 (7.7)	32 (7.6)
min, Q1, median, Q3, max	18, 27, 31, 36, 60	15, 26, 30, 35, 68	15, 27, 31, 35, 68
BMI Class: *n (%)*			
< 25 kg/m^2	50 (15)	65 (18)	115 (17)
25 to < 30 kg/m^2	103 (31)	105 (30)	208 (30)
≥ 30 kg/m^2	183 (54)	181 (51)	364 (53)
Unknown	0	4 (1)	4 (1)
Systolic blood pressure, mmHg**:**			
mean (SD)	128 (16)	128 (16)	128 (16)
min, Q1, median, Q3, max	92, 117, 128, 140, 178	90, 117, 127, 138, 194	90, 117, 127, 139, 194
Diastolic blood pressure, mmHg**:**			
mean (SD)	76 (11)	76 (11)	76 (11)
min, Q1, median, Q3, max	48, 69, 76, 83, 101	45, 69, 76, 82, 104	45, 69, 76, 83, 104
Symptom severity (Villalta) class: *n (%)*			
None (score 0-4)	57 (17)	69 (19)	126 (18)
Mild (score 5-9)	115 (34)	124 (35)	239 (35)
Moderate (score 10-14)	98 (29)	94 (26)	192 (28)
Severe (score ≥ 15)	66 (20)	66 (19)	132 (19)
Unknown	0	2 (<1)	2 (<1)

Table S2: Baseline Characteristics by Treatment Group

Characteristic	PCDT n = 336	Control n = 355	Total N = 691
Qualifying Episode of DVT:			
Side of Index DVT: *n (%)*			
Left	207 (62)	218 (61)	425 (62)
Right	129 (38)	137 (39)	266 (38)
Common Femoral ± iliac vein: *n (%)*	196 (58)	195 (55)	391 (57)
Previous DVT and/or PE	**83 (25)**	**87 (25)**	**170 (25)**
Previous DVT: *n (%)*	75 (90)	84 (97)	159 (94)
Ipsilateral leg	3 (4)	13 (15)	16 (10)
Contralateral leg	37 (49)	40 (48)	77 (48)
Ipsilateral + Contralateral	2 (3)	1 (1)	3 (2)
None	33 (40)	30 (36)	63 (40)
No. of Previous DVT episodes: *mean (SD)* *min, Q1, median, Q3, max*	 1.3 (0.7) 1, 1, 1, 1, 5	 1.5 (1.5) 1, 1, 1, 2, 13	 1.4 (1.2) 1, 1, 1, 1, 13
Previous PE: *n (%)*	21 (25)	16 (18)	37 (22)
No. of Previous PE episodes: *mean (SD)* *min, Q1, median, Q3, max*	 1.0 (0.2) 1, 1, 1, 1, 2	 1.9 (3.0) 1, 1, 1, 1, 13	 1.4 (2.0) 1, 1, 1, 1, 13
DVT diagnosis within 6 weeks: *n (%)****			
Major Surgery	27 (8)	34 (10)	61 (9)
Hospitalization	26 (8)	38 (11)	64 (9)
Plaster cast immobilization	8 (2)	9 (3)	17 (2)
Childbirth	3 (1)	5 (1)	8 (1)
Outpatient: *n (%)*	268 (80)	300 (85)	568 (82)
Days from start of symptoms of qualifying DVT to randomization: *mean (SD)* *min, Q1, median, Q3, max*	 6.8 (4.1) 0, 4, 6, 10, 20	 7.0 (4.3) 0, 4, 6, 9, 21	 6.9 (4.2) 0, 4, 6, 10, 21
Symptoms suggestive of PE: *n (%)*	69 (21)	90 (25)	159 (23)
PE diagnosed (objective tests): *n (%)*	79 (24)	89 (25)	168 (24)
Aspirin within 7 days prior to rand: *n (%)*	68 (20)	74 (21)	142 (21)

Table S2: Baseline Characteristics by Treatment Group

Characteristic	PCDT n = 336	Control n = 355	Total N = 691
Lab Results – Hematology			
Hemoglobin, mg/dL**:** *mean (SD)* *min, Q1, median, Q3, max*	 13 (1.8) 9, 12, 13, 14, 19	 13 (1.7) 9, 12, 13, 14, 17	 13 (1.8) 9, 12, 13, 14, 19
Platelet count, 10^9/L**:** *mean (SD)* *min, Q1, median, Q3, max*	 240 (88) 100, 178, 226, 289, 712	 245 (93) 100, 181, 224, 288, 800	 243 (91) 100, 180, 225, 288, 800
Creatinine, mg/dL**:** *mean (SD)* *min, Q1, median, Q3, max*	 0.9 (0.3) 0.3, 0.7, 0.9, 1.0, 2.3	 0.9 (0.2) 0.4, 0.7, 0.9, 1.1, 1.9	 0.9 (0.2) 0.3, 0.7, 0.9, 1.1, 2.3
eGFR, mL/min**:** *mean (SD)* *min, Q1, median, Q3, max*	 90 (30) 30, 70, 86, 102, 341	 90 (26) 37, 71, 86, 102, 217	 90 (28) 30, 71, 86, 102, 341
Pre-Rand Anticoagulant Therapy*	**314 (93)**	**331 (93)**	**645 (93)**
LMWH, *n (%)*	180 (57)	205 (62)	385 (60)
UFH, *n (%)*	99 (32)	99 (30)	198 (31)
Fondaparinux, *n (%)*	3 (1)	4 (1)	7 (1)
Rivaroxaban, *n (%)*	16 (5)	11 (4)	27 (4)
Warfarin: *n (%)*	154 (49)	179 (57)	333 (52)
Other, *n (%)*	15 (5)	12 (4)	27 (4)
Days from start of AC therapy† to randomization: *mean (SD)* *min, Q1, median, Q3, max*	 2.7 (3.2) 0, 1, 1, 3, 20	 3.1 (3.5) 0, 1, 2, 4, 19	 2.9 (3.3) 0, 1, 2, 4, 20
Days from start of warfarin to randomization: *mean (SD)* *min, Q1, median, Q3, max*	 2.8 (3.0) 0, 1, 2, 3, 19	 3.6 (3.7) 0, 1, 2, 5, 18	 3.2 (3.4) 0, 1, 2, 4, 19

* Subjects may fit into more than one category

† Anticoagulant (AC) therapy that was given after DVT diagnosis and before randomization

Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation; min, minimum; max, maximum; DVT, deep vein thrombosis; PE, pulmonary embolism; rand, randomization; eGFR, estimated glomerular filtration rate; LMWH, low molecular weight heparin; UFH, unfractionated heparin

Table S3: Per Protocol Analysis of PTS

(Villalta ≥ 5 or ulcer)

Group / Extent of DVT	Arm	PTS *Events / N (%)*	PCDT vs. Control	
			RR (95% CI)	P-value
All Subjects	**PCDT**	151 / 325 (46)	(unadjusted) 0.96 (0.82 to 1.13)	0.64
	Control	169 / 350 (48)		
Iliofemoral DVT	**PCDT**	92 / 190 (48)	(adjusted) **0.94* (0.81 to 1.10)**	0.47*
	Control	99 / 191 (52)		
Isolated Femoropopliteal DVT	**PCDT**	59 / 135 (44)		
	Control	70 / 159 (44)		

* Stratified risk ratio (RR) estimates and tests performed using Cochran-Mantel-Haenszel (CMH) methods with stratum factors Extent of DVT and Center

Table S4: Analysis of PTS using Multiple Imputation†

(Villalta ≥ 5 or ulcer)

Group / Extent of DVT	Arm	PTS *Events*† */ N (%)*	PCDT vs. Control	
			RR (95% CI)	P-value
All Subjects	**PCDT**	194 / 336 (58)	(unadjusted) 0.90 (0.78 to 1.04)	0.15
	Control	228 / 355 (64)		
Iliofemoral DVT	**PCDT**	122 / 196 (62)	(adjusted) **0.89* (0.77 to 1.02)**	0.10*
	Control	127 / 195 (65)		
Isolated Femoropopliteal DVT	**PCDT**	72 / 140 (51)		
	Control	101 / 160 (63)		

† Results shown represent the average (counts are rounded) of the 20 data sets imputed using the PMM method (see page 20 of Supplement)

* Stratified risk ratio (RR) estimates and tests performed using Cochran-Mantel-Haenszel (CMH) methods with stratum factors Extent of DVT and Center

Table S5: Binary Outcomes by Treatment Group (Per Protocol)

Outcome	PCDT Arm n = 325		Control Arm n = 350		Risk Ratio		P Value
	Events	(%)	Events	(%)	Estimate	95% CI	
PTS: [1]							
Ulcer (any assessment)	12	(3.7%)	17	(4.9%)			
Villalta ≥ 5 (without ulcer)	138	(42%)	152	(43%)			
Late endovascular procedure only	1	(<1%)	0	(0%)			
Total	151	(46%)	169	(48%)	0.94*	0.81, 1.10	0.47
PTS Incidence Proportion: [2]							
At 6 months	76/282	(27%)	112/282	(40%)	0.68	0.53, 0.86	
At 12 months	89/264	(34%)	87/255	(34%)	0.99	0.78, 1.26	
At 18 months	80/237	(34%)	76/219	(35%)	0.97	0.75, 1.25	
At 24 months	77/251	(31%)	85/234	(36%)	0.84	0.66, 1.09	
Major Non-PTS Treatment Failure	4	(1.2%)	6	(1.7%)	0.69†	0.19, 2.45	0.56
All Treatment Failures [3]	152	(47%)	174	(50%)	0.93*	0.79, 1.08	0.33
Moderate-severe PTS (Villalta ≥ 10) [4]	59	(18%)	84	(24%)	0.72*	0.54, 0.97	0.031

* Cochran-Mantel-Haenszel (CMH) test adjusted for extent of DVT and center; †CMH test adjusted for extent of DVT

[1] Cumulative proportion of patients who developed PTS (ulcer, Villalta ≥ 5 or LEP) at any time between 6 and 24 months inclusive; [2] At each visit, the proportion of patients with any PTS according to the Villalta scale among those who had an assessment performed (denominator); [3] Composite of PTS or major non-PTS treatment failure; [4] Cumulative proportion with moderate or severe PTS (pre-specified analysis).

PTS, post-thrombotic syndrome; CI, confidence interval; VTE, venous thromboembolism

Table S6: Continuous Outcomes by Treatment Group (Per Protocol)

Outcome	PCDT Arm n = 325		Control Arm n = 350		PCDT – Control Difference	
	n	**mean** (SE)	**n**	**mean** (SE)	**Estimate** (SE)	**P-value**
Villalta Mean Scores*: [(1)]						
At 6 months	282	3.13 (0.24)	282	4.37 (0.24)	-1.24 (0.32)	<0.001
At 12 months	264	3.22 (0.23)	255	4.43 (0.23)	-1.21 (0.30)	<0.001
At 18 months	237	3.31 (0.25)	219	4.49 (0.25)	-1.18 (0.32)	<0.001
At 24 months	251	3.40 (0.28)	234	4.56 (0.28)	-1.16 (0.37)	0.0020
VCSS Mean Scores*: [(2)]						
At 6 months	280	1.72 (0.15)	277	2.69 (0.15)	-0.98 (0.21)	<0.001
At 12 months	257	1.82 (0.16)	251	2.38 (0.16)	-0.56 (0.23)	0.013
At 18 months	232	1.73 (0.17)	212	2.82 (0.18)	-1.09 (0.24)	<0.001
At 24 months	228	1.88 (0.18)	211	2.43 (0.19)	-0.55 (0.26)	0.036
SF-36 general Quality of Life†: [(3)]						
PCS: Change, baseline to 24 months	238	11.40 (0.92)	220	10.01 (0.97)	1.39 (1.27)	0.27
MCS: Change, baseline to 24 months	238	2.89 (0.85)	220	2.64 (0.89)	0.24 (1.16)	0.83
VEINES disease-specific Quality of Life†: [(4)]						
Overall: Change, baseline to 24 months	242	28.12 (1.74)	223	23.24 (1.84)	4.88 (2.42)	0.044
Symptoms: Change, baseline to 24 months	241	20.70 (1.73)	223	17.18 (1.83)	3.52 (2.40)	0.14
Leg Pain Severity† (7-point scale)**:** [(5)]						
Change, baseline to Day 10	310	-1.65 (0.10)	320	-1.29 (0.10)	-0.36 (0.14)	0.012
Change, baseline to Day 30	307	-2.20 (0.11)	313	-1.82 (0.11)	-0.38 (0.15)	0.014
Index Leg Circumference† (cm)**:** [(6)]						
Change, baseline to Day 10	298	-0.28 (0.17)	318	0.28 (0.16)	-0.56 (0.24)	0.019
Change, baseline to Day 30	297	-0.77 (0.17)	311	-0.26 (0.17)	-0.51 (0.24)	0.034

* Mean scores, standard errors (SE) and treatment differences estimated using growth curve models and piece-wise linear regression adjusted for strata and baseline covariates (age, sex, BMI, Villalta score)

† Mean change scores, SEs, and treatment differences estimated using multiple regression adjusted for strata

(1) Villalta scores (0-33 range) – higher is worse; (2) VCSS scores (0-27 range) – higher is worse; (3) SF-36 major scales: physical component score (PCS) and mental component score (MCS) – higher is better; (4) VEINES overall score and symptom specific score – higher is better; (5) patient-reported severity of pain in the index leg - higher is worse; (6) leg circumference measured at 10cm below tibial tuberosity of the index leg

Table S7: Major Bleeding Details during First 10 Days by Treatment Group

Group	Age	Sex	Transfusion	Bleeding Site	Embolization	rt-PA total dose (mg)	AC during Lysis
PCDT	75	Female	Yes	Retroperitoneal	Yes	32.0	UFH
	68	Male	No	At PCDT site	No	12.2	UFH
	73	Female	No	At PCDT site	No	22.5	Enoxaparin
	69	Female	Yes	Retroperitoneal	Yes	19.9	Enoxaparin
	65	Female	No	Gastrointestinal	No	21.0	Enoxaparin
	62	Male	Yes	Gastrointestinal	No	20.0	Enoxaparin
Control	68	Female	Yes	Gastrointestinal	No	n/a	n/a

Table S8: Death Details by Treatment Group

Group	#	Sex	Days to Death	Age at Death	Cause of Death
PCDT	1	F	61	56	Multi-organ failure
	2	F	193	55	PE
	3	M	291	58	Extensive trauma due to bike running into car
	4	F	321	67	Metastatic gastric carcinoma
	5	M	404	28	Acute oxycodone and doxylamine intoxication
	6	M	707	40	Acute phencyclidine intoxication
	7	M	750	60	Kidney cancer
Control	1	F	24	68	Multisystem failure secondary to peripheral arterial disease
	2	M	241	67	Pancreatic cancer
	3	M	311	62	Diffuse large B-cell lymphoma
	4	M	339	61	Metastatic lung cancer
	5	M	354	55	Found on the living room floor unresponsive (not PE)
	6	M	441	68	Sepsis
	7	F	671	70	Hospitalized for acute renal failure, leukocytosis; became bradycardic
	8	F	741	63	End stage COPD

Venous Clinical Severity Score (VCSS) Form

Symptom or Sign	RIGHT LEG				LEFT LEG			
	0	1	2	3	0	1	2	3
Pain	☐ None	☐ Occasional	☐ Daily, interferes w/ daily activity	☐ Daily, limits most daily activity	☐ None	☐ Occasional	☐ Daily, interferes w/ daily activity	☐ Daily, limits most daily activity
Varicose Veins	☐ None	☐ Few, scattered	☐ Multiple, confined to calf or thigh	☐ Multiple, involves calf and thigh	☐ None	☐ Few, scattered	☐ Multiple, confined to calf or thigh	☐ Multiple, involves calf and thigh
Venous Edema	☐ None	☐ Limited to foot and ankle	☐ Above ankle but below knee	☐ Extends to knee and above	☐ None	☐ Limited to foot and ankle	☐ Above ankle but below knee	☐ Extends to knee and above
Skin Pigmentation	☐ None or focal	☐ Limited to perimalleolar area	☐ Diffuse over lower third of calf	☐ Wider dist. above lower third of calf	☐ None or focal	☐ Limited to perimalleolar area	☐ Diffuse over lower third of calf	☐ Wider dist. above lower third of calf
Inflammation	☐ None	☐ Limited to perimalleolar area	☐ Diffuse over lower third of calf	☐ Wider dist. above lower third of calf	☐ None	☐ Limited to perimalleolar area	☐ Diffuse over lower third of calf	☐ Wider dist. above lower third of calf
Induration	☐ None	☐ Limited to perimalleolar area	☐ Diffuse over lower third of calf	☐ Wider dist. above lower third of calf	☐ None	☐ Limited to perimalleolar area	☐ Diffuse over lower third of calf	☐ Wider dist. above lower third of calf
Active Ulcers: Number	☐ None	☐ 1	☐ 2	☐ 3 or more	☐ None	☐ 1	☐ 2	☐ 3 or more
Active Ulcers: Duration	☐ N/A	☐ <3 months	☐ 3 to 12 months	☐ Not healed for >12 months	☐ N/A	☐ <3 months	☐ 3 to 12 months	☐ Not healed for >12 months
Active Ulcers: Size (diameter)	☐ N/A	☐ <2 cm	☐ 2-6 cm	☐ >6 cm	☐ N/A	☐ <2 cm	☐ 2-6 cm	☐ >6 cm

VCSS Scoring Description

Pain Pain or other discomfort (i.e. aching, heaviness, fatigue, soreness, burning); Presumes venous origin	**None: (0)**	**Mild: (1)** Occasional pain or other discomfort (i.e. not restricting regular daily activity)	**Moderate: (2)** Daily pain or other discomfort (i.e. interfering with but not preventing regular daily activities)	**Severe: (3)** Daily pain or discomfort (i.e. limits most regular daily activities)
Varicose Veins "Varicose" veins must be ≥ 3 mm diameter to qualify	**None: (0)**	**Mild: (1)** Few: scattered (i.e. isolated branch varicosities or clusters) Also includes corona phlebectatica	**Moderate: (2)** Multiple: confined to calf or thigh	**Severe: (3)** Multiple: involves calf and thigh.
Venous Edema Presumes venous origin (i.e. brawny, not pitting or spongy edema and relieved by elevation)	**None: (0)**	**Mild: (1)** Limited to foot and ankle area.	**Moderate: (2)** Extends above ankle but below knee.	**Severe: (3)** Extends to knee or above
Skin Pigmentation Presumes venous origin; Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases (i.e. vasculitis purpura)	**None: (0)** None or focal	**Mild: (1)** Limited to perimalleolar area	**Moderate: (2)** Diffuse over lower 1/3 of calf	**Severe: (3)** Wider distribution above lower 1/3 of calf
Inflammation More than just recent pigmentation (i.e. erythema, cellulitis, venous eczema, dermatitis)	**None:(0)**	**Mild: (1)** Limited to perimalleolar area	**Moderate: (2)** Diffuse over lower 1/3 of calf	**Severe: (3)** Wider distribution above lower 1/3 of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (i.e. chronic edema with fibrosis, hypodermitis); includes white atrophy and lipodermatosclerosis	**None: (0)**	**Mild: (1)** Limited to perimalleolar area	**Moderate: (2)** Diffuse over lower 1/3 of calf	**Severe: (3)** Wider distribution above lower 1/3 of calf
Number of active ulcers	**0**	**1**	**2**	**≥ 3**
Active ulcers: duration longest active	N/A	< 3 months	>3 mos. but <1 year	not healed for > 1 year
Active ulcers: size largest active	N/A	< 2 cm diameter	2 cm to 6 cm diameter	> 6 cm diameter

Supplementary References

1. Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. *J Thromb Haemost* 2009; 7(5):884-888.

2. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost* 2009; 7(5):879-883.

3. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004; 40:1248-1252.
4. Rutherford RB, Padberg FT, Comerota AJ, Kistner RL, Meissne MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000; 31:1307-1312.

5. Meissner MH, Natiello C, Nicholls SC. Performance characteristics of the venous clinical severity score. J Vasc Surg 2002; 36:889-895.

6. Vasquez MA, Rabe E, McLafferty RB, et al. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. *J Vasc Surg* 2010; 52(5):1387-1396.

7. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient- reported measure of symptoms and quality of life. J Vasc Surg 2003; 37:410-419.

8. Kahn SR, M'lan CE, Lamping DL, Kurz X, Berard A, Abenhaim LA, for the VEINES Study Group. Relationship between clinical classification of chronic venous disease and patient-reported quality of life: results from an international cohort study. J Vasc Surg 2004;39:823-828.

9. Ware JE, Snow KK, Kosinski MA, Gandek B. SF-36 health survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center. 1993.

10. Ware JE, Kosinski M, Keller S. SF-36 physical and mental summary measures: A user's manual. Boston: The Health Institute, New England Medical Center. 1994.

11. Streiner DL, Norman GR. Health measurement scales: A practical guide to their development and use (2nd. edition). Oxford: Oxford University Press; 1995.

12. Bernstein SL, Chang A, Esses D, Gallagher EJ. Relationship between intensity and relief in patients with acute, severe pain. Acad Emerg Med 2005; 12:158-159.

13. Marder VJ, Soulen RL, Atichartakarn V, Budzynski AZ, Parulekar S, Kim JR, Edward N, Zahavi J, Algazy KM. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977; 89(5):1018-1029.

14. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3(4):692-694.

15. Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells PS, Julian JA, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003; 349:631-639.

16. Linkins LA, Stretton R, Probyn L, Kearon C. Interobserver agreement on ultrasound measurements of residual vein diameter, thrombus echogenicity, and Doppler venous flow in patients with previous venous thrombosis. Thromb Res 2006; 17:241-247.

17. Linkins L, Pasquale P, Paterson S, Kearon C. Change in thrombus length on venous ultrasound that supports a diagnosis of recurrent deep vein thrombosis. Arch Intern Med 2004; 164:1793-1796.

18. Prandoni P, Cogo A, Bernardi E, Villalta S, Polistena P, Simioni P, et al. A simple ultrasound approach for detection of recurrent proximal vein thrombosis. Circulation 1993;88:1730-1735.