Clinical Trials in Peripheral Vascular Disease: Pipeline and Trial Designs—An Evaluation of the ClinicalTrials.gov Database

Sumeet Subherwal, MD, MBA[1]; Manesh R. Patel, MD[1]; Karen Chiswell, PhD[1]; Beth A. Tidemann-Miller[2]; William S. Jones, MD[1]; Michael S. Conte, MD[3]; Christopher J. White, MD[4]; William R. Hiatt[5]; John R. Laird, MD[6]; Robert M. Califf, MD[1]

1. Duke University, Durham, NC; 2. NC State University, Raleigh, NC; 3. UC San Francisco, San Franscisco, CA; 4. Ochsner Heart and Vascular Institute, New Orleans, LA; 5. University of Colorado, Aurora, CO; 6. University of California Davis, Sacramento

Background

- Recent advances in therapies of peripheral vascular disease (arterial or venous) have provided greater options for treatment of the underlying disease
- The IOM's top priority topics for comparative effectiveness research lists peripheral artery disease as one of only two cardiovascular conditions in the top 50
- Little is known about the current state of the entire peripheral vascular disease (PVD) trial portfolio and current trial designs
- The Clinicaltrials.gov (CTG) registry comprises over 100,000 trials in 175 countries and is the most utilized source for clinical trial information worldwide.
- The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership founded by the U.S. Food and Drug Administration and Duke University, and includes more than 60 organizations across the clinical trial enterprise, with the goal to identify the quality and efficiency of clinical trials and generate evidence about how to improve the design and execution of clinical trials
- The CTTI has developed a high-quality database of information contained in CTG

Consequently, using the CTTI database of trials registered in the CTG, we sought to describe the current state of clinical trials for treatment of PVD

Methods

- Analysis was limited to those trials of extracardiac vascular disease commonly cared for by vascular specialists including cardiologists, vascular medicine specialists, vascular surgeons, interventional radiologists, and neuroradiologists
- A dataset of 96,346 clinical trials in CTG were downloaded in XML format in October 2010, and captured in a database for aggregate analysis
- Analysis was restricted to 40,970 "interventional" study type from October 2007 through Sept 2010
- Vascular trained physicians at Duke University Medical Center (SS, MRP, WSJ) reviewed 2,797 unique MeSH terms and 1,220 frequently-used free text terms from the CONDITION or NLM-generated CONDITION_BROWSE fields for these studies
- 165 MeSH terms and 55 free text terms as potentially relevant to PVD based were identified

Methods cont.

- An initial subset of 3,175 studies with at least one CONDITION or CONDITION_BROWSE term potentially relevant to PVD was identified and manually reviewed (SS, WSJ)
- Studies of external indwelling devices, management of sequelae of vascular disease (i.e. stroke rehabilitation, amputation rehabilitation), brain A-V malformations, orthostatic hypotension, vasculitis, and chronic cerebrospinal venous insufficiency were excluded
- Each study was categorized as arterial and/or venous studies. Primary and secondary prevention of vascular events were included if there was specific inclusion of patients with history of stroke, carotid disease, or lower extremity peripheral artery disease (PAD)
- Studies enrolling patients with extracardiac vascular disease with the endpoints looking at plaque regression, plaque stabilization, decrease in inflammatory biomarkers, improvements in endothelial function, and measurements of arterial vessel intimal medial thickness were categorized as prevention studies
- Studies of arterio-venous shunts were categorized under venous disease
- Studies including cardiology conditions were identified by cardiology specialists at Duke Clinical Research Institute. PVD studies were excluded from this group which was used as a comparison group
- Studies were allowed to be in more than one subgroup if they enrolled patients categorized within different subgroups
- Within the United States, we described regional access to PVD clinical trials graphically on a map at the zip code level

Results

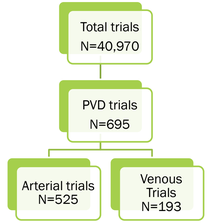


Figure 1: Breakdown of arterial and venous trials in Clinicaltrials.gov

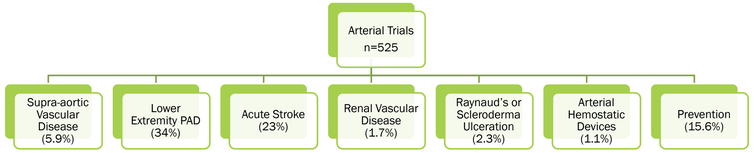


Figure 2: Subgroups of arterial trials

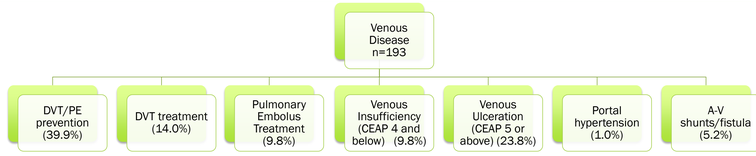


Figure 3: Subgroups of venous trials

Table 1: Overall study characteristics

	Study type		
PARAMETER	**PVD**	**Cardiology**	**Others**
NUMBER OF STUDIES, N	695	2070	38205
Masking (%)			
Open	51.9	52.3	56
Single blind	11.4	15.3	10.9
Double blind	36.7	32.4	33
Allocation (%)			
Randomized	71.2	76.6	68.4
Intervention types (%)			
Drug	50.9	44	61.5
Device	30.8	25.3	8
Procedure	13.1	14.6	9.7
Behavioral	3.2	6.4	8.3
Genetic or Biologic	4.5	2.9	8.2
Radiation	0.1	0.6	2.4
Dietary Supplement	1	2.3	4.1
Other	10.1	12.3	12.5
Phase (%)			
§ Phase Not Applicable	27.1	34.9	26.5
§ Where Phase was applicable			
Phase 0	1.4	1	1.1
Phase 1	8.7	5.4	21.7
Phase 1/Phase 2	5.7	4.1	7.2
Phase 2	24.1	19.8	28.8
Phase 2/Phase 3	7.3	4.7	3.4
Phase 3	26.2	25	20.4
Phase 4	26.6	39.9	17.4
Number of arms (%)			
One	27.4	25.7	32.5
Two	58	61.3	48.1
Three or more	14.6	13.1	19.4
Arm types (%)			
Active Comparator	47.2	50.6	41.6
No Intervention Arm	10.3	13.5	8.4
Experimental arm	72.7	65.1	76.9
Placebo Comparator Arm	26.3	24.3	25.6
Sham Comparator Arm	1.9	1.3	1.4
Other Arm	7.1	8.1	5.5
Enrollment (median Q1,Q3)	110 (48.0, 266.0)	117 (50.0, 316.0)	60 (30.0, 169.0)
Regions with 1 or more sites (%)			
Europe	39.4	43	29.3
North America	50.2	43.6	58.4
Asia/Middle East	23	21.3	18.2
Industry Lead Sponsor (%)	44.2	29.3	37.5
Assumed Funding Source			
Industry	53.2	40.3	46.2
NIH	4.3	4.2	9.0

Figure 4: Breakdown of Aortic Disease Trials

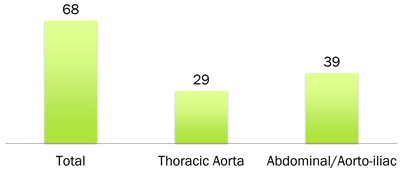


Figure 5: Breakdown of Lower Extremity PAD Trials

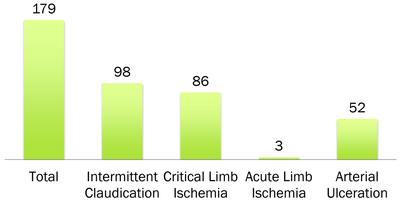
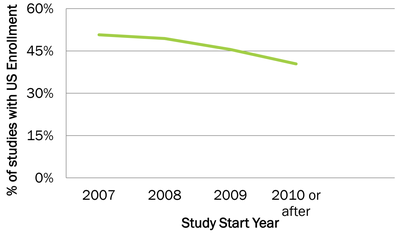


Figure 6: Temporal Trend of PVD Trials With US enrollment



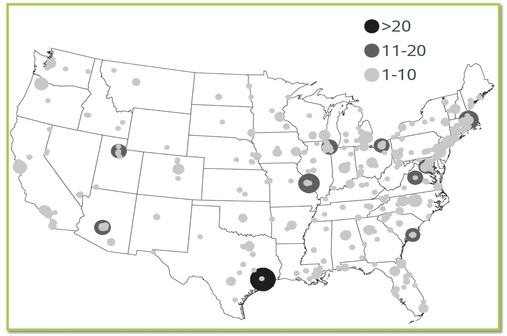


Figure 7: Geographic distribution of PVD studies by ZIP code within the continental United States. Size and color of dot represents number of PVD trials with a site at each ZIP code location.

Limitations

- There is wide heterogeneity in interpretation of the data fields by those entering responses into CTG
- The data were not independently verified in this analysis

Conclusions

- Despite the IOM's priority to perform comparative effectiveness trials in arterial disease, a majority of the PVD trial designs fail to include an active comparator; therefore changes are needed to reduce barriers to perform trials with active comparators, or alternatively, other methods are necessary to compare therapies beyond randomized trials
- PVD trials investigate a greater percentage of drug and device therapies than cardiology trials, and are more likely have industry as lead sponsor and funding source
- Behavioral therapies are under-investigated in PVD trials, despite data demonstrating benefit of exercise therapy in these patients
- ~50% of trials enroll patients from outside of U.S., and there is a trend of increasing enrollment outside of the U.S.
- There is geographic variation in access to clinical trials with populations in the midwest and southern belt having limited geographic access to these trials despite it being known these locations have higher incidence of arterial disease

Disclosures:

SS: None

MRP:Research Grants-Johnson and Johsnson, Pleuristem, Astra Zeneca, Consultant – Baxter, Genzyme, Bayer, OrthoMcNeil Jansen

KC: None

BAT: None

WSJ: None

MSC:Aastrom, Baxter, Humacyte

CJW:Scientific Advisory Board: Boston Scientific; Neovasc; St. Jude and Baxter Cellular Therapies

WRH: : Aastrom, AstraZeneca, Biosense, DNAVEC, GSK, Vermillion

JRL: Consultant/advisory board member: Abbott vascular, boston scientific, bard peripheral vascular, covidien, medtronic

RMC: A complete listing of disclosure information for Dr. Califf is available at www.dcri.org/about-us/conflict-of-interest.

Financial support for this project was provided by grant U19FD002800 from the U.S. Food and Drug Administration awarded to Duke University for the Clinical Trials Transformation Initiative

Contact

Sumeet Subherwal, MD, MBA

sumeet.subherwal@duke.edu

Duke Clinical Research Institute

Duke University

Durham, NC.