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

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Background—Tremendous advances have occurred in therapies for peripheral vascular disease (PVD); until recently, however, it has not been possible to examine the entire clinical trial portfolio of studies for the treatment of PVD (both arterial and venous disease).

Methods and Results—We examined interventional trials registered in ClinicalTrials.gov from October 2007 through September 2010 (n=40970) and identified 676 (1.7%) PVD trials (n=493 arterial only, n=170 venous only, n=13 both arterial and venous). Most arterial studies investigated lower-extremity peripheral artery disease and acute stroke (35% and 24%, respectively), whereas most venous studies examined deep vein thrombosis/pulmonary embolus prevention (42%) or venous ulceration (25%). A placebo-controlled trial design was used in 27% of the PVD trials, and 4% of the PVD trials excluded patients >65 years of age. Enrollment in at least 1 US site decreased from 51% of trials in 2007 to 41% in 2010. Compared with noncardiology disciplines, PVD trials were more likely to be double-blinded, to investigate the use of devices and procedures, and to have industry sponsorship and assumed funding source, and they were less likely to investigate drug and behavioral therapies. Geographic access to PVD clinical trials within the United States is limited to primarily large metropolitan areas.

Conclusions—PVD studies represent a small group of trials registered in ClinicalTrials.gov, despite the high prevalence of vascular disease in the general population. This low number, compounded by the decreasing number of PVD trials in the United States, is concerning and may limit the ability to inform current clinical practice of patients with PVD. (Circulation. 2014;130:1812-1819.)

Key Words: clinical trials as topic • peripheral vascular diseases • prevention and control • registries

With the aging US population, we can expect a greater incidence of peripheral vascular disease (PVD; both arterial and venous disease) and substantial costs associated with its treatment.1–3 Accordingly, the Institute of Medicine has listed the comparison of various therapies for treatment of vascular claudication alone among its top 50 comparative effectiveness research topics, and vascular claudication is the only cardiovascular condition besides atrial fibrillation on this list.4

Editorial see p 1778 Clinical Perspective on p 1819

Recent advances in therapies for PVD have provided greater options for patients and clinicians. Several mechanical devices are now available for endovascular treatment of lower-extremity peripheral artery disease (PAD),5,6 extracranial and intracranial cerebrovascular disease, and aortic disease.7 For patients with advanced PAD with development of critical limb ischemia (CLI), there remains promise for treatment with novel biological compounds.8,9 Furthermore, an evolution has occurred in the prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolus (PE) with novel anticoagulation therapies, as well as the potential for catheter-directed thrombolysis to prevent postthrombotic syndrome and to improve quality of life.10,11 Similarly, percutaneous ablation of lower-extremity venous disease has largely replaced traditional surgical phlebectomy for the treatment of venous claudication and venous reflux.12 Although the number of PVD therapies has grown rapidly,
little is known about the current state of the entire PVD trial portfolio and current trial designs. Using a database developed for analysis of trials registered in ClinicalTrials.gov (CTG), we sought to describe the current state of clinical trials for the treatment of PVD.

Methods

ClinicalTrials.gov

The CTG registry comprises >110,000 clinical research studies conducted in >175 countries and allows analysis of studies from various disciplines. CTG was developed to increase transparency and improve the conduct and monitoring of research, and it now serves as one of the primary repositories for information on clinical studies to be published in all member journals of the International Committee of Medical Journal Editors. The Clinical Trials Transformation Initiative, a public-private partnership developed by the US Food and Drug Administration and Duke University, includes >60 member organizations from across the clinical trial enterprise. Its mission is to identify and promote practices that will increase the quality and efficiency of clinical trials. The Clinical Trials Transformation Initiative has developed a high-quality, downloadable relational database of information contained in CTG.

Development of the CTG Data Set

A data set of 96,346 clinical trials registered in CTG was downloaded in XML format on September 27, 2010. The data were subsequently captured in a database to facilitate aggregate analysis of data from CTG as described previously.

Creation of the PVD Data Set

Analysis was restricted to 40,970 studies with the “interventional” study type registered with CTG between October 1, 2007, and September 27, 2010. The PVD study data set was developed by use of the disease condition terms (Medical Subject Headings [MeSH] and non-MeSH) provided by the data submitters and additional condition MeSH terms generated by the National Library of Medicine algorithm. One primary Duke vascular-trained clinical investigator (S.S.) and 2 secondary vascular-trained investigators (M.R.P. and W.S.J.) reviewed 2797 unique MeSH terms and 1220 frequently used free-text terms from the conditions or National Library of Medicine–generated condition browse fields for these studies. The investigators annotated 165 MeSH terms and 55 free-text terms as potentially relevant to PVD. The investigators included any term that might potentially be associated with extracardiac arterial or venous disease. These terms identified an initial potential subset of 3175 studies with at least 1 condition term potentially relevant to PVD. The investigators manually reviewed each of these study descriptive entries within CTG. Only studies that examined therapies for PVD and included the enrollment of patients with PVD were included in the final data set. We sought to describe the registered trials of extracardiac vascular disease commonly cared for by most cardiologists, vascular medicine specialists, vascular surgeons, interventional radiologists, and neuroradiologists. Aneurysmal disease (such as thoracic or abdominal aortic aneurysm) was included. We excluded studies of external/indwelling devices, management of sequelae of vascular disease (ie, stroke rehabilitation, amputation rehabilitation), brain arteriovenous malformations, arteriovenous grafts/shunts, orthostatic hypotension, vasculitis, hemostatic devices for arterial or venous procedures, and chronic cerebrospinal venous insufficiency. Any study that did not explicitly state whether the therapy was being investigated in patients with established PVD was excluded. This yielded a final data set of 676 PVD trials.

Subgroups of PVD Data Set

Each of the PVD studies was categorized into trials of arterial disease or venous disease (Figure 1) and then further subcategorized (Figure 2). Descriptions and rationale for these subcategories are provided in the online-only Data Supplement.

Analysis

Counts and percentages are provided for categorical trial characteristics, and continuous characteristics are presented as median (first and third quartiles). Missing values were excluded from the calculations unless indicated otherwise. The portfolio characteristics included phase of study, study design, enrollment, lead sponsor, collaborators, and study location. Study design attributes included interventions, comparators, masking, allocation, and purpose of intervention. Lead sponsor was defined as the primary organization that oversaw the implementation of the study and was responsible for data analysis (eg, National Institutes of Health or a pharmaceutical company). Collaborators were defined as other organizations (if any) that provided support, including funding, design, implementation, data analysis, and reporting. The assumed funding source was derived from the lead sponsor and collaborators fields and is described in the online-only Data Supplement. International regional variation was described

![Figure 1](http://circ.ahajournals.org/figure/19372111-19372111-f1.jpg)

**Figure 1.** Subgroups of trials of therapies for (A) arterial and (B) venous studies. Studies were allowed to be in >1 subgroup if they enrolled patients categorized within different subgroups. Four arterial studies with other conditions are not included. Seven venous studies were counted in >1 subgroup. CEAP indicates clinical, etiologic, anatomical, and pathophysiological; DVT, deep vein thrombosis; PAD, peripheral artery disease; and PE, pulmonary embolus.
by location of enrolling sites. We compared the characteristics of the PVD studies with characteristics of cardiology trials (excluding any PVD studies) and the entire cohort of studies in CTG. The online-only Data Supplement includes data on the methodology for identification of cardiac trials by cardiology specialists at Duke University; these data have been previously presented17 and published.18

Within the United States, we further described the geographic access to PVD clinical trial sites graphically on a map by locating trial sites at the county level. Study sites were excluded if they did not provide a valid ZIP Code or if the city and state entered in CTG did not match the ZIP Code. Additionally, to illustrate how geographic access to clinical trials compared with geographic prevalence of end-stage disease, we compared the geographic variation of sites with lower-extremity PAD and geographic variation in amputation rates per state versus with the national average among Medicare beneficiaries.19 The map of geographic variation was developed by calculating annual rates of amputation from 2000 to 2008 among Medicare beneficiaries and mapping the geographic variation of ratio of amputation in each state compared with the national average.

### Results

The PVD trial portfolio represents only 1.7% (n=676) of the 40970 interventional clinical trials registered within CTG from October 1, 2007, through September 27, 2010. Among the PVD trial portfolio, the vast majority of studies focused on therapies for arterial conditions compared with venous disease (n=493 arterial only, n=170 venous only, n=13 both arterial and venous; Figure 1). Most of the arterial studies sought to investigate treatment for lower-extremity PAD and acute stroke (35% and 24%, respectively). Most venous trials sought to investigate therapies for DVT/PE prevention (42%) or venous ulceration (25%; Figure 1).

The proportion of PVD trials enrolling patients within the United States declined over the study period. Among studies starting enrollment in 2007, 51% (36 of 71) had sites enrolling patients within the United States compared with 49% (77 of 156) of the trials in 2008, 45% (73 of 163) in 2009, and 41% (44 of 108) in 2010.

### Comparison of PVD Studies With Other Disciplines

PVD trials were much more likely to investigate the use of devices and procedures and less likely to investigate drug, behavioral, and genetic therapies compared with studies of noncardiology disciplines. Rates of randomization were similar among PVD and other disease states (71% versus 68%, respectively). However, compared with trials of other disease states, PVD studies were more likely to be double-blinded than the aggregate of studies of other disciplines (Table). Similar to cardiology trials, PVD studies were more likely to be later phase and larger compared with studies of other disciplines. Although the use of an active comparator was greater than in noncardiology disciplines, an active comparator was used in fewer than half (47%) of the PVD studies.

### Arterial and Venous Disease Trials

Most trials of supra-aortic, aortic, and lower-extremity PAD sought to investigate device therapies for treatment: For supra-aortic disease, 67% of intracranial studies examined device therapies, and 67% of extracranial trials investigated devices. For aortic disease, 62% of thoracic and 67% of abdominal/aortoiliac studies investigated devices. For lower-extremity PAD, 53% of intermittent claudication studies, 50% of CLI studies, and 67% of acute limb ischemia studies investigated devices (Table I in the online-only Data Supplement). Behavior modification was investigated in 10% of the intermittent claudication trials. For CLI, 17% of trials investigated genetic or biological therapies. Whereas intermittent claudication trials tended to be later phase (87% were phases 2–4), CLI trials included earlier-phase therapies (33% were phase 1 or 1/2). Meanwhile, for acute stroke, most trials examined the use of

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**Figure 2.** Subcategorization of (A) supra-aortic, (B) aortic, (C) lower-extremity peripheral artery disease, and (D) acute stroke trials. Studies were allowed to be in >1 subgroup if they enrolled patients categorized within different subgroups.
Table. Overall Trial Characteristics of PVD Trials Versus Cardiology Trials Versus Other Disease Trials Registered in ClinicalTrials.gov From October 2007 Through September 2010

<table>
<thead>
<tr>
<th>Masking, n/N (%)</th>
<th>PVD (n=676)</th>
<th>Cardiology (n=2077)</th>
<th>Other (n=38217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>348/671 (51.9)</td>
<td>1074/2051 (52.4)</td>
<td>20812/37149 (56.0)</td>
</tr>
<tr>
<td>Single blind</td>
<td>73/671 (10.9)</td>
<td>315/2051 (15.4)</td>
<td>4069/37149 (11.0)</td>
</tr>
<tr>
<td>Double blind</td>
<td>250/671 (37.3)</td>
<td>662/2051 (32.3)</td>
<td>12268/37149 (33.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allocation, n/N (%)</th>
<th>PVD (n=669)</th>
<th>Cardiology (n=2041)</th>
<th>Other (n=36530)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>474/669 (70.9)</td>
<td>1562/2041 (76.5)</td>
<td>24991/36530 (68.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention types, n/N (%)</th>
<th>PVD (n=676)</th>
<th>Cardiology (n=2077)</th>
<th>Other (n=38217)</th>
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</thead>
<tbody>
<tr>
<td>Drug</td>
<td>351/676 (51.9)</td>
<td>911/2077 (43.9)</td>
<td>23489/38217 (61.5)</td>
</tr>
<tr>
<td>Device</td>
<td>205/676 (30.3)</td>
<td>529/2077 (25.5)</td>
<td>3065/38217 (8.0)</td>
</tr>
<tr>
<td>Procedure</td>
<td>85/676 (12.6)</td>
<td>304/2077 (14.6)</td>
<td>3715/38217 (9.7)</td>
</tr>
<tr>
<td>Behavioral</td>
<td>21/676 (3.1)</td>
<td>133/2077 (6.4)</td>
<td>3153/38217 (8.3)</td>
</tr>
<tr>
<td>Genetic or biological</td>
<td>31/676 (4.6)</td>
<td>59/2077 (2.8)</td>
<td>3144/38217 (8.2)</td>
</tr>
<tr>
<td>Dietary supplement</td>
<td>7/676 (1.0)</td>
<td>47/2077 (2.3)</td>
<td>1549/38217 (4.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase, n/N (%)</th>
<th>PVD (n=497)</th>
<th>Cardiology (n=1352)</th>
<th>Other (n=28089)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>179/676 (26.5)</td>
<td>725/2077 (34.9)</td>
<td>10128/38217 (26.5)</td>
</tr>
<tr>
<td>0</td>
<td>7/497 (1.4)</td>
<td>14/1352 (1.0)</td>
<td>295/28089 (1.1)</td>
</tr>
<tr>
<td>1</td>
<td>43/497 (8.7)</td>
<td>74/1352 (5.5)</td>
<td>6105/28089 (21.7)</td>
</tr>
<tr>
<td>1/2</td>
<td>26/497 (5.2)</td>
<td>55/1352 (4.1)</td>
<td>2024/28089 (7.2)</td>
</tr>
<tr>
<td>2</td>
<td>122/497 (24.5)</td>
<td>267/1352 (19.7)</td>
<td>8095/28089 (28.8)</td>
</tr>
<tr>
<td>2/3</td>
<td>36/497 (7.2)</td>
<td>64/1352 (4.7)</td>
<td>955/28089 (3.4)</td>
</tr>
<tr>
<td>3</td>
<td>130/497 (26.2)</td>
<td>339/1352 (25.1)</td>
<td>5728/28089 (20.4)</td>
</tr>
<tr>
<td>4</td>
<td>133/497 (26.8)</td>
<td>539/1352 (39.9)</td>
<td>4887/28089 (17.4)</td>
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<table>
<thead>
<tr>
<th>No. of arms, n/N (%)</th>
<th>PVD (n=600)</th>
<th>Cardiology (n=1866)</th>
<th>Other (n=32629)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>185/667 (27.7)</td>
<td>522/2031 (25.1)</td>
<td>11869/36547 (32.5)</td>
</tr>
<tr>
<td>2</td>
<td>383/667 (57.4)</td>
<td>1244/2031 (61.3)</td>
<td>17578/36547 (48.1)</td>
</tr>
<tr>
<td>≥3</td>
<td>99/667 (14.8)</td>
<td>265/2031 (13.0)</td>
<td>7098/36547 (19.4)</td>
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<table>
<thead>
<tr>
<th>Arm types, n/N (%)</th>
<th>PVD (n=600)</th>
<th>Cardiology (n=1866)</th>
<th>Other (n=32629)</th>
</tr>
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<tbody>
<tr>
<td>Active comparator</td>
<td>282/600 (47.0)</td>
<td>945/1866 (50.6)</td>
<td>13587/32629 (41.6)</td>
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<tr>
<td>No intervention arm</td>
<td>59/600 (9.8)</td>
<td>252/1866 (13.5)</td>
<td>2745/32629 (8.4)</td>
</tr>
<tr>
<td>Experimental arm</td>
<td>438/600 (73.0)</td>
<td>1215/1866 (65.1)</td>
<td>25082/32629 (76.9)</td>
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<tr>
<td>Placebo comparator arm</td>
<td>159/600 (26.5)</td>
<td>451/1866 (24.2)</td>
<td>8347/32629 (25.6)</td>
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<tr>
<td>Sham comparator arm</td>
<td>12/600 (2.0)</td>
<td>24/1866 (1.3)</td>
<td>454/32629 (1.4)</td>
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<tr>
<td>Other arm</td>
<td>42/600 (7.0)</td>
<td>152/1866 (8.1)</td>
<td>1806/32629 (5.5)</td>
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</table>

<table>
<thead>
<tr>
<th>Median enrollment (Q1, Q3)</th>
<th>PVD (n=672)</th>
<th>Cardiology (n=2053)</th>
<th>Other (n=38217)</th>
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<tbody>
<tr>
<td>114.5 (49.5, 280.0)</td>
<td>117.0 (50.0, 316.0)</td>
<td>60.0 (30.0, 169.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size of trial (enrollment), n/N (%)</th>
<th>PVD (n=672)</th>
<th>Cardiology (n=2053)</th>
<th>Other (n=38217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1/672 (0.1)</td>
<td>0/2053 (0.0)</td>
<td>85/37641 (0.2)</td>
</tr>
<tr>
<td>1–100</td>
<td>317/672 (47.2)</td>
<td>984/2053 (47.9)</td>
<td>24085/37641 (64.0)</td>
</tr>
<tr>
<td>101–1000</td>
<td>308/672 (45.8)</td>
<td>877/2053 (42.7)</td>
<td>12241/37641 (32.5)</td>
</tr>
<tr>
<td>1001–5000</td>
<td>40/672 (6.0)</td>
<td>150/2053 (7.3)</td>
<td>1045/37641 (2.8)</td>
</tr>
<tr>
<td>&gt;5000</td>
<td>6/672 (0.9)</td>
<td>42/2053 (2.0)</td>
<td>185/37641 (0.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age eligible for enrollment, n/N (%)</th>
<th>PVD (n=672)</th>
<th>Cardiology (n=2053)</th>
<th>Other (n=38217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study excludes age &gt;65 y</td>
<td>27/672 (4.0)</td>
<td>84/2053 (4.0)</td>
<td>12936/38217 (33.9)</td>
</tr>
<tr>
<td>Study excludes age &lt;65 y</td>
<td>2/672 (0.3)</td>
<td>28/2053 (1.4)</td>
<td>442/38217 (1.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study site locations, n/N (%)</th>
<th>PVD (n=672)</th>
<th>Cardiology (n=2053)</th>
<th>Other (n=38217)</th>
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<tbody>
<tr>
<td>Africa</td>
<td>21/628 (3.3)</td>
<td>29/1928 (1.5)</td>
<td>767/34964 (2.2)</td>
</tr>
<tr>
<td>Central and South America</td>
<td>38/628 (6.1)</td>
<td>104/1928 (5.4)</td>
<td>1651/34964 (4.7)</td>
</tr>
<tr>
<td>Europe</td>
<td>249/628 (39.6)</td>
<td>829/1928 (43.0)</td>
<td>10233/34964 (29.3)</td>
</tr>
<tr>
<td>North America</td>
<td>315/628 (50.2)</td>
<td>840/1928 (43.6)</td>
<td>20426/34964 (58.4)</td>
</tr>
<tr>
<td>Asia/Middle East</td>
<td>146/628 (23.2)</td>
<td>411/1928 (21.3)</td>
<td>6362/34964 (18.2)</td>
</tr>
</tbody>
</table>

(Continued)
drug therapies (66% of trials for ischemic stroke and 74% for hemorrhagic stroke).

Most venous disease trials examined either treatment or prevention of DVT or PE (57%, 104 of 183), with 8 of these being studies of treatment with vena cava filters. A large percentage of registered venous trials examined drug treatments: 70% of trials for DVT treatment were drug trials versus 15% device trials; for DVT/PE prevention studies, 82% were drug trials and 13% were device trials; for venous insufficiency (CEAP ≤4), 42% were drug trials and 21% were device trials; and for PE treatment, 95% were drug trials and 11% were device trials. None of the trials for venous insufficiency used compression therapy as a comparator; 1 study compared duration of compression therapy after venous ablation. However, for treatment of venous ulceration (CEAP ≥5), most trials investigated the use of devices (50%) compared with drugs (26%). Other important trial characteristics of venous trials are provided in Table II in the online-only Data Supplement.

Geographic Variation

Geographic access to PVD clinical trials within the United States is pictured in Figure 3. Most trials were concentrated in metropolitan areas with greatest population density, with the New England region having the most access to PVD trials. The counties with the greatest access to PVD trials were Suffolk County, Massachusetts (n=43); New York County, New York (n=41); Los Angeles County, California (n=39); Harris County, Texas (n=37); and Cook County, Illinois (n=36).

To demonstrate how geographic access to a trial can differ from the geographic distribution of disease, Figure 4 describes the regional distribution of amputation rates (terminal state for progression of PAD), and Figure 5 shows the geographic variation in access to lower-extremity PAD trials. Although the Southeast has the greatest rates of amputation, there remains relatively limited access to clinical trials in this region of the United States.

Discussion

The present analysis is the first characterization of the current clinical trial portfolio of studies seeking treatment of PVD. This research provides a foundation for discussion and policy on ways to optimize the PVD trial portfolio to best inform clinical practice. Despite a large percentage of the population having vascular disease, invasive trials of PVD represent a small fraction of the studies registered in CTG. Compared with other disease states, PVD trials are more likely to be later phase (phases 2–4), to have greater enrollment rates, to investigate devices, and to be industry sponsored and funded, and they are less likely to investigate behavioral interventions. PVD trials also allow enrollment of older patients (age >65 years) in a vast majority of cases (96%), which correctly represents the older population typically representative of vascular disease. The proportion of studies being registered with US enrollment was noted to decrease over time such that 40% of PVD studies starting enrollment during 2010 included US enrollment. Additionally, there remains geographic variation in access to trials within the United States.

One major theme echoed from the analysis of the PVD trials is the discordance between the current trial portfolio for arterial disease and the current need for data to inform clinical practice. The 121 investigational trials for treatment of acute stroke or transient ischemic attack represent a small fragment (0.3%) of the entire CTG ischemic attack trial portfolio of investigational trials. Such a number is strikingly low, given that stroke was the fourth leading
behavioral therapies are underinvestigated, given the lack of most studies are industry sponsored, it is not surprising that Of note, behavior therapies have the potential to be underrepresented by the US Food and Drug Administration Amendments Act of 2007 study registration mandate, although they do need to improve outcomes among the stroke population.

With regard to lower-extremity PAD studies, there is also discordance between the large percentage of registered trials in the current portfolio examining device therapies for PAD and behavioral modification/interventional therapies (trials that include the following type of interventions: psychotherapy, lifestyle counseling/modification [walking/exercise, educational workshops, or educational printed materials], and physical therapy). For instance, we found that only 10% of studies for intermittent claudication included investigation of behavioral intervention (compared with 53% investigating device therapies). Although some trial data demonstrate efficacy and guidelines support the use of lifestyle modification, including smoking cessation and exercise, the optimal behavior modification therapies remain unknown. Additionally, behavior modification trials may be less common because of the potential difficulty in getting subjects to comply with these interventions. The greater rate of device trials potentially reflects the need for regulatory approval with devices compared with behavior modifications. This also parallels current trends in the use of minimally invasive therapies (compared with surgical treatment) of PAD seen nationally.24

The present analysis provides several lessons about the current PVD trial portfolio. Importantly, there is a limited footprint of nonindustry funding sources in the PAD arena. This can be included in a registry to satisfy International Committee of Medical Journal Editors requirements. With respect to DVT trials investigating the use of vena cava filters, none of the registered trials address the longer-term safety of these devices. Given current US Food and Drug Administration concern about the fracture, migration, and perforation of such devices, future trials will need to have longer longitudinal follow-up.

There seems also to be discordance at the patient level with access to trials for PVD. Within the United States, access to PVD trials is largely limited to major metropolitan areas, which tend to be the usual locations of larger medical centers and universities. However, the geographic variation of amputations is largely limited to major metropolitan areas, which suffer from higher relative amputation rates. Although it can be argued that these patients may also benefit from access to trials given the increased severity of disease burden in the areas.

Compounding this situation is the finding that the number of trials enrolling patients in the United States is decreasing despite the increasing number of trials for PVD. To ensure a broad representation of enrolled patients, future PVD trials should consider a wider geographic catchment area representative of the entire US population with the disease. Additional efforts to enroll patients at such locations may potentially help with recruitment in trials, given the higher prevalence of disease in these regions. Future efforts may need to target policy to define and to ensure appropriate representation of US patients within trials, given that therapies may have different efficacies in different populations.

The present analysis provides several lessons about the current PVD trial portfolio.
suggests that the majority of trials are done by industry to support registration and marketing. Although such trials may promote science and care of patients, a much healthier balance of investigator-initiated, multicenter trials and comparative effectiveness studies is needed. Such trials will need to address and compare the effectiveness of noninterventional (medical, exercise) and interventional (endovascular and surgical) therapies for the treatment of claudication and the effectiveness of surgery versus angioplasty/stenting as a revascularization strategy for intermittent claudication or CLI treatment. Within noninterventional therapies themselves, questions remain as to the optimal strategy for behavioral modification for PVD in general, as well as identification of optimal medical therapy for secondary prevention of atrial disease (including the use of antplatelet or antithrombotic therapies). On a similar note, given the rising healthcare costs, a cost-effectiveness approach that includes quality-of-life assessment of novel therapies (primarily devices and genetics) will be required to justify their costs. Although we did not analyze the symptomatic status of patients proposed for trials in this data set, future trials should consider differential treatment effect according to symptomatic status, given that PVD tends to present across a spectrum of disease.

Because of the high cost of development and subsequent trials, particularly among devices and biologics, novel approaches to trial designs will be needed. One potential solution to these gaps includes partnering academia with industry to design new registries or to leverage existing registries to answer questions of efficacy at lower operational costs than with traditional trials. Such registries could be linked to administrative registries (such as the Centers for Medicare & Medicaid Medicare data set) to provide insight into longer-term outcomes and to determine which patients benefit most from interventional therapies. Additionally, trial methodologies other than traditional time-to-event analysis may be considered to provide greater assessment of the efficacy and safety of PVD therapies.

There are several limitations to the CTG data set. Primarily, there is no obligation to register phase 1 trials or studies that do not involve a drug, biological, or device intervention. In addition, trials performed outside the United States do not need to be registered unless they are conducted under an Investigational New Drug or Investigational Device Exemption. However, to monitor this, and it is possible that not all enrolled patients with established extracardiac vascular disease; those trials of early-phase therapies with a potential target for treatment of PVD that are tested in normal subjects (those without PVD) were excluded in the present analysis. Additionally, our search strategy included condition terms (those focused on disease conditions), not specific interventions. Given that our main goal was to identify trials seeking treatment of various disease states within PVD, this was a reasonable approach.

Conclusions

The present analysis demonstrates that PVD studies represent a small proportion of trials registered in CTG despite the high prevalence of vascular disease in the general population. Most studies investigate therapies for arterial disease and specifically lower-extremity PAD and acute stroke. Compared with other trials within CTG, PVD trials tend to be later phase, more likely to investigate devices, more likely to be industry sponsored and funded, and less likely to investigate behavioral interventions. There remains geographic variation in access to PVD trials for patients in the United States. In aggregate, the present analysis is the first step in understanding the clinical trial portfolio of PVD studies. It will serve as a basis for future discussions and policy aimed at changing the portfolio to reflect those questions of most clinical importance in the field.

Sources of Funding

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Disclosures

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Despite advances in therapies for peripheral vascular disease (PVD) in both arterial and venous disease, little is known about the PVD trials in the United States is concerning and may limit the ability to inform current clinical practice of patients with PVD.

In the ClinicalTrials.gov database of 40,000 trials, only 1,600 of these trials met the criteria for being PVD trials in the United States. Despite advances in therapies for peripheral vascular disease (PVD) in both arterial and venous disease, little is known about the PVD trials in the United States is concerning and may limit the ability to inform current clinical practice of patients with PVD.


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

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Subcategories of Peripheral Vascular Disease (PVD) Data Set
Studies of 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). Within the category of lower extremity PAD, given that critical limb ischemia (CLI) by definition includes ulceration or ischemic rest pain secondary to significant PAD, the subcategory of CLI trials included those trials that explicitly enrolled PAD patients with arterial ulceration or rest pain and investigated CLI treatment. Meanwhile, the arterial ulceration subcategory of lower extremity PAD studies included those studies that did not specifically define whether patients had flow-limiting PAD and those studies which specifically documented that patients had adequate arterial perfusion (such as therapies investigating treatment of diabetic foot ulcers). Studies enrolling patients with extra-cardiac vascular disease with the endpoints examining plaque regression, plaque stabilization, decrease in inflammatory biomarkers, improvements in endothelial function, and measurements of arterial vessel intimal medial thickness were categorized under the prevention of vascular events category. The subgroups of venous studies are described in Figure 1. Studies were allowed to be in more than 1 subgroup if they enrolled patients categorized within different subgroups (e.g., studies enrolling patients with both arterial and venous ulceration were included in both the arterial ulceration subgroup and venous ulceration subgroup). Venous ulcers were included if they were CEAP class 5 or above. Trials of therapies for pressure ulcers were excluded if they enrolled patients with only pressure ulcers but did not include patients with arterial or venous ulcers.

Development of Cardiology Data Set
The cardiology subset was identified using the same method used to identify the PVD subset. Two Duke cardiologists reviewed a subset of the 2010 MeSH thesaurus and frequently occurring free-text condition terms for relevance to cardiovascular disease. An initial subset of 3503 studies were identified with at least 1 MeSH or condition term relevant to cardiovascular disease. The cardiologists manually reviewed individual studies and their listed conditions to identify those related to cardiovascular disease in adult patients. They included only those that enrolled adults (maximum age ≥18 years) and studied conditions related to the diagnosis, treatment, or prevention of diseases of the heart (e.g., cardiovascular diseases, disorders of heart structure or function, or cardiovascular imaging). Conditions related to venous and pulmonary embolic disease; general risk factors such as diabetes, smoking, and hypertension in patients without coexisting cardiology disease; and other non-cardiology populations or conditions were excluded. Studies enrolling healthy volunteers were reviewed, and those that specified no cardiac
disease state were excluded. This left a final population of 2325 clinical studies. Those 248 studies that were also identified under the PVD data set were excluded from the cardiology data set (n=2077) for the analysis presented in this manuscript.

**Derivation of Assumed Funding Source**

If the lead sponsor was from private industry, or the National Institutes of Health (NIH) was neither a lead sponsor nor collaborator and at least 1 collaborator was from industry, then the study was categorized as industry-funded. If the lead sponsor was not from industry, and the NIH was either a lead sponsor or a collaborator, then the study was categorized as NIH-funded. Otherwise, if the lead sponsor and collaborator fields were non-missing, then the study was considered to be funded by other sources.
### Table 1. Characteristics of Arterial Disease Trials

<table>
<thead>
<tr>
<th></th>
<th>Acute stroke</th>
<th>Renal vascular disease</th>
<th>Supra-aortic vascular disease</th>
<th>Aortic</th>
<th>Lower extremity peripheral artery disease</th>
<th>Critical</th>
<th>Primary and secondary prevention</th>
<th>Raynaud’s or scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=77</td>
<td>Hemorrhagic N=46</td>
<td>Ischemic N=15</td>
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<td>Abdominal/aortoiliac N=39</td>
<td>Intermittent claudication N=98</td>
<td>Lower limb ischemia N=91</td>
<td>Arterial ulceration N=48</td>
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<td>Masking</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Open</td>
<td>28/76 (36.8%)</td>
<td>20/46 (43.5%)</td>
<td>7/9 (77.8%)</td>
<td>12/15</td>
<td>13/16 (81.3%)</td>
<td>22/29</td>
<td>32/39 (82.1%)</td>
<td>57/98 (75.9%)</td>
</tr>
<tr>
<td>Single blind</td>
<td>676 (7.9%)</td>
<td>646 (13.0%)</td>
<td>0/9 (0.0%)</td>
<td>0/15 (0.0%)</td>
<td>2/16 (12.5%)</td>
<td>0/29 (0.0%)</td>
<td>3/39 (7.7%)</td>
<td>21/98 (21.4%)</td>
</tr>
<tr>
<td>Double blind</td>
<td>42/76 (55.3%)</td>
<td>20/46 (43.5%)</td>
<td>2/9 (22.2%)</td>
<td>3/15 (20.0%)</td>
<td>1/16 (6.3%)</td>
<td>7/29 (24.1%)</td>
<td>4/39 (10.3%)</td>
<td>20/98 (20.4%)</td>
</tr>
<tr>
<td>Allocation</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td>62/76 (81.6%)</td>
<td>32/46 (69.6%)</td>
<td>7/9 (77.8%)</td>
<td>8/15 (53.3%)</td>
<td>7/16 (43.8%)</td>
<td>9/29 (31.0%)</td>
<td>10/38 (26.3%)</td>
<td>62/98 (63.3%)</td>
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<tr>
<td>Non-randomized</td>
<td>14/76 (18.4%)</td>
<td>14/46 (30.4%)</td>
<td>2/9 (22.2%)</td>
<td>7/15 (46.7%)</td>
<td>9/16 (56.3%)</td>
<td>20/29 (69.0%)</td>
<td>28/38 (36.7%)</td>
<td>36/98 (41.9%)</td>
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<tr>
<td>Intervention types</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>51/77 (66.2%)</td>
<td>34/46 (73.9%)</td>
<td>4/9 (44.4%)</td>
<td>3/15 (20.0%)</td>
<td>3/18 (16.7%)</td>
<td>9/29 (31.0%)</td>
<td>5/39 (12.8%)</td>
<td>20/98 (20.4%)</td>
</tr>
<tr>
<td>Device</td>
<td>13/77 (16.9%)</td>
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<td>7/9 (77.8%)</td>
<td>10/15 (66.7%)</td>
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<td>18/29 (62.1%)</td>
<td>26/39 (66.7%)</td>
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<tr>
<td>Procedure</td>
<td>4/77 (5.2%)</td>
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<td>4/9 (44.4%)</td>
<td>4/15 (26.7%)</td>
<td>6/18 (33.3%)</td>
<td>3/29 (10.3%)</td>
<td>10/39 (25.6%)</td>
<td>18/98 (18.4%)</td>
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<tr>
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<td>0/18 (0.0%)</td>
<td>0/29 (0.0%)</td>
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<td></td>
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<tr>
<td>Active comparator</td>
<td>25/68 (36.8%)</td>
<td>15/43 (34.9%)</td>
<td>5/9 (55.6%)</td>
<td>8/15 (53.3%)</td>
<td>8/16 (50.0%)</td>
<td>8/19 (42.1%)</td>
<td>9/28 (32.1%)</td>
<td>39/82 (47.6%)</td>
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<td>No intervention arm</td>
<td>9/68 (13.2%)</td>
<td>6/43 (14.0%)</td>
<td>0/9 (0.0%)</td>
<td>1/15 (6.7%)</td>
<td>0/16 (0.0%)</td>
<td>0/19 (0.0%)</td>
<td>2/28 (7.1%)</td>
<td>6/82 (7.3%)</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th></th>
<th>Acute stroke</th>
<th>Renal vascular disease</th>
<th>Supra-aortic vascular disease</th>
<th>Aortic</th>
<th>Lower extremity peripheral artery disease</th>
<th>Critical</th>
<th>Primary and secondary prevention</th>
<th>Raynaud’s or scleroderma</th>
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</thead>
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<tr>
<td></td>
<td>Ischemic N=77</td>
<td>Hemorrhagic N=46</td>
<td>N=9</td>
<td>N=15</td>
<td>N=18</td>
<td>N=29</td>
<td>N=39</td>
<td>N=91</td>
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<td>Enrollment‡</td>
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<td></td>
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<tr>
<td></td>
<td>(Q1,Q3)</td>
<td>(36.0,370.0)</td>
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<td>(80.0,150.0)</td>
<td>(85.0,500.0)</td>
<td>(135.0,453.5)</td>
<td>(50.0,250.0)</td>
<td>(44.0,194.0)</td>
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</tbody>
</table>

Data are n/N (%) except where indicated. Q1 indicates first quartile; Q3, third quartile.

* A study may have more than 1 intervention type.

† A study may have more than 1 arm type.

‡ Enrollment is either anticipated (for studies that had not completed enrollment on September 27, 2010) or actual.
### Table 2. Characteristics of Venous Disease Trials

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<tr>
<th></th>
<th>DVT treatment</th>
<th>DVT/PE prevention</th>
<th>Venous insufficiency</th>
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<th>Venous ulceration</th>
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<td>N=77</td>
<td>N=19</td>
<td>N=19</td>
<td>N=46</td>
<td>N=2</td>
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<tr>
<td><strong>Masking</strong></td>
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</tr>
<tr>
<td>Open</td>
<td>17/26 (65.4%)</td>
<td>43/76 (56.6%)</td>
<td>10/19 (52.6%)</td>
<td>7/19 (36.8%)</td>
<td>27/46 (58.7%)</td>
<td>1/2 (50.0%)</td>
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<tr>
<td>Single blind</td>
<td>2/26 (7.7%)</td>
<td>5/76 (6.6%)</td>
<td>4/19 (21.1%)</td>
<td>4/19 (21.1%)</td>
<td>4/46 (8.7%)</td>
<td>1/2 (50.0%)</td>
</tr>
<tr>
<td>Double blind</td>
<td>7/26 (26.9%)</td>
<td>28/76 (36.8%)</td>
<td>5/19 (26.3%)</td>
<td>8/19 (42.1%)</td>
<td>15/46 (32.6%)</td>
<td>0/2 (0.0%)</td>
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<tr>
<td><strong>Allocation</strong></td>
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<td></td>
<td></td>
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<tr>
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<td>16/26 (61.5%)</td>
<td>54/75 (72.0%)</td>
<td>17/19 (89.5%)</td>
<td>17/19 (89.5%)</td>
<td>38/46 (82.6%)</td>
<td>2/2 (100.0%)</td>
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<tr>
<td>Non-randomized</td>
<td>10/26 (38.5%)</td>
<td>21/75 (28.0%)</td>
<td>2/19 (10.5%)</td>
<td>2/19 (10.5%)</td>
<td>8/46 (17.4%)</td>
<td>0/2 (0.0%)</td>
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<td><strong>Intervention types</strong></td>
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<td></td>
</tr>
<tr>
<td>Device</td>
<td>19/27 (70.4%)</td>
<td>63/77 (81.8%)</td>
<td>8/19 (42.1%)</td>
<td>18/19 (94.7%)</td>
<td>12/46 (26.1%)</td>
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<tr>
<td>Procedure</td>
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<td>2/77 (2.6%)</td>
<td>6/19 (31.6%)</td>
<td>0/19 (0.0%)</td>
<td>5/46 (10.9%)</td>
<td>2/2 (100.0%)</td>
</tr>
<tr>
<td>Behavioral</td>
<td>1/27 (3.7%)</td>
<td>0/77 (0.0%)</td>
<td>0/19 (0.0%)</td>
<td>0/19 (0.0%)</td>
<td>2/46 (4.3%)</td>
<td>0/2 (0.0%)</td>
</tr>
<tr>
<td>Genetic or biologic</td>
<td>0/27 (0.0%)</td>
<td>2/77 (2.6%)</td>
<td>0/19 (0.0%)</td>
<td>0/19 (0.0%)</td>
<td>2/46 (4.3%)</td>
<td>0/2 (0.0%)</td>
</tr>
<tr>
<td><strong>Arm types†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Active comparator</td>
<td>11/23 (47.8%)</td>
<td>41/73 (56.2%)</td>
<td>12/18 (66.7%)</td>
<td>12/17 (70.6%)</td>
<td>20/39 (51.3%)</td>
<td>2/2 (100.0%)</td>
</tr>
<tr>
<td>No intervention arm</td>
<td>5/23 (21.7%)</td>
<td>11/73 (15.1%)</td>
<td>2/18 (11.1%)</td>
<td>0/17 (0.0%)</td>
<td>6/39 (15.4%)</td>
<td>0/2 (0.0%)</td>
</tr>
<tr>
<td><strong>Enrollment‡</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>289.5</td>
<td>300.0</td>
<td>180.0</td>
<td>129.0</td>
<td>62.0</td>
<td>141.5</td>
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<tr>
<td>(Q1,Q3)</td>
<td>(50.0,692.0)</td>
<td>(100.0,669.0)</td>
<td>(105.0,280.0)</td>
<td>(41.0,1000)</td>
<td>(25.0,200.0)</td>
<td>(130.0,153.0)</td>
</tr>
</tbody>
</table>

Data are n/N (%) except where indicated. DVT indicates deep vein thrombosis; PE, pulmonary embolus; Q1, first quartile; Q3, third quartile.

*A study may have more than 1 intervention type.

†A study may have more than 1 arm type.

‡Enrollment is either anticipated (for studies that had not completed enrollment on September 27, 2010) or actual.