Pharmacomechanical thrombolysis treatment of DVT and preservation of valve competency

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and/or pulmonary embolism (PE), affects approximately 5% of the population at some point in their lives and is estimated to occur in 300,000 – 600,000 persons in the United States each year, Most patients undergo systemic anticoagulation and compression stocking therapy, a treatment strategy intended to minimize propagation of the clot and prevent pulmonary embolization. The thrombus is not removed, but rather relies upon the endogenous fibrinolytic system to eventually resolve the thrombus and recanalize the vein. However when treated with anticoagulation alone, it is estimated that in only 12-47% of cases is there complete lysis of the offending clot within 6 months, increasing the risk of recurrent DVT and post thrombotic syndrome (PTS), a debilitating late sequela of DVT.

Post thrombotic syndrome (PTS) occurs in nearly 30-50% of patients following an episode of DVT and is characterized by chronic leg pain and swelling that limits activity, the ability to work, and potentially results in leg ulcers. PTS is thought to be caused by venous hypertension and impaired venous return due to the persistent (residual) venous obstruction. Valvular reflux also frequently occurs after DVT, likely via thrombus-induced activation of inflammation, fibrous scarring by acute and resolving thrombus, or by venous dilation distal to the obstructed segment. Risk factors of PTS include symptom severity at 1-month post DVT diagnosis, thrombosis of the common femoral or iliac vein, higher body mass index (BMI), previous ipsilateral venous thrombosis, older age, and female gender. The occurrence of PTS has been shown to be directly related to the degree of residual clot; conversely, in cases where when there is a high degree of clot lysis, rethrombosis is avoided and patients have a minimal risk of PTS. Furthermore, it has been recently shown that the use of compression stockings do not prevent the occurrence of PTS after DVT nor do they influence the severity of PTS or the rate of recurrent VTE.

Including early clot removal in the treatment strategy for management of DVT has been shown to be associated with a significant reduction in the occurrence of persistent venous obstruction, recurrent thrombosis, PTS, valvular incompetence (reflux) and improved quality of life (QOL), presumably by rapidly restoring venous patency and preserving or limiting damage to venous values.

Due to the significant impact of both PTS and recurrent thrombosis on QOL and productivity as well as the cost associated with managing these conditions, the Society for Vascular Surgery (SVS) has recently updated clinical practice guidelines suggesting early removal of thrombus in patients most likely to benefit from the procedure. As defined by the SVS, early thrombus removal is indicated for patients with:

- A first episode of acute iliopelural DVT
- Symptoms of <14 days in duration
- Low bleeding risk
- Ambulatory with good functional capacity and an acceptable life expectancy, who would benefit from a reduced long-term risk of PTS and DVT reoccurrence

First-line therapies for early thrombus removal include catheter-directed pharmacologic thrombolysis (CDT) and pharmacomechanical thrombolysis (PMT). Catheter-directed thrombolysis involves infusion of a thrombolytic agent in the region of the venous thrombus through a percutaneously placed catheter. Catheter-directed thrombolysis is limited by the risk of bleeding (5-11%), prolonged infusion time required for the thrombolysis procedure (average 48-53 hours), and the cost associated with the frequent requirement of patient monitoring in the ICU. Pharmacomechanical thrombolysis (PMT) was developed to address these limitations through the adjunctive use of mechanical devices, involving rotational, rheolytic or ultrasound technologies, to deliver the thrombolytic agent as well as produce some combination of thrombus fragmentation, distribution of thrombolytic drug through the thrombus and/or thrombus aspiration.

Comparisons of CDT with PMT have shown that PMT is associated with:

- Comparable rates of treatment success and risk of complications
- Shorter treatment times
- Lower doses of thrombolytic drug required
- Reduced ICU and total hospital stay and hospital costs

Recognizing the benefits of PMT over CDT, the SVS now suggests the use of PMT over catheter-directed thrombolysis alone if expertise and resources are available.

Despite these advantages, concerns remain that mechanical device may damage vein valves as compared to CDT. The effect of PMT on venous valve function as compared with conventional CDT therapy has been recently evaluated by Vogel and colleagues. Post procedural phlebograms were reviewed to determine residual obstruction; valve function (reflux) was evaluated using duplex ultrasonography at follow-up. A total of 20 limbs were evaluated that were treated with CDT alone, 49 were treated with PMT (n=35 with the Trellis catheter, n =14 with AngioJet™ System). Similar rates of success were achieved with both CDT and PMT. At a mean length of follow-
up of 44 months, there was no difference in the rate of reflux demonstrated between patients treated with CDT (65%) and PMT (53%) (p=.42). Limbs treated with the Trellis catheter exhibited a reflux rate of 57% vs. 43% in limbs treated with AngioJet System (p=.53). Although the sample size was insufficient to demonstrate statistical significance, the risk of valve reflux following treatment with PMT was shown to be at least equivalent, and possibly slightly lower, than that which occurs following CDT.

Studies have reported a wide variation in rates of reflux after the use of CDT or anticoagulation alone, depending on the method of assessment and length of follow-up, as shown in Table 1. The results of the Vogel series are consistent with other reports evaluating valvular function following treatment of DVT.

The AngioJet System is a rheolytic PMT technology that is used extensively to treat DVT, acute limb ischemia and thrombosis of hemodialysis access grafts. Data collected on 329 lower extremity DVT patients as a part of the PEARL Registry, a study following AngioJet patients funded by Boston Scientific has shown that:

- Thrombectomy with Power Pulse™ or rapid lysis was utilized in 87% of the patients.
- An average reduction of 96% in thrombus immediately post AngioJet PMT therapy.
- Rates for freedom from rethrombosis at 6 and 12 months were 88% and 84%, respectively.
- Clinically and statistically significant improvements in both physical and mental components of QOL measures from baseline to 3, 6, and 12 months.
- 75% of AngioJet cases were completed in ≤ 24 hours.
- Procedure-related complications included bleeding requiring transfusion (N=1), hematoma at access site (2) arrhythmia during the AngioJet procedure (3), Acute renal failure (1) or Transient renal failure (1), and pulmonary embolism (1).

As shown in Table 2 below, the lower extremity outcomes for AngioJet PMT therapy as reported in the PEARL registry aligned favorably with the CDT experience as reported by the Venous Registry with considerably less lytic drip times when CDT is used in combination with AngioJet therapy. In addition, the PEARL registry reported greater thrombus removal both acute and chronically with fewer bleeding complications with AngioJet Thrombectomy use in the treatment protocol.

### Table 1: Summary of literature evaluating venous valve function following treatment for DVT

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>DVT Therapy</th>
<th>Method for Determination of Venous Valve Closure Time</th>
<th>Length of Follow-up (months)</th>
<th>% with Normal Valve Function</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogel, 2012</td>
<td>20</td>
<td>CDT</td>
<td>Duplex Ultrasonography</td>
<td>44</td>
<td>CDT: 35% PMT: 47%</td>
<td>.42</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>PMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arko, 2007</td>
<td>30</td>
<td>PMT</td>
<td>Duplex Ultrasonography</td>
<td>12</td>
<td>88%</td>
<td>–</td>
</tr>
<tr>
<td>Elsharawy, 2002</td>
<td>17</td>
<td>Anticoagulation</td>
<td>Photoplethysmography</td>
<td>6</td>
<td>Anticoag: 59% CDT: 89%</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>CDT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VanHaarst, 1996</td>
<td>24</td>
<td>Anticoagulation</td>
<td>Duplex Ultrasonography</td>
<td>33</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85</td>
<td>40%</td>
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</tbody>
</table>

### Table 2: Comparison of PEARL Registry and Venous Registry patient populations and outcomes in the treatment of lower extremity DVT

<table>
<thead>
<tr>
<th></th>
<th>Venous Registry</th>
<th>PEARL Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>287</td>
<td>329</td>
</tr>
<tr>
<td># of sites</td>
<td>63</td>
<td>32</td>
</tr>
<tr>
<td>Prior DVT</td>
<td>31%</td>
<td>40%</td>
</tr>
<tr>
<td>Concomitant stent placement</td>
<td>33%</td>
<td>35%</td>
</tr>
<tr>
<td>Primary access</td>
<td>Popliteal</td>
<td>Popliteal</td>
</tr>
<tr>
<td>Mean age</td>
<td>47.5 years</td>
<td>52 years</td>
</tr>
<tr>
<td>% Male</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>Primary treatment</td>
<td>CDT</td>
<td>PMT with or without CDT</td>
</tr>
<tr>
<td>Primary lytic</td>
<td>Urokinase</td>
<td>TPA</td>
</tr>
<tr>
<td>CDT drip times (mean)</td>
<td>48 hours</td>
<td>17 hours (when CDT was utilized)</td>
</tr>
<tr>
<td>Procedure time (median)</td>
<td>NA</td>
<td>CDT: 41 hours CDT+PMT: 22 hours PMT: 2 hours</td>
</tr>
<tr>
<td>Acute: % thrombus removal</td>
<td>86%</td>
<td>97%</td>
</tr>
<tr>
<td>Chronic: % thrombus removal</td>
<td>68%</td>
<td>95%</td>
</tr>
<tr>
<td>Primary Patency</td>
<td>6 month: 65% 12 month: 60%</td>
<td>NA</td>
</tr>
<tr>
<td>Freedom from Rethrombosis</td>
<td>NA</td>
<td>6 month: 88% 12 month: 84%</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>11% major 16% minor</td>
<td>5% (major + minor)</td>
</tr>
</tbody>
</table>
Conclusions

While definitive, randomized trials evaluating the late outcomes for treatment of DVT using anticoagulation alone vs. aggressive early intervention with PMT are ongoing, the consistent results reported by an accumulating, large body of research comprised of smaller studies and registries supports the benefit of early thrombus removal using PMT:

- Catheter based thrombus removal for DVT treatment has been shown to improve patient outcomes.
- Advantages of PMT treatment of DVT are not compromised by adverse effects on vein valve function.
- Studies support PMT as a safe method for the treatment of symptomatic acute DVT with excellent rates of patency reported.
- Rates of recurrent venous thromboembolism have been shown to be lower in treatment groups receiving percutaneous venous intervention.

References

ANGIOJET™ ULTRA CONSOLE

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator’s Instructions.

INTENDED USE/INDICATIONS FOR USE: The Console is intended for use only in conjunction with an AngioJet Ultra Thrombectomy Set. Refer to the individual Thrombectomy Set Information for Use manual for specific clinical applications.

CONTRAINDICATIONS: Refer to the individual Thrombectomy Set Information for Use manual for specific contraindications.

WARNINGS and PRECAUTIONS:
• Use the AngioJet Ultra Console only with an AngioJet Ultra Thrombectomy Set. This Console will not operate with a previous model pump set and catheter.
• Do not attempt to bypass any of the Console safety features.
• If the catheter is removed from the patient and/or is inoperative, the waste tubing lumen, guide catheter, and sheath should be flushed with sterile, heparinized solution to avoid thrombus formation and maintain lumen patency. Reprime the catheter by submerging the tip in sterile, heparinized solution and operating it for at least 20 seconds before reintroduction to the patient. • Refer to the individual AngioJet Ultra Thrombectomy Set Information for Use manual for specific warnings and precautions.
• Do not move the collection bag during catheter operation as this may cause a collection bag error. • Monitor thrombotic debris/fluid flow exiting the catheter through the waste tubing during use. If blood is not visible during console activation, the catheter may be occlusive within the vessel or the outflow lumen may be blocked. • Ensure adequate patient anticoagulation to prevent thrombus formation in outflow lumen. • Refer to individual Thrombectomy Set Instructions for Use manual for specific instructions regarding heparinization of the Thrombectomy Set. • The Console contains no user-serviceable parts. Refer service to qualified personnel. • Removal of outer covers may result in electrical shock. • Do not place Console near sensitive equipment when operating. • Do not reposition or push the console from any point other than the handle designed for that purpose. A condition of overbalance or tipping may ensue. • Portable and mobile RF communications equipment can affect MEDICAL ELECTRICAL EQUIPMENT. • The use of accessories and cables other than those specified, with the exception of accessories and cables sold by Bayer HealthCare as replacement parts for internal components, may result in increased EMISSIONS or decreased IMMUNITY of the Ultra Console. • MEDICAL ELECTRICAL EQUIPMENT needs special precautions regarding Electro-Magnetic Compatibility (EMC) and needs to be installed and put into service according to the EMC information provided in the tables provided in the IFU.

ADVERSE EVENTS: Refer to the individual Thrombectomy Set Information for Use manual for specific observed and/or potential adverse events.

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