ATTRACTION Trial and Impact on Treatment of Deep Venous Thrombosis

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Venous Thromboembolism (VTE) Statistics

- 460,000 people in EU and 300,000 people in North America annual deep vein thrombosis (DVT) incidence
- ~100,000 annual deaths - PE
- Complications of VTE estimated ~$10 billion in US annually for associated costs
- VTE standard therapy over past 50 years has changed little – anticoagulation (AC)
Post-thrombotic Syndrome (PTS)

• Chronic pain, edema and fatigue of affected limb after DVT

• Severe PTS may result in venous claudication, stasis dermatitis, subdermal fibrosis and ulceration -> tissue loss

• ≥40% of patients within 2 years of first lower extremity DVT
Post-thrombotic Syndrome (PTS)

• As assessed by Villalta score\(^5\), more severe PTS is predicted by:
  • Common femoral or iliac DVT (IFDVT)
  • Higher BMI
  • Prior ipsilateral DVT
  • Older age
  • Female gender

• Patients with PTS have overall lower QOL scores and less improvement in symptoms over time\(^6\) with conventional therapy
Brief Literature Review of PTS and Therapy

• Active clot removal improves patency rates of iliofemoral veins
  • Surgical/endovascular thrombectomy and catheter-directed or systemic thrombolysis

• Considerable data suggests early and more aggressive thrombus removal in IFDVT decreases PTS incidence
  • Cochrane review 700 patients (Catheter-directed thrombolysis [CDT] vs anticoagulation [AC])
    • Early clot lysis significantly improved compared to late (RRR 4.14 vs 2.71)
    • Reduced PTS (RR: 0.66)

• One of the goals of ATTRACT is to provide level 1 evidence
• CaVenT, PEARL Registry
Catheter-directed thrombolysis for deep vein thrombosis (CaVenT)$^2$ - Norway

- n=176 IFDVT patients followed to 5 years
- 1:1 randomization to catheter-directed thrombolysis (CDT) and anticoagulation vs. anticoagulation alone
- End-point: assess development of PTS
- 43% CDT group vs. 71% of control developed PTS (p = 0.0001)
- QOL scores not statistically significant between groups
- **28% Absolute risk reduction** (95% CI 14-42%)
**PEARL Registry³ (Boston Scientific)**

- n=329 patients with image-confirmed DVT (66% iliac involvement)
- **Treatment groups**
  - Rheolytic thrombectomy (RT) without lytics (4%)
  - Pharmacomechanical catheter-directed therapy (PCDT) (35%)
  - PCDT and catheter-directed thrombolysis (CDT) (52%)
  - RT and CDT (9%)
- **End-point:** assess procedure/patient outcomes of endovascular treatment of DVT with RT
PEARL Registry³

- Median procedure times
  - RT alone: **1.4 h**
  - PCDT: **2 h**
  - PCDT/CDT: 22 h
  - RT/CDT: 41 h (P = 0.05, Kruskal–Wallis test)

- 36% procedures done within 6 hours; 86% required ≤ 2 sessions

- 3-, 6-, and 12-month freedom from re-thrombosis rates
  - 94%, 87%, and 83%, respectively

- Physical/mental SF-12 QOL scores sig. improved 3-, 6- & 12-month f/u

- Interpretation: PCDT may reduce need/duration of CDT for DVT tx
The “Open Vein Hypothesis”

• Development of PTS is associated with persistent venous thrombosis
• Does active elimination of DVT prevent PTS?
• Support comes from studies linking:
  • Poor thrombus clearance to venous valve dysfunction and recurrent VTE\textsuperscript{8,9}
  • Residual venous thrombus or valve incompetence and PTS\textsuperscript{10}
  • Systemic thrombolysis, surgical thrombectomy or CDT to reduced incidence of PTS\textsuperscript{11-14}
ATTRACT Trial Design

- Multicenter, randomized, open-label, assessor-blinded, parallel two-arm, controlled clinical trial sponsored by National Heart, Lung, and Blood Institute of the U.S. National Institutes of Health

- SIR Foundation, Boston Scientific, BSN Medical, Covidien/Medtronic, and Genentech provided additional support

- 692 subjects enrolled in 56 US Centers followed for 24 mo
  - 337 randomized to PCDT
  - 355 randomized to no PCDT
ATTRACT Trial Objectives

• Primary objective:
  • Determine if PCDT with standard DVT therapy reduces development of PTS after 24 month follow-up compared to standard DVT therapy alone

• Secondary objectives:
  • Evaluate for major bleeding, symptomatic VTE and death
  • Venous disease-specific QOL
  • Relief of acute DVT symptoms
  • Pretreatment predictors of response to PCDT in preventing PTS
  • Compare medical costs and cost-effectiveness
  • Determining technical, anatomical and physiologic endpoints of therapy
ATTRACTION Trial – Standard DVT Therapy

- Weight-based low molecular weight heparin or IV unfractionated heparin then Warfarin
- International guidelines for INR 2-3, duration of therapy (3 months or longer)
- 30-40 mmHg knee-high elastic compression stockings at 10 day follow-up
ATTRACT Trial – PCDT Intervention

• One of three methods for rt-PA delivery (max 25 mg initially; max 35 mg total)
  1. “Isolated Thrombolysis” with Trellis Peripheral Infusion System (Covidien, Inc.)
  2. “PowerPulse Thrombolysis” with AngioJet Rheolytic Thrombectomy System (Boston Scientific)
ATTRACT Trial – PCDT Intervention

• One of three methods for rt-PA delivery (max 25 mg initially; max 35 mg total)

3. “Infusion-First Thrombolysis” with multisidehole catheter through thrombus, up to 1 mg/h rt-PA for max 30 hours
   • Subsequent therapy with balloon maceration, aspiration thrombectomy and/or mechanical thrombectomy allowed for residual thrombus

http://www.angiodynamics.com/images/userfiles/UnifuseIllustration.jpg
ATTRACT Trial – Endpoints and Efficacy

• \( \geq 90\% \) thrombus clearance with restored flow
• 35 mg maximum rt-PA dose or 30 h maximum infusion time reached
• Overt clinical bleeding or other complications necessitating cessation

• Evaluation for PTS in index limb at 6-24 months after randomization
• Villalta PTS scoring used
  • Combines patient and clinician evaluation
  • PTS defined as Villalta score \( > 5 \) or presence of ulcer
ATTRACT Trial – Initial Results SIR 2017
“The Bad & Ugly”

- PCDT not found to reduce incidence of PTS compared to AC alone

- PTS 46.7% for PCDT vs 48.2% for no-PCDT (p= 0.56)

- Recurrent VTE higher in PCDT vs no-PCDT (12.5% vs 8.5%; p=0.09)

- Major and any bleeding rates statistically higher in PCDT arm (1.7% vs 0.3%; p=0.49 and 4.5% vs 1.7%; p=0.034) – in line with prior studies
  - NO intracranial or fatal hemorrhages
ATTRACTION Trial – Initial Results SIR 2017

• IFDVT vs femoropopliteal DVT (FPDVT)
  • Trends to more benefit in IFDVT
  • Study not powered to sufficient power to statistically significant differences between subgroups
ATTRACTION Trial – Results SIR 2017 – “The Good”

• Leg pain and swelling significantly improved in PCDT vs. no-PCDT out to 30 days (p=0.019 and p=0.05)
  • PCDT helpful for acute symptoms

• 25% fewer patients in PCDT arm developed moderate or severe PTS vs no-PCDT (17.9% vs 23.7%; p=0.035)
  • “Open Vein hypothesis”
**ATTRACT Trial – Results SIR 2017 – “The Good”**

- In IFDVT mod-severe PTS was 18.4% vs 28.2% in PCDT vs no-PCDT

- In FPDVT little difference (17.1% vs 18.1% moderate to severe PTS)

- PCDT was less effective in patients ≥ 65 y/o
ATTRACTION Trial Summary and Learning points

• Ambitious well-designed RCT, failed primary endpoint, but not the end

• Helps us strategize for appropriate care

• Who to and not to treat
  • Same as CaVenT: iliofemoral DVT, younger and functional patients
  • Femoropopliteal DVT alone patients do not derive same benefit
  • Older patients do not derive same benefit
  • Prevent bleeding and cost in inappropriate patients
ATTRACT Trial Learning points

• Do we fully understand the pathophysiology of PTS?
  • Is the “Open Vein Hypothesis” enough?

• We know thrombolysis works, but are recent tech advances enough to merit further trials (Boston-Scientific ZelanteDVT, Inari Flow-Triever, Penumbra Indigo, Argon Cleaner, etc.)?
ATTRACT Trial Learning points

- Same-session therapy vs. prolonged ICU time for thrombolysis?
  - Cost and resource analysis
  - Patient experience

- Role of IVUS in treatment of iliofemoral disease?
  - Likely to be an integral component of development of new technologies

- Femoropopliteal subgroup did not derive benefit
  - Did we look sufficiently at the iliac segments for evidence of compression?
Questions?

• Thank you
References


15. https://www.cdc.gov/ncbddd/dvt/ha-vte.html
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