Evidence Summary: Treatment of Chronic Venous Thrombosis with Ongoing Venous Obstruction (Post-Thrombotic Syndrome)

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DISCLOSURES

- National Heart Lung and Blood Institute (NHLBI)
  - U01-HL088476 (ATTRACT Trial)
  - U54-HL112321 (Thrombosis Research Center)
  - U34-HL123831 (C-TRACT Trial Planning Grant)

- Other Research Support (to Washington University)
  - Current – BSN Medical, Volcano, Cook, Therakos
  - Previous - Boston Scientific, Covidien, Genentech
  - Cook, Therakos (>$10K)

Post-Thrombotic Syndrome Harms Patients
(Greater Awareness Among Providers)

- Moderate-severe PTS: develops after proximal DVT in 15-25%, the most important predictor of Quality of Life
  - Kahn SR et al. Ann Intern Med 2008.
  - Kahn SR et al. J Thromb Haemost 2008.

- Degree of QOL impairment parallels severity of PTS => COPD, arthritis
  - Kahn SR et al. Arch Intern Med 2002.
  - Kahn SR et al. Arch Intern Med 2005.

Conservative Therapy Has Limitations

Lifestyle

- Two small RCTs (n=73) supervised exercise => improved PTS, QOL, calf pump function
- BUT: not severe PTS, no standard protocols

Medications

- Recommend pentoxyfilline for venous ulcers
- RCTs aescin, flavinoids, rutosides, ASA defibrotide, hidrosmin => inconsistent results
- AND: side effects, not FDA approved

Compression

- Strongly recommended for venous ulcers
- Suggested for no-ulcer PTS: low risk of harm
- BUT: compliance & patient perceptions vary
- BUT: weak & conflicting evidence (no-ulcer)

Venous Obstruction Worsens the Disease

- Residual thrombus => recurrence & PTS
  - Hull RD et al. Am J Med 2001. (11 RCTs)
  - Prandoni P et al. J Thromb Hem 2005 (RCT)
- Chronic iliac vein obstruction => massive edema, painful venous claudication, poor QOL, frequent use of pain medications
  - Kahn SR et al. Ann Intern Med 2008.
  - Delis et al. Ann Surg 2004.
- Intravascular ultrasound helps diagnosis
  - Gagne P et al. Presented AVF 2016.

Relieving Venous Obstruction in Acute DVT Indirect Support from Multicenter RCT (CAVENT)

Outcome	CDT	Control	P Value
2-yr PTS (Villalta)	41.1%	55.6%	**0.047**
5-yr PTS (Villalta)	42.5%	70.8%	**< 0.0001**
5-yr Mod-Sev PTS	6.9%	15.7%	Not Stated
5-yr VEINES-QOL	50.5	49.6	NS

Thrombolysis + stents for obstructive iliac vein lesions

Enden T et al. Lancet 2012; 379:31-38.

Haig Y et al. Lancet Haematol 2016; 3(2):e64-71.

PTS: Stents Re-Open Veins & Provide Relief

- Systematic meta-analysis (n=1118) => stents improve pain (69%), swelling (63%), venous ulcer healing (70%)
  - Not RCTs but treatment effects consistent, few complications
  - Razavi MK et al. Circ Cardiovasc Intervent 2015; 8:e002772.

- Dutch prospective cohort: stents for severe PTS (n=61)
  - Better VEINES-QOL and SF-36 scores at 3 and 12 mo ($p < 0.01$)
  - Catarinella FS et al. Phlebology 2014; 29(1S):104–111.

- Retrospective comparison (n=216): stents reduce PTS severity and ulcer recurrence compared with ECS alone
  - Yin M et al. Eur J Vasc Endovasc Surg. 2015 Jul;50(1):101-7.

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- Brazilian RCT: stent + standard tx versus standard tx alone
  - 50 limbs, half with previous DVT (= PTS), all C3-C6 with pain
  - Stents=> improved pain (VAS), PTS (VCSS), QOL (SF-36)
  - Rossi et al. Presented at the 2015 AVF Meeting; NCT 02149212

Relieving Iliac Vein Obstruction and Saphenous Reflux May Be Even Better

- Iliac vein stenting + endovenous ablation (not RCTs)

- River Oaks review (n=464): reduction in pain (< 0.001 using VAS), severe pain (41% to 11%), severe swelling (36% to 18%), ulcer healing (68%), QOL improvement
  - Neglen P et al. J Vasc Surg 2006; 44(4):828-833.

- Washington University retrospective review (n=45)
  - Improvement in pain (74%), swelling (75%), ulcer (83%)
  - Proportion with “any pain” reduced from 83% to 30%
  - Nayak L et al. J Vasc Interv Radiol 2012; 23:1165-1173.

Published Guidelines Support Endovascular Therapy but Encourage Stronger Evidence

- AHA (2014) (PTS) – consider PTA/stent for severely symptomatic patients with iliac vein or IVC occlusion (Grade II, Level B)
  - Kahn SR et al. Circulation 2014; 130(18):1636-1661.

- SVS-AVF (2014) (Venous Ulcer) – recommend PTA/stent for patients with IVC/iliac vein chronic obstruction associated with venous leg ulcer or skin changes at risk for ulcer (Grade I, Level C)
  - O'Donnell Jr. TF. J Vasc Surg 2014; 60:3S-59S.

- Anticoagulation Forum (2016) – for moderate-severe PTS with iliac vein obstruction, consult endovascular specialist for guidance
  - Kahn SR et al. J Thromb Thrombolysis 2016; 41:144–153.

the Attract STUDY

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STUDY ENROLLMENT
Patient with proximal DVT meets eligibility criteria and provides informed consent

↓

PRE-RANDOMIZATION PROCEDURES
Initiation of AC (LMWH or UFH) and completion of baseline assessments

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RANDOMIZATION (1:1 Ratio)

↙ ↘

CONTROL ARM SUBJECTS
Complete 5 days heparin therapy (LMWH or UFH) and immediately bridge to warfarin (INR 2.0 – 3.0)

PCDT ARM SUBJECTS
Complete 5 days heparin therapy (LMWH or UFH) concurrent with performance of PCDT procedure, then bridge to warfarin (INR 2.0 – 3.0)

↘ ↙

LONG-TERM TREATMENT - ALL SUBJECTS
Long-term (≥ 3 months) warfarin therapy and daily use of graduated elastic compression stockings (initiated 10 days post-randomization)

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FOLLOW-UP VISITS – ALL SUBJECTS
Early (10 days & 30 days post-randomization)
Late (6, 12, 18, & 24 months post-randomization)

FULLY ENROLLED RESULTS in 2017

PCDT: "PHARMACO-MECHANICAL" LYSIS

C-TRACT STUDY

STUDY ENROLLMENT
Patient with SIO-PTS meets eligibility criteria, completes run-in period, and provides consent

ALL PATIENTS
Compression, DVT-appropriate AC, local preferences for "allowed" PTS treatments

RANDOMIZATION (1:1 Ratio)

CONTROL ARM SUBJECTS
Continue conservative therapy with adjustments at 2-month and 4-month follow-up visits if non-improving

ENDOVASCULAR ARM SUBJECTS
Iliac vein stent placement
Endovenous saphenous vein ablation
Same conservative therapy as Control

FOLLOW-UP VISITS – ALL SUBJECTS
Scheduled: 2, 4, 6, 12, 18 months post-RAND
Unscheduled: as needed for symptoms & recurrence

OUTCOME ASSESSMENTS
Primary: Change in VEINES-QOL from 0 to 6 months
Secondary: Change VEINES-QOL, VCSS, Villalta
Secondary: Ulcer healing, safety events, costs

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Multicenter, open-label, assessor-blind RCT (1:1)

Endorsed: AVF, SIR, SVM, ACP, NATF

CONCLUSIONS

- PTS is important to patients => cause of pain, limitation of life activities, and poor QOL => urgent need & opportunity
- Practice evolution driven by more awareness & diagnosis, limitations of conservative options, data suggesting that endovascular intervention reduces pain and improves QOL
  - Direct data from major collaborative RCTs is coming
  - CMS collaboration can facilitate trials & quality care

APPENDIX

Exercise & Drugs: Inconsistent, Limited Data

- Supervised Exercise – two small published pilot RCTs
  - Structured exercise improves calf muscle pump function (n = 30)
  - Exercise training => better 6-mo PTS and venous QOL (n = 43)
  - Limitations: severe PTS, lack of widely used/validated protocols
  - Padberg et al. J Vasc Surg 2004; 39(1):79-87.
  - Kahn SR et al. CMAJ 2011; 183(1):37-44.

- Small RCTs to evaluate short courses of aspirin, flavinoids, rutosides, aescin, defibrotide, hidrosmin => effects small, imprecise and/or inconsistent so not recommended
  Exception - pentoxyfilline may assist venous ulcer healing
  - Jull AD et al. Cochr Database Syst Rev 2012; 12:CD001733.

Compression: Effective but with Limitations

- Elastic Compression Stockings & Multilayer Compression
  - Ulcer – 9-RCT meta-analysis shows compression to aid healing
    - Mauck KF. J Vasc Surg 2014; 60:73S-92S.
  - No ulcer: Weak and conflicting evidence from small RCTs
    - Clinical: many patients state benefits, some cannot don, low risk of harm
    - Frulla M et al. Thromb Haemost 2005; 93:183-185.
    - Ginsberg JS, et al. Arch Intern Med 2001; 161(17):2105-2109.

- Compression Devices – crossover RCTs - advanced PTS
  - Intermittent pneumatic compression (n=35) => benefit
    - Ginsberg JS et al. CMAJ 1999; 160:1303-1306. (but cumbersome to use)
  - Portable venous-return assist device (n=32) => possible benefit
    - Improved symptoms (31 vs 13%, p = 0.11) and VEINES-QOL scores
    - O'Donnell MJ, et al. Thromb Haemost 2008; 99:623-629.

Comparative Studies: Relief of Venous Obstruction

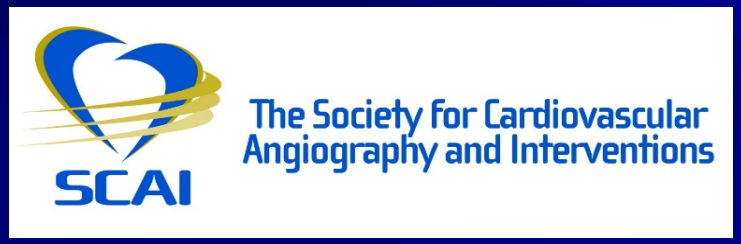
Catheter-Directed Thrombolysis (CDT) Prevents PTS

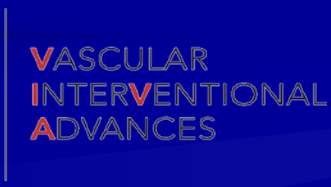
- Prospective multicenter registry - acute iliofemoral DVT
  - CDT-treated registry patients versus matched controls (AC alone)
  - CDT recipients (n=68) had better QOL at 20 months ($p < 0.01$)
  - Comerota AJ et al. J Vasc Surg 2001.

- Single-center RCT (Egypt) – streptokinase CDT
  - CDT = more normal venous function, less reflux at 6 mo ($p < 0.01$)
  - Elsharawy E et al. Eur J Vasc Endovasc Surg 2002.

- TORPEDO - single-center RCT pharmaco-mechanical CDT
  => reduced 2-year PTS (Sharifi M et al. J Endovasc Ther 2012)

Working collaboratively to ensure appropriate care for our patients





Venous Care Partnership