Superficial Vein Thrombosis:
The “Rodney Dangerfield” of Venous Thromboembolism

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Family Medicine Update
Big Sky, MT
January 2017
Disclosures

- Speaker’s Bureau: Bristol Myers Squibb/Pfizer
- Should not influence content of this talk.
What is SVT?
“Doc, my vein is hard and painful”

- Inflammation + thrombosis in a superficial vein
  - Warm, tender, red, swollen area along the course of a superficial vein; often palpable as a “cord”
- Great Saphenous Vein → small saphenous → upper extremity veins
  - 60-80% GSV; 10-20% LSV
- Recent “shift” in nomenclature....”phlebitis” → SVT
  - Emphasis on the thrombotic potential more so than the associated inflammation
Why this “lack of Respect”

• We are just more comfortable when we can see it!!
• A step back in time...
  • 125 years ago...no understanding of hypercoagulability; no US.
  • Thus, because SVT was so easily identifiable, it was held separate and apart from the more subtle and occult DVT
• 1885 leading medical treatise:
  • “Except in the cases of superficial veins, in which the vessel may be felt as a hard cord, the affliction cannot be recognized in life.”
• Bottom-line:
  • The ease of clinical diagnosis somehow was translated into its being safer than its more occult and dangerous cousin DVT
What SVT is not...

• Superficial femoral vein thrombosis ≠ Superficial vein thrombosis
  • The “fatal misnomer”
  • SFV is a **deep** vein (and a large one at that)
  • All professional societies have *banned* this term!

• Infusional thrombosis
  • Localized Inflammation of a small peripheral IV related to IV or chemical irritation
    • Usually resolves with removal of the IV and conservative cares (warm compresses, compression, topical NSAID gel)
    • AC not needed

• Suppurative superficial thrombophlebitis
  • Remove the line, “source control” (if abscess present) and start prompt IV abx
  • Again, really no role for AC
  • Septic = systemic s/s → fever, Leukocytosis, hemodynamic compromise
Epidemiology

- Likely, **not as common** as DVT (Similar to PE)
  - ~ 125K cases per year in USA
  - 0.64/1000 person years → recent community-based study in France*
- Female > Males
  - 3:2 ratio?
- Increasing incidence with increasing age (irrespective of gender)
  - Mean age 60
  - Likely d/t fact that other risk factors increase with age.
  - Complication are less likely with advancing age?
- a/w obesity and VV
  - VV → 10-20% lifetime incidence of SVT!!
  - > 75% SVT occur in VV
- Less mortal than DVT/PE
  - 1% vs ~5%
  - Likely d/t differences in the frequency of comorbid disease

What contributes to SVT?

- Trauma
- IVDU
- IV catheters
- Direct blow
- Thick blood
- Acute illness
- Thrombophilia
- Pregnancy
- IV catheters
- Hormones
- Inflammatory states
- Malignancy
- Obesity
- Stasis
- Post op
- Varicose veins
Natural h/o SVT

• Symptom resolution is almost always in 1st 6 weeks
• Thrombus takes forever to resolve!
  • Complete thrombus resolution is rare and less frequently occurs vs DVT
    • 9/68 pts showing complete resolution
• Thrombus burden and intrinsic thrombolysis likely more important than AC dose for recanalization.
  • Intermediate vs prophylactic dose LMWH → no difference in regression
• Thrombus regression
  • Distal > proximal
  • Females > males

SVT and D dimer

• DVT Dx 101
  - USA: clinical suspicion $\rightarrow$ US $\rightarrow$ done
  - Rest of the world: clinical suspicion $\rightarrow$ Formal PTP determination (Well’s) $\rightarrow$ if low/intermediate risk $\rightarrow$ D dimer
    
    ![Diagram]
    
    done \hspace{1cm} US

  - High PTP $\rightarrow$ US $\rightarrow$ done
  - So what about the DD for SVT?
  - Several studies, all with similar conclusion $\rightarrow$ unacceptably high false negative rate.
  - So...by pure luck, we in the USA are on the right track!!

Which statement is correct regarding DVT in the setting of known SVT?

A. Overall incidence is ~10%
B. When present, it is almost always contiguous with SVT
C. Incidence is variable depending on pt. characteristics
D. All are correct
The link b/t SVT and VTE

• The link suspected for years
  • Historically, poor data from small, non-prospective trials

• Current understanding: definite association with VTE
  • 3 large prospective epidemiological trials
  • 25-30% with SVT have concomitant DVT or symptomatic PE at first presentation
  • ~5% having PE!
  • ~50% DVT were “proximal”
    • More prone to embolization
  • ~40-50% were NOT contiguous to the SVT

• Consistent predictors of concomitant DVT:
  • SVT in non-varicose veins
    • Only 10-20% of SVT
  • Age > 75 years
  • Inpatient status
  • Active cancer

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<tr>
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<tbody>
<tr>
<td>Setting</td>
<td>Secondary/tertiary</td>
<td>Secondary/tertiary</td>
<td>Primary</td>
</tr>
<tr>
<td>No. of patients with SVT, no. (%)</td>
<td>844</td>
<td>788</td>
<td>171</td>
</tr>
<tr>
<td>Concomitant DVT or PE, no. (%)*</td>
<td>210 (24.9)</td>
<td>232 (29.4)</td>
<td>45 (26.3)</td>
</tr>
<tr>
<td>Concomitant DVT, no. (%)†</td>
<td>198 (23.5)</td>
<td>227 (28.8)</td>
<td>42 (24.6)</td>
</tr>
<tr>
<td>Proximal</td>
<td>82</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Distal</td>
<td>114</td>
<td>128 (16.2)</td>
<td>23</td>
</tr>
<tr>
<td>Not contiguous to the SVT</td>
<td>83</td>
<td>–</td>
<td>19</td>
</tr>
<tr>
<td>Concomitant symptomatic PE, no. (%)</td>
<td>33 (3.9)</td>
<td>54 (6.8)†‡</td>
<td>8 (4.7)</td>
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Ask SVT pts about s/s of PE!!
POST Trial: Key Pearls

• 8% rate of symptomatic thromboembolic complication at 3 months!
  • 0.5% pulmonary embolism
  • 2.8% deep vein thrombosis
  • 3.3% SVT extension
  • 1.9% SVT recurrence

• Predictors for thromboembolic complications at three months:
  • Male sex
  • h/o DVT/PE
  • Cancer
  • Absence of VV

Despite 90.5% Rx c some form of AC!!

OPTIMEV Trial: Key Pearls

• Even with varicose vein SVT, rate of concomitant DVT far from negligible i.e. 23.3%!

• Localized signs and symptoms of SVT helpful but not good enough
  • 14% with localized s/s still had concomitant DVT!

Do I need to worry about the other leg??

- **D/t** high rate of non-contiguous DVT and the finding of contralateral LE DVT, some (mostly Europeans) advocate B LE CUS*
- **POST:** 5/844 with isolated DVT in *only* the contralateral limb.
  - To be clear, there were a total of 34 DVTs in the contralateral limb but most (85%) also had DVT in the affected limb.
  - All isolated contralateral DVTs were “distal”
- Thus, < 1% rate of isolated DVT and overwhelmingly distal.
- **Bottom line:** Probably do NOT need to scan the other leg ***

**Quere I. et al. Superficial venous thrombosis and compression ultrasound imaging JVS 2012;56:1032-8

DVT in SVT

Summary

• Concomitant DVT common → ~ 25%!!
  • Several large prospective trials now provide convincing evidence

• Isolated SVT deserves close f/u
  • 8% thrombo-embolic complication rate at 3 months

• Features of SVT that should “raise your antenna”
  • h/o of DVT, absence of varicose veins, males, cancer

• We're not good enough to rule out DVT by clinical exam alone
  • About ¾ of the time, underestimated!
  • DVT often non-contiguous but rarely only in the other leg
Which statement is correct regarding DVT in the setting of known SVT?

- A. Overall incidence is ~10% 25%
- B. When present, it is almost always contiguous with the SVT
- C. Incidence is variable depending on pt characteristics
- D. All are correct

Incidence of almost 40% if SVT occurring in the absence of VV
Unprovoked SVT, like VTE, is clearly associated with cancer.
“So great, in my opinion, is the semiotic value of phlegmasia in the cancerous cachexia, that I regard this phlegmasia as a sign of the cancerous diathesis as certain as sanguinolent effusion into the serous cavities.”
SVT and Cancer

- Unprovoked DVT/PE clearly associated with subsequent development of cancer
  - 2-4 fold increased risk of cancer within 1 year of diagnosis
  - About 1 in 10 (over 2 ys) will eventually present with malignancy
- So...was Trousseau right?
SVT and Cancer

- Van Doormaal FF, et al. 2010
- N= 250; all with unprovoked first SVT
  - After analyzing 38K records b/t 1995-2004
- Age and Gender matched controls 2:1 and followed for 2 years
- 2% incidence new malignancy *both* groups
- Take-home:
  - No increased risk of cancer with first episode of unprovoked SVT
SVT and cancer

- Prandoni et al *blood* 2011
- 737 with isolated SVT not involving the SFJ. Retrospective
- 2:1 control/case followed for 2 years
- Cancer rate: 3.5% case vs. 3.9% controls
- Conclusion:
  - no increased risk
Cancer and SVT

Summary

• SVT, unlike DVT and PE, *may not* be a strong predictor of future cancer development.

• With SVT, exhaustive cancer search *not* recommended
  • Even if unprovoked

• May not apply to migratory SVT in unusual places (i.e. Trousseau’s)
SVT and Thrombophilia

• Many studies showing similar prevalence when compared with DVT.
• Think about a thrombophilia:
  • Lack of trauma
  • absence of VV
  • Concomitant DVT especially in the setting on non VV SVT
• Ask yourself: Will it change management?
  • Hint: often, it will not
In SVT, which Rx has the best data for prevention of VTE?

• A. Take 2 ASA and call me in the morning
• B. Rivaroxiban 15 mg po BID x 3 wks followed by 20 mg po qd x 9 additional weeks
• C. prophylactic dose LMWH SQ daily for 30 days
• D. Prophylactic dose fondaparinux SQ daily for 45 days
Management

• The “Curbside Barometer”

• Rx all over the map:
  • POST ➔ dose from “prophylactic” to “therapeutic”. Rx duration: 1-262 days
  • Netherlands ➔ only 20% with Rx and most with NSAIDs only.
Management

• Two principles of SVT treatment:
  • 1. symptom relief
  • 2. prevention of thromboembolic complications

• Symptom relief → NSAIDs, relative rest, avoidance of trauma, anticoagulants
  • Once symptoms controlled → graduated compression garments (Esp. varicose veins)

• Generally, a trend toward more aggressive Rx with anticoagulants
  • d/t clearer understanding of the potential morbidity of untreated disease

• Unfortunately, (still) no solid trials on which to base therapy
  • To date: only one RCT demonstrating clear superiority for a prophylactic dose of Fondaparinux
  • All other studies had serious flaws
    • Dose to small
    • Duration woefully too short
    • Only short term f/u
The typical study...

- Arch of Int Med 2003
- Double blind trial 427 pts with acute symptomatic SVT of the legs
- 3 groups:
  - 1. SQ intermediate dose enoxaparin daily
  - 2. SQ enoxaparin 1.5 mg/kg daily
  - 3. oral Tenoxicam (a British NSAID) once daily
  - 4. oral placebo once daily
- Each given once daily for.....
  - 8-12 days!? (are you kidding me??)
- Of the 30 randomized trials of SVT Rx, 27 are about the same as above!
  - Cochrane Collaboration 2013
A randomized double-blind study of low-molecular-weight heparin (parnaparin) for superficial vein thrombosis: STEFLUX (Superficial ThromboEmbolism and Fluxum)

B. COSMI,* M. FILIPPINI,* D. TONTI,† G. AVRUSCIO,‡ A. GHIRARDUZZI,§ E. BUCHERINI,* G. CAMPORESE,** D. IMBERTI,†† and G. PALARETI,* ON BEHALF OF THE STEFLUX INVESTIGATORS

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STEFLUX
(LMWH trial)

- RDBCT LMWH for SVT
  - Inclusion:
    - out-patients; acute, symptomatic LE SVT; age >18; b/t 50-130 kg; at least 4 cm long
  - Exclusion: several but not as restrictive as CALISTO
    - Allowed those with h/o of previous SVT or DVT/PE

- The players:
  - “intermediate dose” LMWH for 10 days
  - “intermediate dose” LMWH for 30 days
  - “Prophylactic dose” LMWH for 30 days
STEFLUX
outcomes assessed

• Primary outcome (at 30 days):
  • Composite of symptomatic and asymptomatic DVT
  • Relapse and/or symptomatic or asymptomatic local extension of SVT
  • Symptomatic PE

• Secondary outcome:
  • Reduction in local symptoms during Rx
  • Combined efficacy endpoint (see above) at 90 days

• Primary safety outcome:
  • Major bleeding

• Secondary safety outcome:
  • Minor bleeding, thrombocytopenia, or any other allergic reactions
STEFLUX
Efficacy Results

- **Stopped early** d/t large difference in the rate of primary outcome among the three groups.
  - Short course (10 days) “intermediate” dose: 11.3%
  - 30 d course of “prophylactic” dose: 5.7%
  - 30 d course of “intermediate” dose: 1.5%

- **Absolute Risk Reduction:**
  - 30 d “intermediate” dose vs. 10 d “intermediate” dose: 13.7% (p < 0.001)
    - NNT 7 (5-12)
    - RRR 88% (67-95%)

- **Safety:**
  - No major bleeding either during Rx or in f/u period
  - No thrombocytopenia
  - 2 with LFT elevations, mild with return to baseline after study completion
  - 2.5% rate of mild injection site hematoma
STEFLUX
Take home points

• Prophylactic dose LMWH inferior to intermediate dose.
  • Don’t use Lovenox 40 mg SQ daily!!

• Rx duration very important!!
  • 10d Rx came in last!!
  • Once active Rx stopped (no matter the Rx), event rates immediately increased across all three groups
    • ? Need for even longer Rx duration
Fondaparinux for the Treatment of Superficial-Vein Thrombosis in the Legs

Hervé Decousus, M.D., Paolo Prandoni, M.D., Ph.D., Patrick Mismetti, M.D., Ph.D., Rupert M. Bauersachs, M.D., Zoltán Boda, M.D., Benjamin Brenner, M.D., Silvy Laporte, Ph.D., Lajos Matyas, M.D., Saskia Middeldorp, M.D., Ph.D., German Sokurenko, M.D., and Alain Leizorovicz, M.D., for the CALISTO Study Group*
CALISTO Trial

• Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo trial

• International, multicenter, randomized, double blind, placebo-controlled study; circa 2007-2009

• ~3000 subjects → 2.5 mg fondaparinux SQ daily vs. injection with NACL (placebo) daily over 45 days

• 171 centers in 17 countries
Subject criteria

- Inclusion criteria: Acute, symptomatic lower limb superficial vein thrombosis at least 5 cm long (on standard duplex)
  - Age > 18
  - Hospitalized or non-hospitalized
- Exclusion criteria: Several.
- Key differences b/t CALISTO and STEFLUX
  - Hospitalized pt *allowed* in CALISTO (not in STEFLUX)
  - Generally CALISTO more restrictive
    - Any previous DVT/PE within last 6 months excluded
    - Major surgery in the past 3 months (CALISTO) vs. 1 month (STEFLUX)
CALISTO
Study Protocol

• f/u visits on day 10,30,45, 75
• No routine US exams required during f/u
• All encouraged to wear graduated compression stockings
• Allowed to take acetaminophen or topical NSAID.
**CALISTO**

Outcomes assessed...

- **Primary efficacy outcome:**
  - Composite of death from any cause, symptomatic PE, symptomatic DVT or symptomatic extension of SVT (to < 3 cm from SFJ/SPJ) up to day 47

- **Secondary efficacy outcome:**
  - as above, only now out to 77 days
  - Surgery for SVT

- **Primary safety outcome:**
  - major bleeding

- **Other Safety outcomes:**
  - clinically relevant non-major, minor and any bleeding
CALISTO Results

• Primary efficacy outcome:
  • 13 of 1502 (0.9%) fonda group vs. 88/1500 (5.9%) placebo group
  • RR 0.15 (95CI 0.08-0.26) P <0.001
  • NNT→20
  • Each component with significantly less occurrence in fonda group; including PE
    • Exception= incidence of death similar in each group
    • NNT to prevent 1 PE = 300 (similar to NNT for chemical prophylaxis in acutely ill medical patients)
  • Risk of DVT or PE reduced by 85% in fonda group

• All efficacy results *maintained* at day 77
  • Recall clear “rebound” in LMWH studies up to 30 days duration (STEFLUX)

• Surgery for SVT much more common in placebo group than fonda group
  • 52 (3.5%) vs. 8 (0.5%) or 81% RRR
**Figure 1.** Kaplan–Meier Estimates of the Probability of the Primary Efficacy Outcome, According to Study Group.

The primary efficacy outcome was a composite of death from any cause, symptomatic pulmonary embolism, symptomatic deep-vein thrombosis, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis. Data from patients who were lost to follow-up were censored at the time of the last contact. Error bars indicate 95% confidence intervals.

End of treatment
CALISTO
Safety results

• Major, Clinically relevant non-major, minor, and any bleeding no difference b/t groups
• Similar at both 45 days (active treatment phase) and 77 days
• No clinically relevant between group differences in the incidence of any other adverse events.
• No episodes of thrombocytopenia in fonda group.
CALISTO
Take home points

• Fonda superior over placebo for prevention of VTE/SVT extension
• Efficacy seems to “hold” after Rx discontinuation
  • No “catch-up” after Rx drug stopped
• Fonda 2.5 mg daily:
  • safe and well tolerated
  • prevents many surgical procedures for SVT
  • lower % requiring “Step up” therapy to full-dose systemic anticoagulation
• Caveat: Was this “real world”?
  • Cancer, h/o VTE in past 6 months, IV catheter, SVT < 3 cm of SFJ...all excluded!
    • Related to the ethics of higher risk with placebo arm
Where the rubber meets the road...

- Price seems to be as important (often more) than management/prognosis

- Out-of-pocket price of Fondaparinux (2.5 mg SQ x 45d)
  - A. $123.48
  - B. $269.58
  - C. $485.69
  - D. $685.79
  - E. $749.50
  - F. Son, forget about college this year...
Expense

- Fonda x 45 days → $749.50
- LMWH (intermediate dose) x 45 days → $723.51
- LMWH x 10 days → $168.11
  - VKA mild additional expense
The “Rub”:
Even though the *relative* effectiveness (of fonda) is substantial, the *absolute* difference b/t drug and placebo was quite modest.

Simple MATH: $750/SVT \times 300 \text{ SVT} = $225,000 to PREVENT 1 PE
Cost effectiveness results

• Fonda: ICER of $500,000 per QALY (10x higher than a “cost effective” ICER per QALY)
  • Strikingly different compared to other indications for anticoagulants
    • prophylaxis after total joint surgery; DVT prophylaxis is cost SAVING
      • Cost per VTE avoided = $141,000

• Prevents 123 VTE’s and 2 deaths per 10,000 pts!!

• Take home:
  • HIGH cost/MODEST benefit
  • Specific subgroups should be targeted. (h/o VTE, cancer, lack of VV)

• Caveat:
  • Fondaparinux 5 times cheaper in Europe
What about Stockings?

- Relatively cheap, certainly safe but... What does the data show?
Therapeutic Effect of Compression Stockings Versus no Compression on Isolated Superficial Vein Thrombosis of the Legs: A Randomized Clinical Trial

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Department of Dermatology, Division of General Dermatology, Medical University Vienna, Waehringer Guertel 18–20, A-1090 Vienna, Austria

Stockings and SVT

- The only RCT, single center (Austria) 21 days
- 73 patients...
  - 39 compression vs. 41 no compression
    - 23-32 mm hg, thigh length
    - No sham stocking in the “no compression” group.
- All received LMWH at prophylactic dosage
  - NSAID use allowed
- Standard compression US done weekly
- Primary outcome: pain relief
- Secondary outcome: analgesics consumed, skin erythema, thrombus length
- Safety outcome: symptomatic OR asymptomatic DVT and HITT

Stockings and SVT

Results...

- Pain: no difference
- Thrombus regression: faster early but no difference by day 21
- DVT or HIT: no difference
- Conclusion:
  - *No benefit* to wearing compression stockings for a prolonged period of time in addition to LMWH and NSAIDs
  - Perhaps some benefit early on (1\textsuperscript{st} week)
    - Thrombus regression in 1\textsuperscript{st} week
  - Bandages or Velcro devices better?

On the Horizon...
SURPRISE trial

• Prospective, randomized, open label, blinded adjudication non-inferiority trial
• 45 days of prophylactic fondaparinux vs prophylactic dose Rivaroxaban
• Estimated 450 pts
• Only treating “high risk” SVT; at least one of the following:
  • Age > 65
  • Male sex
  • Previous DVT/PE/SVT
  • Active or h/o cancer, autoimmune disease
  • SVT in a non-varicose vein
What SURPRISE may tell us

• Risk stratification may be beneficial
  • Seems to be a group of SVT that perhaps does not require AC
    • Placebo arms of many studies find low rates of thromboembolic complications
      • CALLISTO: 5.9% with DVT, PE, or SVT extension
  • Better bang for our buck?
    • Recall the $500,000 ICER/QALY?

• Effective Rx in oral form...i.e. better adherence
  • High non-adherence rates→ known issue with any injectable.

• Caveats:
  • NOT double blinded
  • Drug company sponsored

So...what should I do?

- SVT + DVT?.... Therapeutic AC
- SVT thrombus head within 3 cm of SFJ or SPJ?.....Therapeutic AC
- High risk SVT?
  - Intermediate-dose LMWH OR fondaparinux 2.5 mg x 45 days
    - Prophylactic dose and any duration less than 45 days clearly inferior
  - NSAID for pain relief
    - Warn about GIB, especially if also on AC
  - Perhaps stockings for 1st week
    - Inform them this intervention is not expected to have any impact on pain, erythema or the rate of thrombus regression in 21 days!!
- Low risk SVT?
  - NSAID, modalities, elevation.
  - Assess individual pt value system RE: the (unlikely) risk of a complication
    - Is it worth $750 to prevent DVT/PE with ~ 94% chance of doing just fine
Summary

• Although quite common, SVT remains poorly understood.
• SVT’s underlying pathophysiology and causes similar to DVT
• Concomitant DVT/PE is not uncommon with SVT
  • “big 4” risk factors…h/o prior VTE; absence of varicose veins; cancer; males
• Venous Duplex recommended in SVT→ r/o DVT, extent of SVT
• Malignancy likely not as closely a/w SVT when compared to DVT
• Management strategies evolving with better understanding of risk for VTE
Thank You!