



Case SIGNOUT:

Mr. G is a 61-year-old man with hypertension and a history of varicose veins who presents from his PMD's office for superficial venous thrombosis. He reports lower extremity swelling and pain for the past several months, especially after standing all day at work, as well as a palpable cord in his right leg. He's had no associated SOB, chest pain, weight loss, or melena/hematochezia, and age-appropriate cancer screening is up to date. He has no personal or family history of thrombosis. On admission, his VS were wnl and exam showed a tender, palpable cord extending from the right lower calf to the thigh and U/S showed thrombosis of the right greater saphenous vein, with no associated DVT.

Clinical Question: Should patients with superficial venous thrombosis without concomitant deep vein thrombosis or symptomatic PE at presentation receive anticoagulation therapy?

Background:

- Superficial Venous Thrombosis (SVT):
 - Thrombosis of the greater or lesser saphenous veins or their tributaries
 - Common, with an incidence that may exceed DVT- estimated to be 3-11% in the general population
 - Migrating superficial venous thrombosis is often a marker for carcinoma
 - Presents with induration, tenderness, and pain along a superficial vein, +/- palpable cord
- Risk factors for the development of SVT:
 - Virchow's triad (venous stasis, endothelial dysfunction, hypercoagulable state)
 - The majority of cases occur in varicose veins
 - IV catheters/infusion (stasis + endothelial injury)
 - Thrombophilia is only weakly associated with SVT
- Complications of SVT:
 - While SVT in and of itself cannot cause PE, it is NOT a benign condition
 - Can lead to thromboembolic complications (in one large prospective study, SVT led to thromboembolic complications in 8.3% of patients with PE or DVT in 3.3% of patients)
- Goals of Treatment:
 - Alleviation of symptoms: leg elevation, warm compresses, NSAIDs
 - Prevention of extension to the deep venous system: anticoagulants (LMWH, factor X inhibitors, NSAIDs)
- Treatment Strategies:
 - NSAIDs: shown in a small RCT to significantly reduce extension and recurrence of SVT
 - Anticoagulants: LMWH can reduce extension/recurrence of SVT by 70%, but efficacy in reducing PE/DVT is unknown
 - Dosing: existing studies are small, but show no benefit of therapeutic vs. prophylactic dose
 - Duration: unclear, in studies using 12-30 days of a/c many thromboembolic complications occurred at >30 days
 - Vein ligation/excision: associated with higher rates of DVT compared with anticoagulant therapy; in cases of recurrent SVT vein stripping can be performed after initial inflammation has subsided
- Indications for Anticoagulation:
 - American College of Chest Physicians guidelines: anticoagulation if SVT \geq 5cm, \leq 5cm away from saphenofemoral junction, or patients with positive medical risk factors (recent surgery, cancer, h/o DVT)
 - Patients with SVTs secondary to venous ablation therapy do NOT need to be anticoagulated – this etiology of SVT is more benign with less propensity for embolization

Search Strategy

Database: PubMed: (((venous thrombosis[MeSH Terms]) AND superficial) AND anticoagulant) AND randomized controlled trial[Publication Type]) AND English[Language] → 26 results

Decousus H, Prandoni P, Mismetti P, Bauersachs RM, Boda Z, Brenner B, Laporte S, Matyas L, Middeldorp S, Sokurenko G, Leizorovicz A, CALISTO Study Group. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *New England Journal of Medicine*. 2010;**363**(13):1222-32.



Group	Criteria or definition	n
Population screened	Hospitalized or non-hospitalized patients at 171 centers in 17 countries	?
Inclusion criteria	18 years or older with symptomatic SVT at least 5 cm long measured by compression ultrasound	?
Exclusion criteria	Symptoms >3 wks; treated for cancer w/in 6 mo; DVT/PE currently or in past 6 mo; thrombosis a/w sclerotherapy or IV catheter; thrombus w/in 3cm of saphenofemoral junction; SVT w/in 3mo; antithrombotic therapy for >48hrs or NSAID for >72hrs; major surgery w/in 3mo, plt <100,000, CrCl <30, hepatic impairment	?
Treatment group	Fondaparinux 2.5mg SQ daily (prophylactic dose) x45 days	1502
No treatment group	Placebo 2.5mg SQ daily x45 days	1500

Primary endpoints: composite of death from any cause, symptomatic pulmonary embolism, symptomatic DVT, symptomatic extension of SVT to saphenofemoral junction, or symptomatic recurrence of SVT; all up to day 47

Secondary endpoints: composite primary outcome up to day 77, as well as the following up to day 47 and day 77: each component of the 1° outcome detailed above, composite of symptomatic DVT or PE, and surgery for symptomatic SVT

• **Are the Results of the Trial Valid?**

- Randomized: YES, 3002 patients were randomized to one of the two study arms
- All patients accounted for at end: NO, 18 patients in the fondaparinux group and 22 patients in the placebo group did not undergo evaluation on day 47. Reasons included withdrawal from study, loss to follow-up, adverse event, not meeting eligibility criteria, and non-compliance
- Intention to treat: YES, no crossover was reported and all patients who underwent randomization were included in outcome analysis; only patients who received at least one dose of med/placebo were included in safety analysis)
- Blinding: YES, the study was double-blinded – both investigators and patients
- Groups similar at start of trial: YES, clinical characteristics, meds/interventions received prior to study, and adherence (seen by # of returned empty vs. full syringes) were not statistically significantly different between the two groups. However, patients in the placebo group received anticoagulants and NSAIDS more frequently than in the fondaparinux group. Of note, almost all patients were outpatients (10 patients in treatment group and 11 in placebo group were hospitalized)
- Equal treatment of groups: YES
 - Follow-up visits at days 10±2, 30±2, 45±2, and 75±2
 - U/S only if clinical signs/symptoms of DVT or worsening ST, at discretion of the physician
 - Fondaparinux and placebo delivered to patients as visually identical pre-filled syringes
 - All patients filled out injection diary and were encouraged to self-administer drug
 - Patients were encouraged to wear compression stockings and allowed to take acetaminophen and/or NSAIDs as needed (although ASA ≤325mg was discouraged)
- Did randomization work: YES

• **Are the Results of the Trial important?**

- Size of treatment effect: significant in both primary and secondary outcomes, with the exception of the incidence of death, which did not differ significantly between the groups
- Precision of the estimate of the effect: given that this trial has a large sample size the estimate of the effect is likely quite precise.

Endpoint	Result F n=1502 P n=1500	Significance	ARR	NNT
Primary composite outcome	F: 13 P: 88	<0.001	-5%	20
Secondary Outcomes at 47d				
1. Death	F: 2 P: 1	1.00	0.1%	--
2. PE	F: 0 P: 5	0.03	-0.3%	333
3. DVT	F: 3 P: 18	<0.001	-1.0%	100
4. DVT or PE	F: 3 P: 20	<0.001	-1.1%	88
5. Extension of SVT	F: 4 P: 51	<0.001	-3.1%	32
6. Recurrence SVT	F: 5 P: 24	<0.001	-1.3%	77
7. Surgery for SVT	F: 11 P: 57	<0.001	-3.1%	32
Morbidity	Result F n=1499 P n= 1488	Significance	ARI	NNH
Major Bleeding	F: 1 P: 1	1.00	0%	--
Clinically relevant bleeding	F: 5 P: 7	--	--	--
Minor bleeding	F:9 P:6			
Any bleeding	F: 15 P 13			
Arterial thrombosis	F: 0 P: 3			

**F=fondaparinux, P=placebo

• **Can I apply these results to my patient**

- Comparison of my patient to trial patients: My patient likely would have qualified for this trial in terms of clot length (>5cm) and absence of relevant co-morbidities or recent anti-thrombotic therapy. His characteristics are similar to the baseline characteristics of the study population. His U/S report did not comment on proximity of the clot to the saphenofemoral junction, and so it may have extended to w/in 3cm of the junction, placing him at higher risk for DVT/PE than the subjects of this trial
- All clinically important outcomes considered: YES. Prevention of PE is the most relevant endpoint in considering the clinical significance of SVT. Other endpoints (extension/recurrence of SVT and DVT) are significant primarily as surrogate endpoints for PE risk, and are probably less important; although some of these other endpoints may have an impact on patient's symptoms and quality of life
- Likely benefits outweigh potential harms and cost: Unclear
 - Does show that fondaparinux decr risk of SVT progressing to DVT/PE w/out adverse effects
 - NNT for PE prevention is similar to that of LMWH DVT ppx in acutely ill medical patients, which we feel is a clinically indicated treatment
 - However, DVT/PE rate of 1.3%, which is similar to the false negative rate of accepted diagnostic tools for DVT or PE diagnosis (venous Doppler, VQ scan, CTA) – so how much are we gaining?
 - An informal cost analysis in the NEJM found that taking into account cost of fondaparinux verses cost saved by preventing DVT/PE → net cost of \$1900/pt, without any lives saved
 - Cost-effectiveness analysis based on this trial published in *Chest* in 2012 concluded fondaparinux for 45 days is not cost-effective for treatment of isolated SVT in the legs
 - Brings to light the importance of scrutinizing clinical trials beyond just whether or not they show a statistically significant result

References:

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