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Implications from the ACCP 2012 Consensus Guidelines for the Management of Thrombosis: a case based approach

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About the ACCP guidelines

Widely considered the gold standard for thrombosis prevention and therapy:

- Since 1986 every few years, authoritative reviews
- consists of 24 articles, 801 pages, **600 recommendations**
- Electronically freely accessible
- Dealing with oral and parenteral anticoagulants & antiplatelet drugs, prevention & **treatment of VTE**, perioperative management of antithrombotic therapy, and antithrombotic therapies for cardiovascular diseases

http://journal.publications.chestnet.org

42-year old male (JR)

1994 proximal DVT (right leg) and symptomatic PE
- after surgery (knee operation)

6-months OAC **→ACCP 2012**

9th ACCP Guidelines (2012) on VTE treatment

Duration of anticoagulant treatment following DVT/PE

Condition	Recommendation Grade
Proximal DVT or PE	Minimum 3 months (1B)
First **provoked** proximal DVT or PE	**3 months (1B if surgical,** 2B if non-surgical and low or moderate bleeding risk [BR])
First **unprovoked** proximal DVT or PE	Extended if BR low or moderate (2B), 3 months if BR high (1B)

Chest 2012;141;e419S-e494S

9th ACCP Guidelines (2012) on VTE treatment

Why 3 months rather than 6 or 12 months?

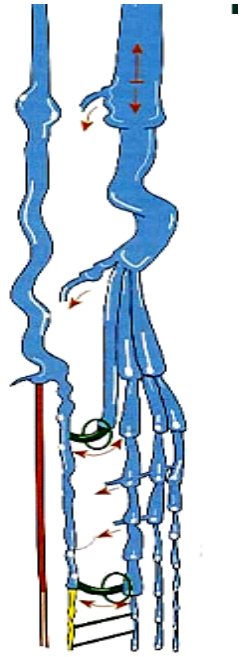
Table 17—*[Section 3.1.1-3.1.4] Summary of Findings: Six or Twelve Months vs Three Months as Minimum Duration of Anticoagulation for VTE*[a,b,167,203,204]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With 3 mo	Risk Difference With 6 or 12 mo (95% CI)
Recurrent VTE	2,061 (6 studies), 1-3 y	Moderate[c-e] due to imprecision	RR 0.89 (0.69-1.14)	115 per 1,000	13 fewer per 1,000 (from 36 fewer to 16 more)
Major bleeding	2,061 (6 studies), 1-3 y	High[f]	RR 2.49 (1.2-5.16)	9 per 1,000	13 more per 1,000 (from 2 more to 37 more)
Mortality[g]	1,331 (5 studies), 1-3 y	Moderate[d] due to imprecision	RR 1.3 (0.81-2.08)	44 per 1,000	13 more per 1,000 (from 8 fewer to 47 more)

42-year old male (JR)

1994 proximal DVT (right leg) with submassive PE
- after surgery (knee operation)
  3-months OAC (ACCP 2012)

2002 superficial vein thrombosis (right leg)
6-months OAC **→ACCP 2012**



Postthrombotic syndrome
- chronisch venous insufficiency → ulcer
- varicosis → superficial vein thrombosis

Recommendation: stockings after DVT (2B)

9th ACCP Guidelines (2012) on VTE treatment

Superficial vein thrombosis (SVT)

8.1.1. In patients with superficial vein thrombosis (SVT) of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

Remarks: Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.

A prospective study of 844 pts with acute SVT of 5 cm:
4% symptomatic PE, 10% proximal DVT, 13% additional distal DVT

9th ACCP Guidelines (2012) on VTE treatment

Superficial vein thrombosis

Table 31—*[Section 8.1] Summary of Findings: Fondaparinux vs Placebo for Acute SVT*[a-c,382]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With No Fondaparinux	Anticipated Absolute Effects: Risk Difference With Fondaparinux (95% CI)
Mortality	3,002 (1 study), 3 mo	Moderate[d-g] due to imprecision	RR 1.99 (0.18-21.87)	4 per 1,000[h]	4 more per 1,000 (from 3 fewer to 83 more)
VTE	3,002 (1 study), 3 mo	High[d]	RR 0.18 (0.06-0.53)	33 per 1,000[h]	27 fewer per 1,000 (from 16 fewer to 31 fewer)
SVT recurrence	3,002 (1 study), 3 mo	High[d]	RR 0.31 (0.14-0.68)	19 per 1,000[h]	13 fewer per 1,000 (from 6 fewer to 16 fewer)
Major bleeding	2,987(1 study), 47 d	Moderate[d,e,i] due to imprecision	RR 0.99 (0.06-15.86)[e]	1 per 1,000	0 fewer per 1,000 (from 1 fewer to 10 more)

CALISTO (Comparison of ARIXTRA in lower Limb Superficial Thrombophlebitis with Placebo).

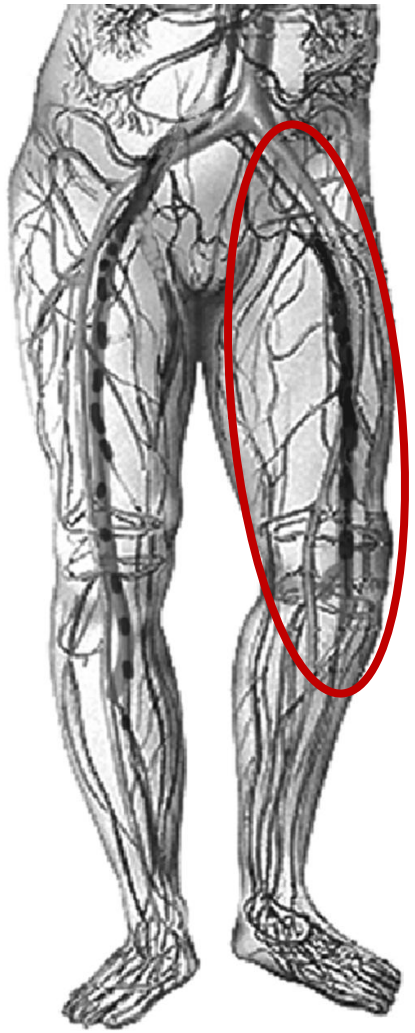
N Engl J Med. 2010;363(13):1222-1232.

42-year old male (JR)

2/2003 unprovoked, proximal DVT (left leg)

extended OAC

→ACCP 2012



9th ACCP Guidelines (2012) on VTE treatment

Duration of anticoagulant treatment following DVT/PE (I Recurrence)

… has to be based on etiology and bleeding risk (BR)

Table 19—*[Section 3.1.1-3.1.4] Estimated Absolute Difference in Recurrent VTE and Major Bleeding Events (Including Fatal Events) With 5 Years of vs No Extended Anticoagulation*

	Outcomes After 5 y of Treatment	Risk of Bleeding: Low	Intermediate	High[a]
First VTE provoked by surgery	Recurrent VTE reduction per 1,000	↓26 (19-27) (1 fatal)[b]	↓26 (19-27) (1 fatal)[b]	↓26 (19-27) (1 fatal)[b]
	Major bleeding increase per 1,000	↑24 (2-73) (3 fatal)[b]	↑49 (1-173) (5 fatal)[b]	↑98 (1-346) (11 fatal)[b]
First VTE provoked by a nonsurgical factor/first unprovoked distal DVT	Recurrent VTE reduction per 1,000	↓132 (93-137) (5 fatal)[c]	↓132 (93-137) (5 fatal)[c]	↓132 (93-137) (5 fatal)[b]
	Major bleeding increase per 1,000	↑24 (2-73) (3 fatal)[c]	↑49 (1-173) (5 fatal)[c]	↑98 (1-346) (11 fatal)[b]
First unprovoked proximal DVT or PE	Recurrent VTE reduction per 1,000	↓264 (186-273) (10 fatal)[d]	↓264 (186-273) (10 fatal)[d]	↓264(186-273) (10 fatal)[b]
	Major bleeding increase per 1,000	↑24 (2-73) (3 fatal)[d]	↑49 (1-173) (5 fatal)[d]	↑98 (1-346) (11 fatal)[b]
second unprovoked VTE	Recurrent VTE reduction per 1,000	↓396 (279-409) (14 fatal)[e]	↓396 (279-409) (14 fatal)[d]	↓396 (279-409) (14 fatal)[c]
	Major bleeding increase per 1,000	↑24 (2-73) (3 fatal)[e]	↑49 (1-173) (5 fatal)[d]	↑98 (1-346) (11 fatal)[c]

42-year old male (JR)

→ poor compliance

20.9.2007 superficial vein thrombosis (GSV, SSV)
- start OAC without LMWH

25.9.2007 proximal **progression SVT** (right leg)
- INR 2.9, switch to LMWH once daily

1.10.2007 **bilaterale PE** with recurrent DVT (external iliac vein, right leg)
→ LMWH ↑, twice daily, IVC filter

42-year old male (JR)

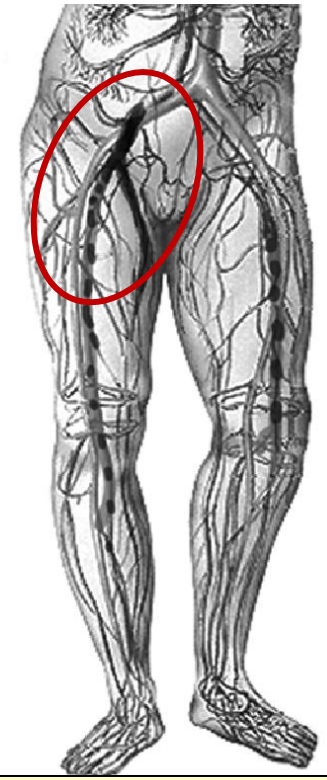
→ poor compliance

20.9.2007 superficial vein thrombosis (GSV, SSV)
- start OAC without LMWH

25.9.2007 proximal **progression SVT** (right leg)
- INR 2.9, switch to LMWH once daily

1.10.2007 **bilaterale LE** with **recurrent DVT** (external iliac vein, right leg)
→ LMWH ↑, twice daily, IVC filter

42-year old male (JR)



10/2007 recurrent, unprovoked,
proximal DVT (right leg)

→ACCP 2012

Diagnosis of recurrent DVT:

Recommendation: proximal CUS or highly sensitive D-dimer (grade 1B)

Recommendation: abnormal but nondiagnostic CUS → **venography (1B)**

or

- serial proximal CUS (2B)
- sensitive D-dimer test with serial proximal CUS if positive (2B)

42-year old male (JR)

→ poor compliance

20.9.2007 superficial vein thrombosis (GSV, SSV)
- start OAC without LMWH

25.9.2007 proximal **progression SVT**
- INR 2.9, switch to LMWH once daily

1.10.2007 **bilaterale LE** with recurrent DVT (external iliac vein, right leg)
→ **LMWH ↑, twice daily**, IVC filter

9th ACCP Guidelines (2012) on VTE treatment

Once or twice daily dosing of LMWH

5.4.2. In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C). same for DVT

Table 8—*[Section 2.5.2] Summary of Findings: LMWH Once vs Twice Daily for Initial Anticoagulation of Acute VTE*[a,b,81]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Twice Daily	Anticipated Absolute Effects: Risk Difference With LMWH Once Daily (95% CI)
Mortality	1,261 (3 studies), 3 mo	Low[c-e] due to inconsistency and imprecision	RR 1.05 (0.57-1.94)	31 per 1,000	2 more per 1,000 (from 13 fewer to 29 more)
VTE recurrence	1,261 (3 studies), 3 mo	Low[c,e,f] due to inconsistency and imprecision	RR 0.86 (0.52-1.42)	49 per 1,000	7 fewer per 1,000 (from 24 fewer to 21 more)
Major bleeding	1,522 (5 studies), 10 d	Moderate[c,e] due to imprecision	RR 1.13 (0.48-2.66)	12 per 1,000	2 more per 1,000 (from 6 fewer to 20 more)

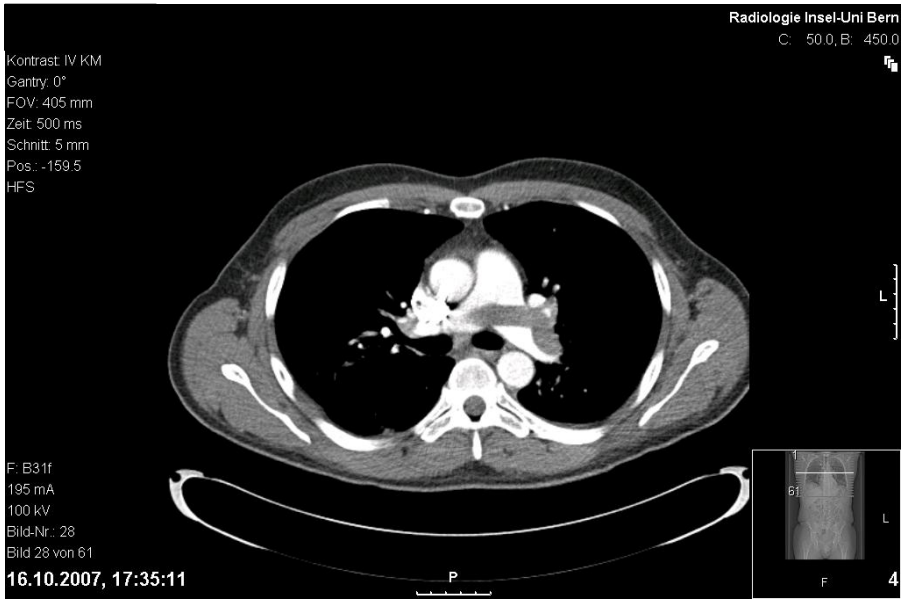
42-year old male (JR)

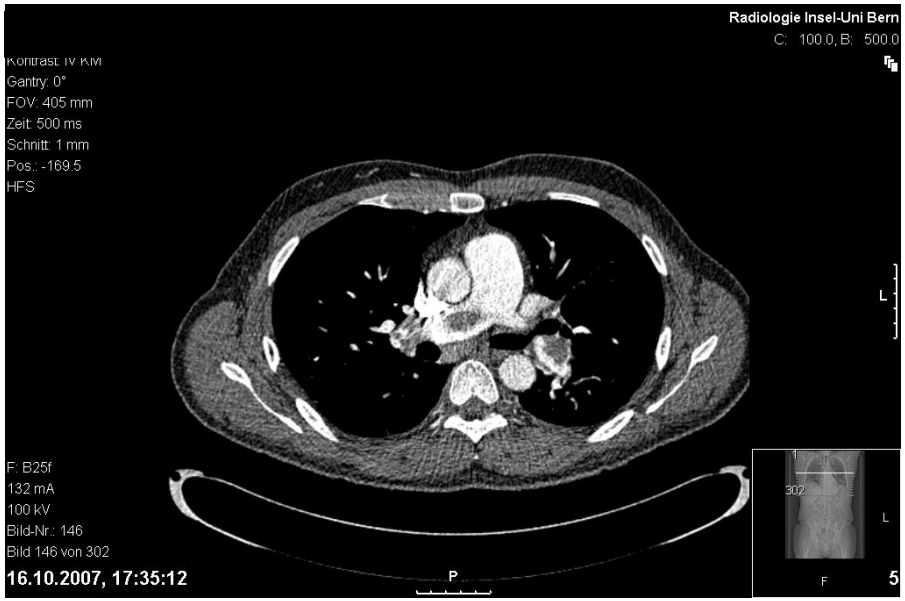
→ poor compliance

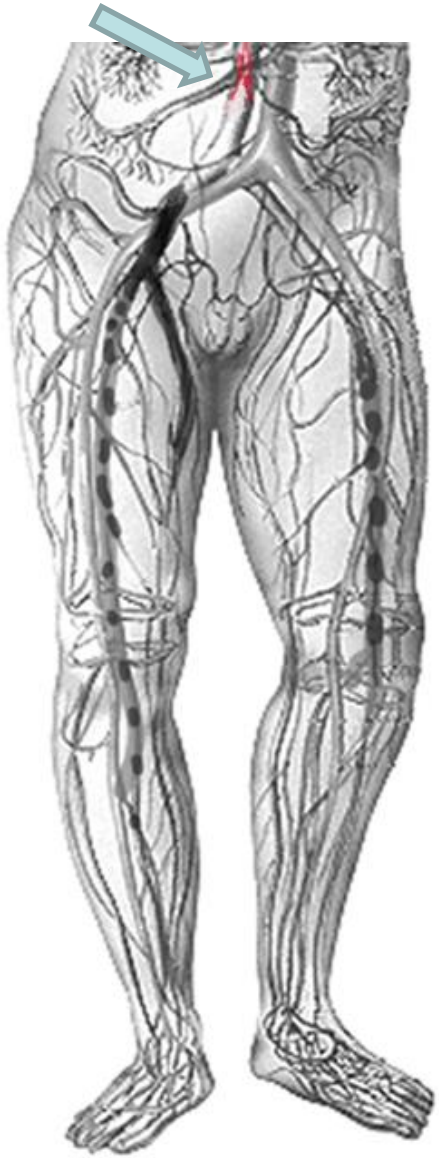
20.9.2007 superficial vein thrombosis (GSV, SSV)
- start OAC without LMWH

25.9.2007 proximal **progression SVT**
- INR 2.9, LMWH once daily (compliance?)

1.10.2007 **bilaterale LE** with recurrent DVT (external iliac vein, right leg)
→ LMWH ↑, twice daily**, IVC filter**







Cavafilter

→ACCP 2012 …

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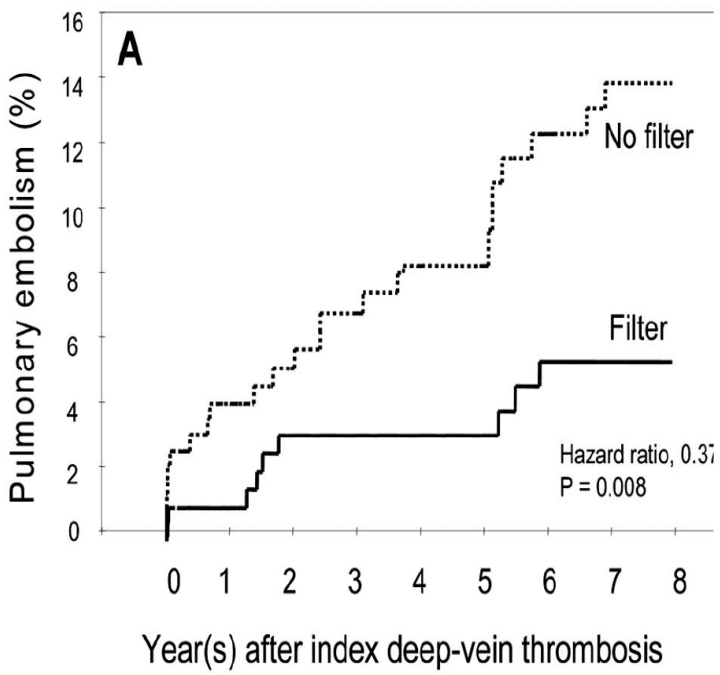
9th ACCP Guidelines (2012) on VTE treatment

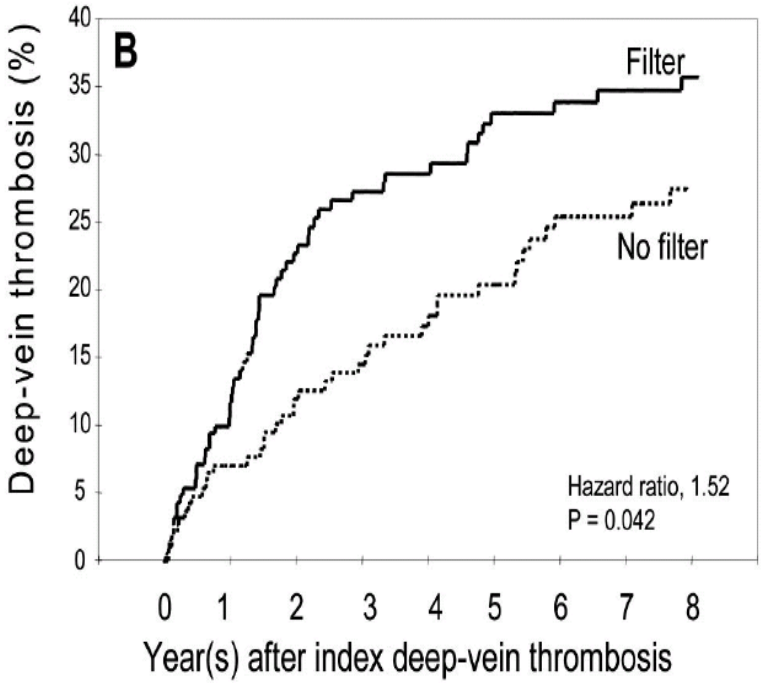
IVC filters for the initial treatment of VTE

5.9.1. In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B). same for DVT

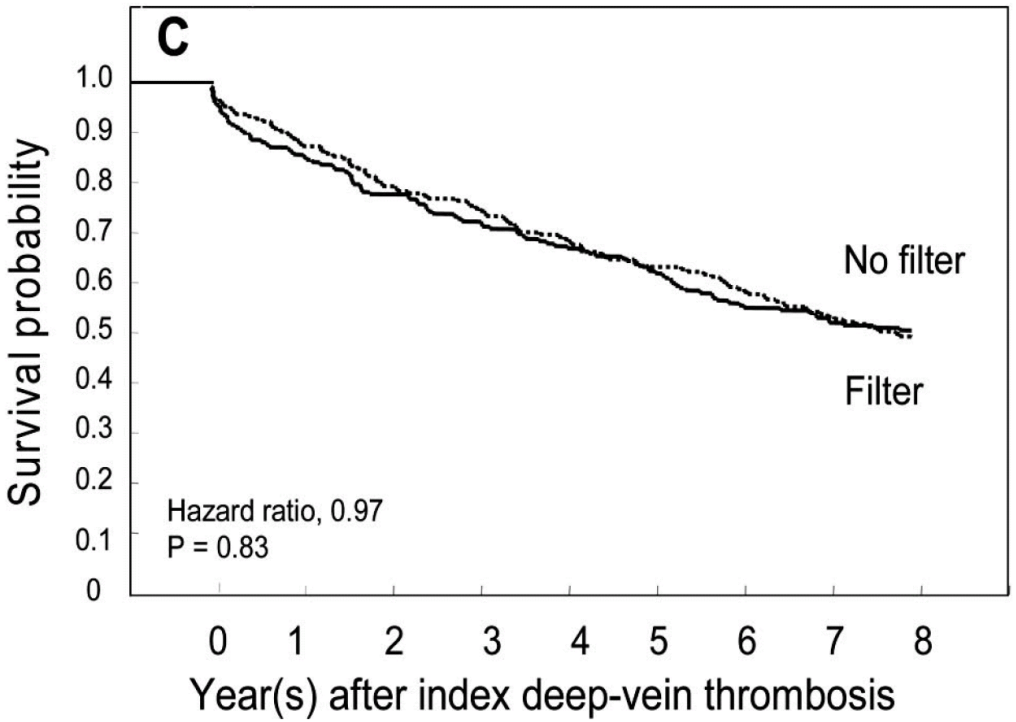
5.9.2. In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B). same for DVT

IVC filter do not eliminate risk of PE and increase risk of DVT





Circulation 2005;112:416-22



.. IVC filter do not alter combined frequency of DVT and PE (i.e. recurrent VTE) and mortality.

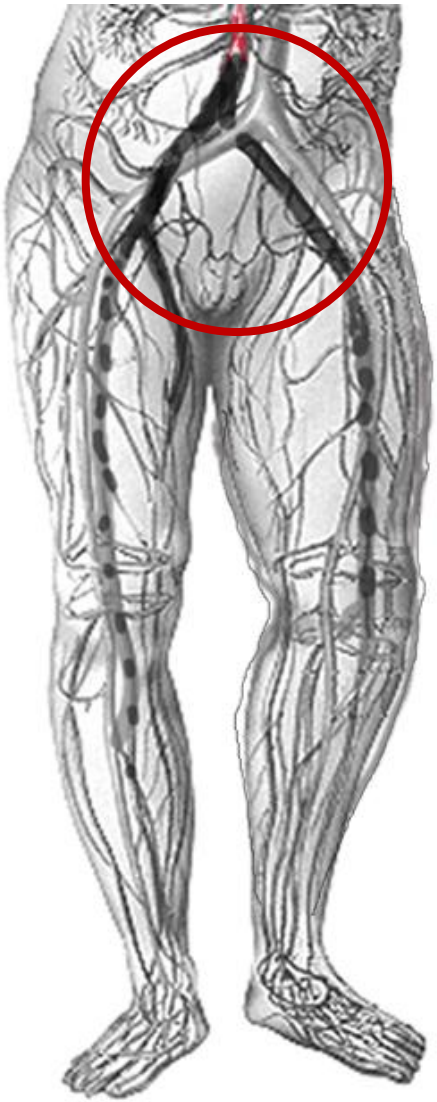
Circulation 2005;112:416-22

42-year old male (JR)

2.12.2007 ascending
iliofemoro-caval DVT
→ INR 2.1 (compliance?)

new INR target 3-4

→ACCP 2012



9th ACCP Guidelines (2012) on VTE treatment

Intensity of anticoagulant effect

3.2. In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B).

Chest 2012;141;e419S-e494S

9th ACCP Guidelines (2012) on VTE treatment

Thrombus removal in acute iliofemoral DVT

2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT (see text)* and attach a high value to prevention of PTS and a lower value to the initial complexity, cost, and risk of bleeding with CDT are likely to choose CDT over anticoagulation alone.

* Patients with **DVT that involves the iliac and common femoral veins** are at highest risk of PTS, recurrent VTE and, therefore, are the subset with greatest potential to benefit from thrombus removal strategies.

Chest 2012;141;e419S-e494S

CaVenT Study

multicentre, open-label, RCT of efficacy and safety of additional CDT with alteplase in first-time acute iliofemoral DVT

co-primary effect variables: iliofemoral patency @ 6 mo and frequency of PTS @ 24 mo

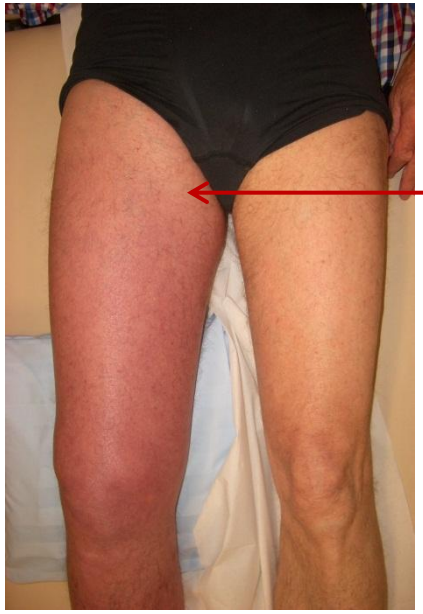
	Additional catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)		p value*
	n	% (95% CI)	n	% (95% CI)	
Post-thrombotic syndrome at 24 months†	37	41·1% (31·5–51·4)	55	55·6% (45·7–65·0)	0·047
Iliofemoral patency at 6 months†‡	58	65·9% (55·5–75·0)	45	47·4% (37·6–57·3)	0·012
Post-thrombotic syndrome at 6 months§	27	30·3% (21·8–40·5)	32	32·2% (23·9–42·1)	0·77

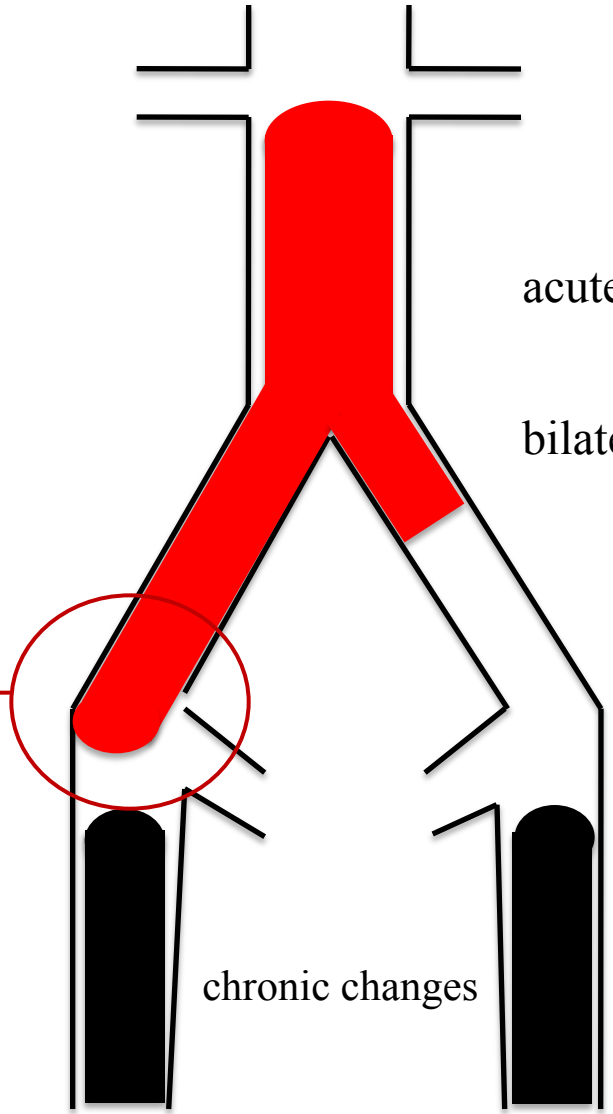
ARR of PTS @ 24 mo 14·4% *[95% CI 0·2–27·9]*; NNT 7 *[95% CI 4–502]*

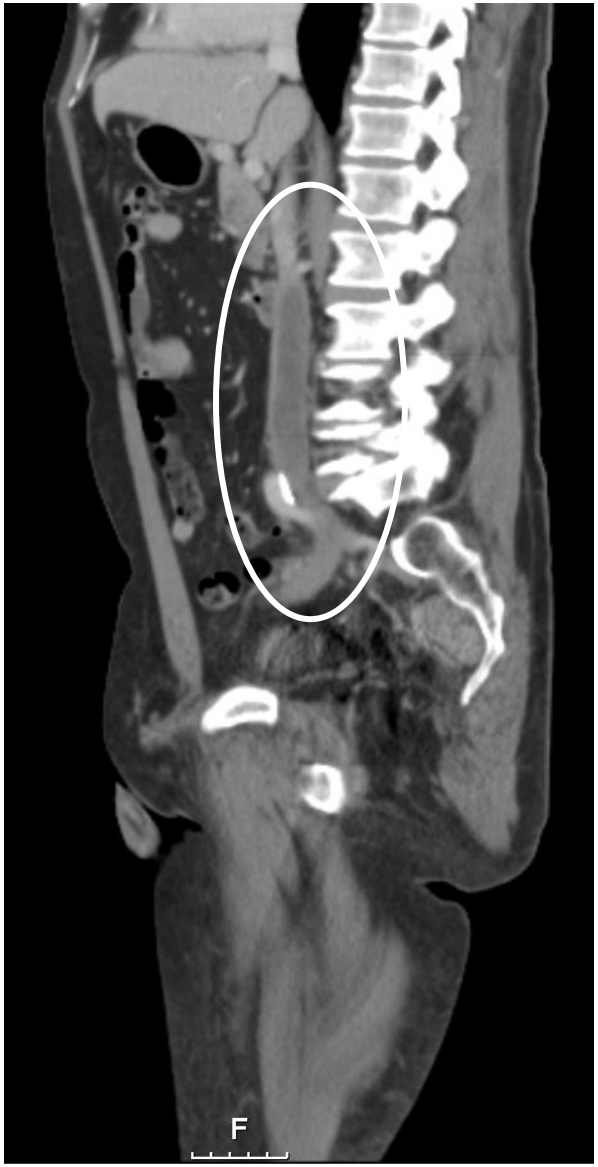
Lancet. 2012; 379(9810):31-8

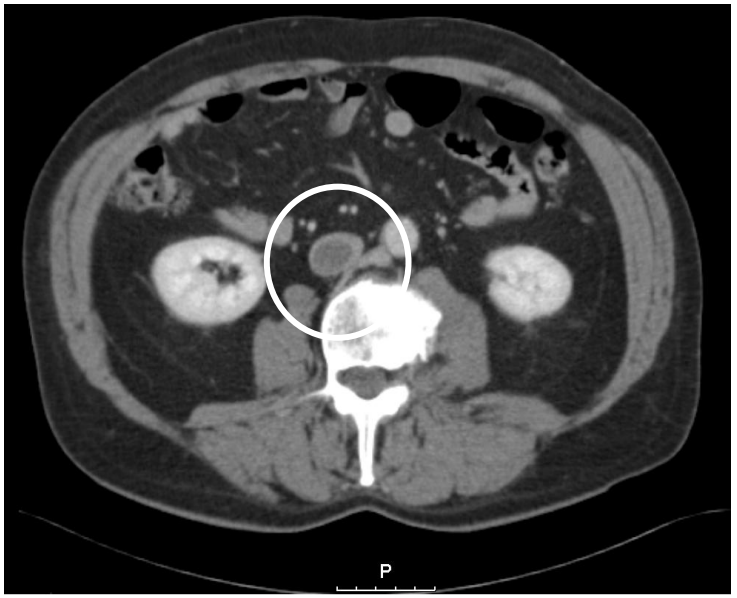
Acute-on-chronic ascending iliofemoral DVT

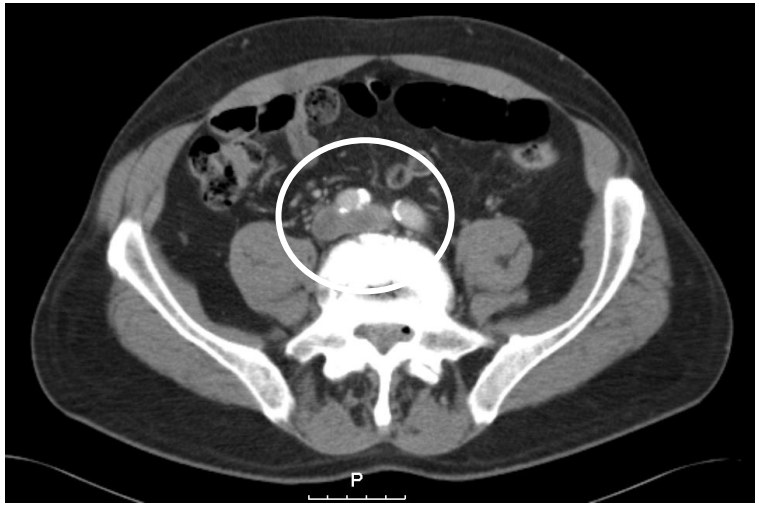
history of bilateral femoral DVT











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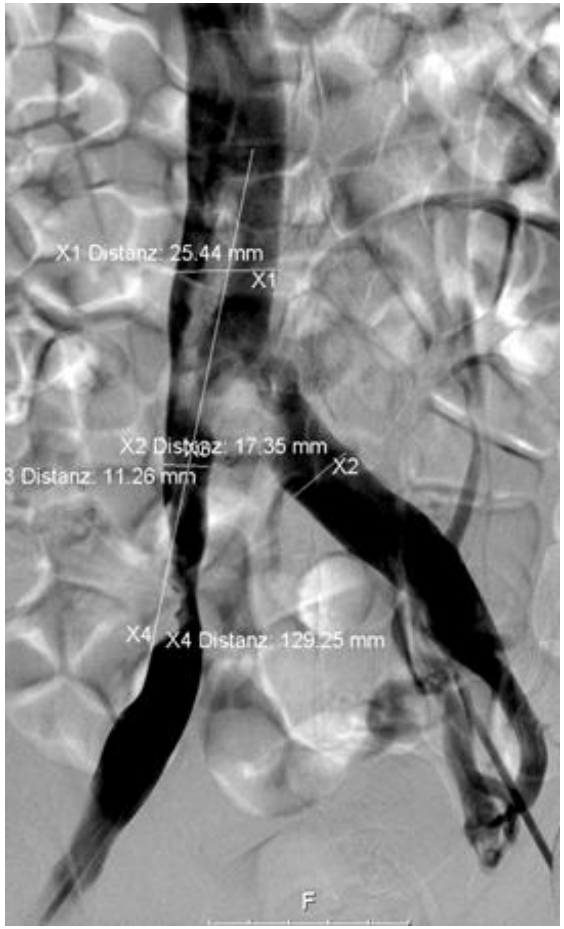
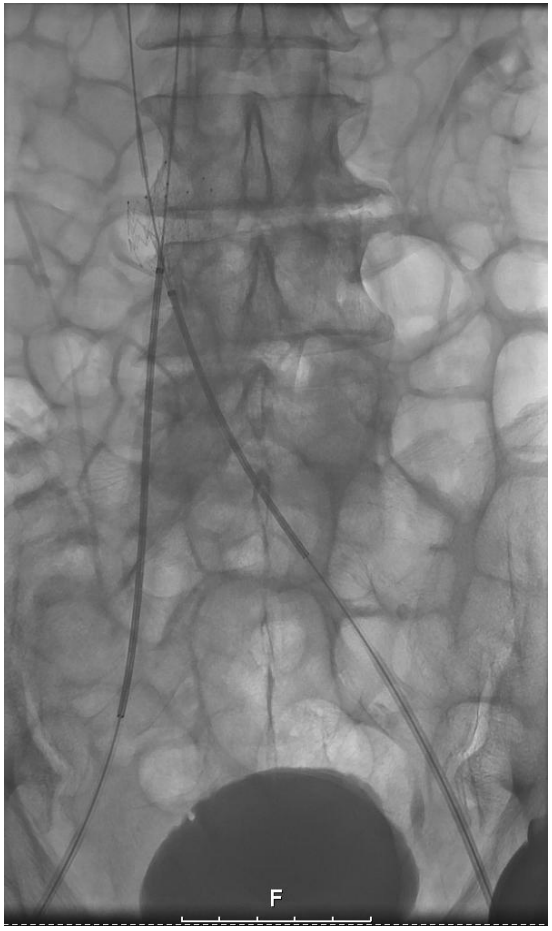
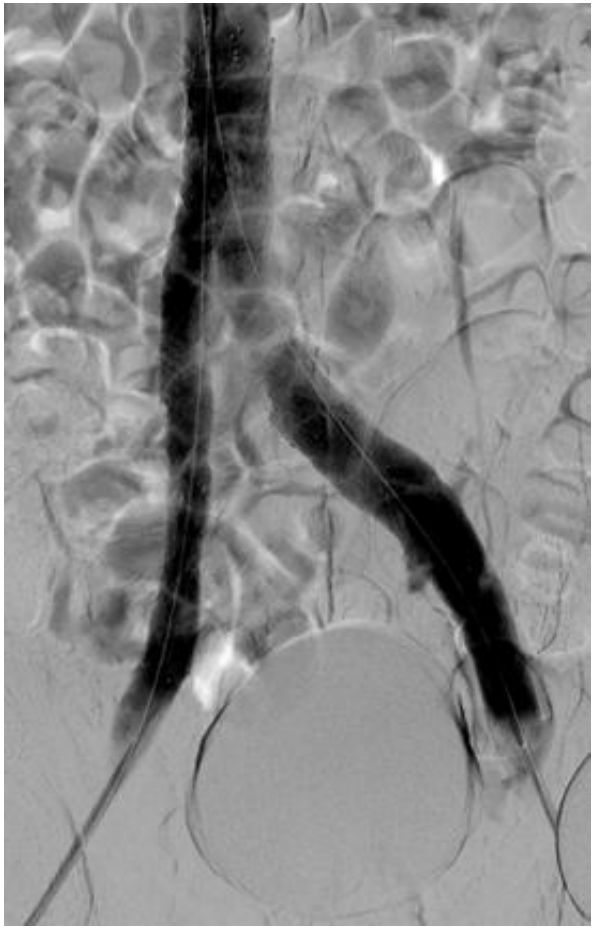
Pharmacomechanical (PMT) thrombus removal

(15-hour EKOS CDT [t-PA 20 mg], thrombusaspiration [Angiojet] and stenting)

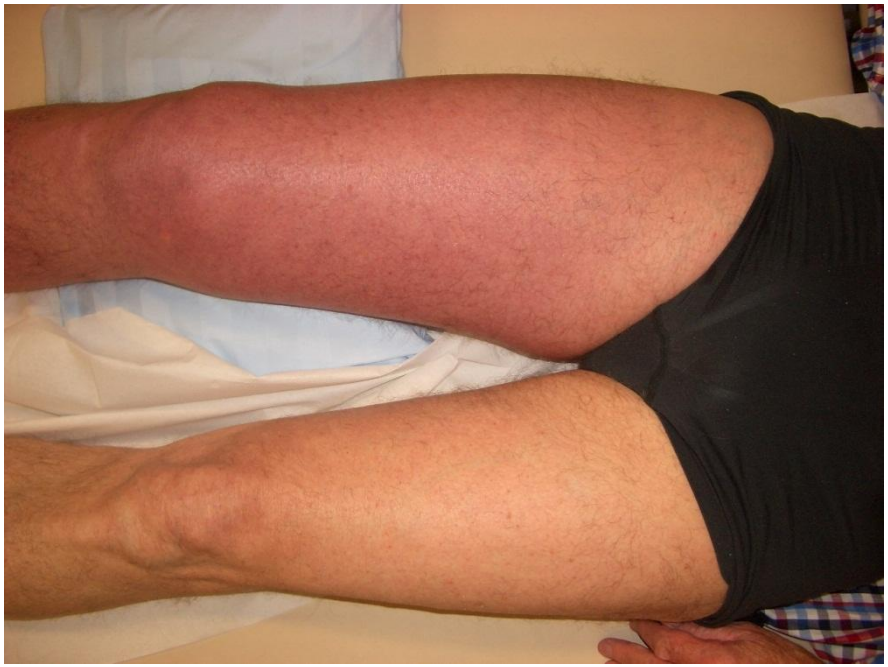




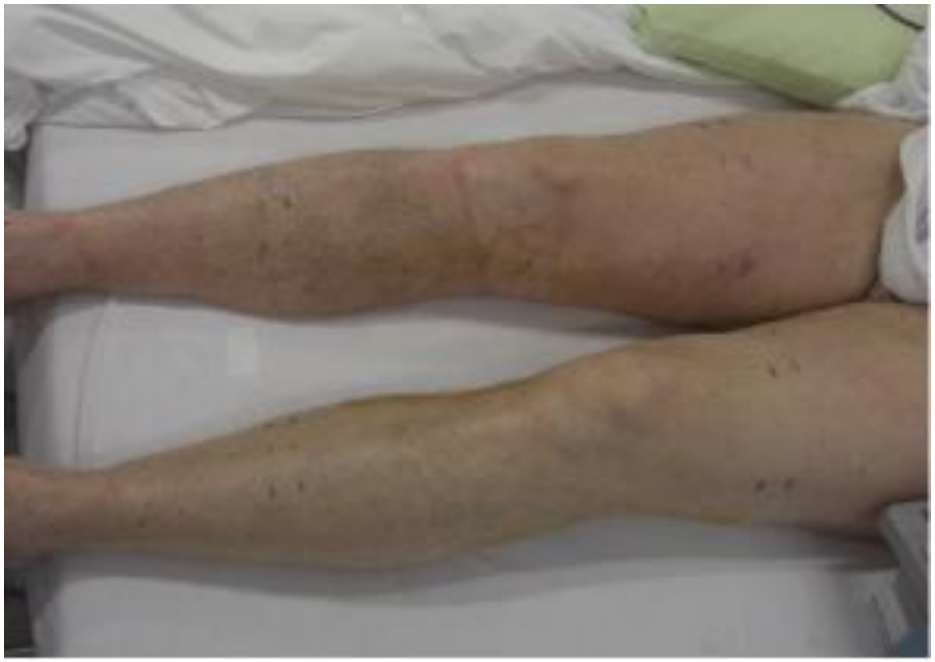


Pharmacomechanical (PMT) thrombus removal

(clinical result @ 24 hours)



before



after

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The Bern DVT Experience 2010-2012

fixed-dose EKOS thrombolysis (CDT) regimen: t-PA 20 mg/15 hours

N = 52	Acute (symptoms ≤ 14 days) N = 33	Subacute or chronic (symptoms >14 days) N = 19
Clot lysis ≥ 50%	87.9%	47.4%

Different to CaVent

Additional interventional treatment (n=52)	
Mechanical thrombectomy	27%
Stenting	71%

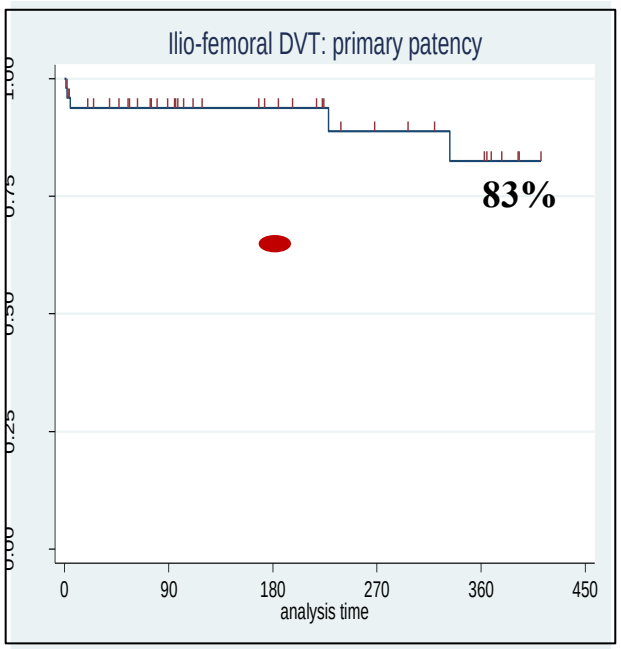
The Bern DVT Experience 2010-2012

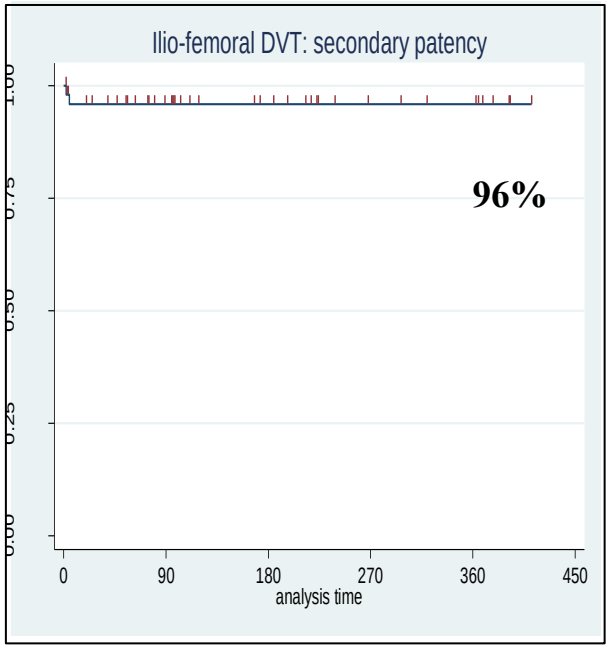
fixed-dose EKOS thrombolysis (CDT) regimen: t-PA 20 mg/15 hours

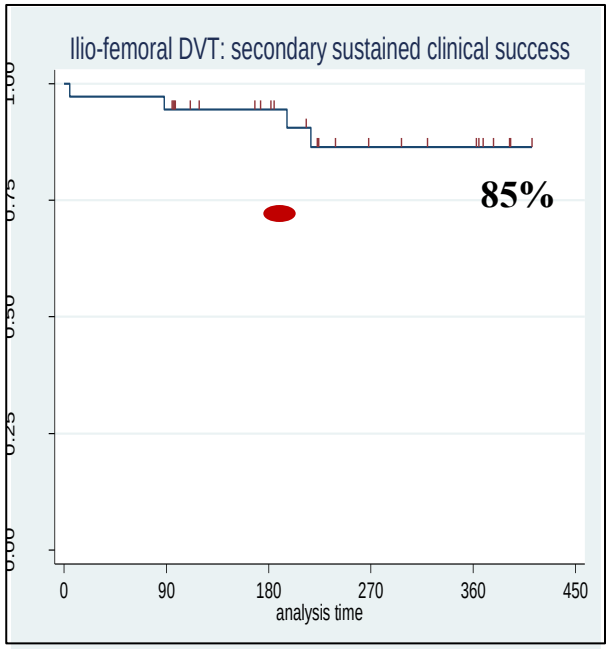
Complications (n=52)		
Complications	None	83%
Bleeding complications	Minor, n=5	9.6%
	Major, n=1	1.9%
Other complications	Painful intervention	3.8%
	Transient foot drop	1.9%

The Bern DVT Experience 2010-2012

Patency and PTS @ 12 months







- clinical outcome in CaVent @ 6 months

9th ACCP Guidelines (2012) on VTE treatment

Conclusions

In patients with acute VTE*, we suggest …

- prophylactic dose of fondaparinux or LMWH in SVT for 45 day (2B)
- either 3 months or extended OAC in acute VTE* (1B or 2B)
  INR target 2-3 (1B)
- anticoagulant therapy alone over CDT (2C)
  patients who are most likely to benefit from CDT are likely to choose CDT over anticoagulation alone (*DVT that involves the iliac and common femoral vein)*
- against use of an IVC filter in addition to anticoagulants (1B)

*acute proximal DVT and PE

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

Thank you for your attention