

Disclosure belangen spreker: Arina ten Cate

Nederlands Trombose Congres – 5 november 2020

(potentiële) Belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Geen
<ul style="list-style-type: none">• Sponsoring of onderzoeksgeld• Honorarium of andere (financiële) vergoeding• Aandeelhouder• Andere relatie, namelijk:	ZonMw (171101001) Maastricht UMC+ BTG-Interventional Medicine. Geen

Is trombolysen nuttig bij acute uitgebreide diepe veneuze trombose?

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Epidemiology PTS

- Occurs in 20-50% of patients with DVT ^{1,2}
- More than 2-times higher risk of recurrence^{3,4}
- Incurs significant costs⁵, reduces QOL considerably⁶
- IFDVT 2-times greater risk of PTS², more severe PTS⁷

¹Prandoni (1996), ²Kahn, Ginsberg (2004), ³Douketis (2001) ⁴Stain (2005) ,⁵Philips (1994), ⁶Heit (2001), ⁷ O'Donell (1997)

PTS heeft mijn leven totaal veranderd



Het verhaal van PTS-
patiënt Lowie Bijvelds

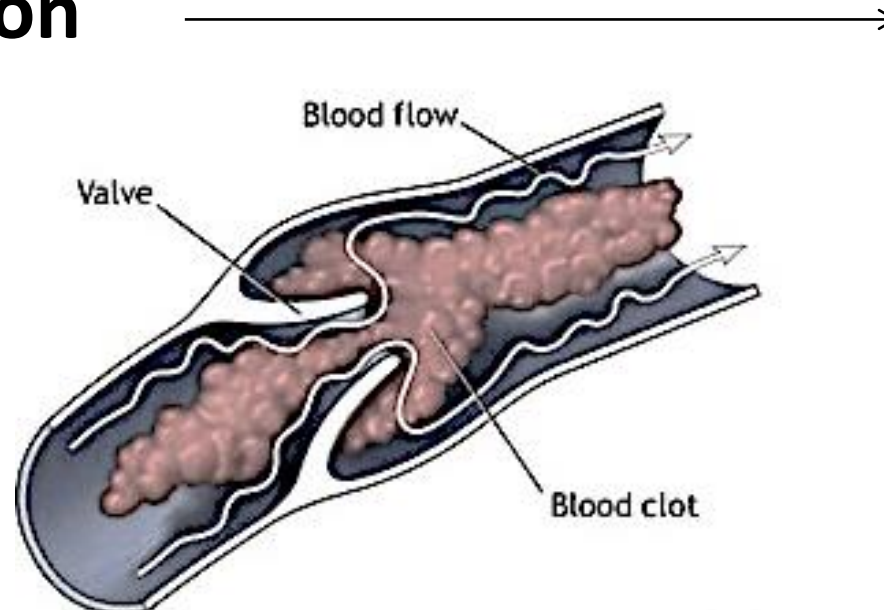
[Lees zijn verhaal](#)

- *“ . Sporten gaat al lang niet meer en ook mijn werk als metaalbewerker ging steeds slechter.”*
- Mijn onderbeen deed pijn en ik had **erge krampen en pijnsteken**. Na een lange tijd van klachten werd het **been helemaal dik en opgezwollen**. Het werd alsmaar erger. Op het laatst kon ik gewoon niet meer staan.
- De pijn werd zo ondraaglijk dat ik op gegeven moment riep: ‘Haal dat onderbeen er maar af’.”

Pathophysiology PTS

Thrombus Resolution

Inflammation / fibrosis



Valve damage

Valvular reflux

Venous hypertension

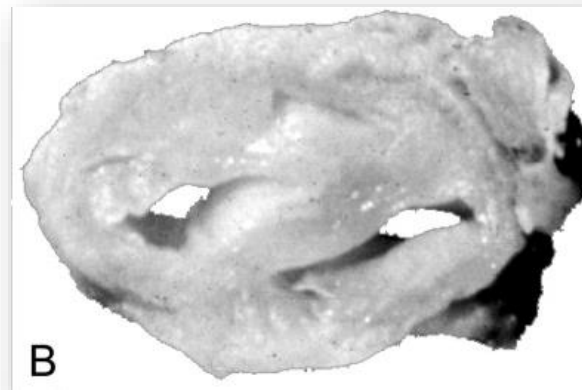
Venous outflow restriction

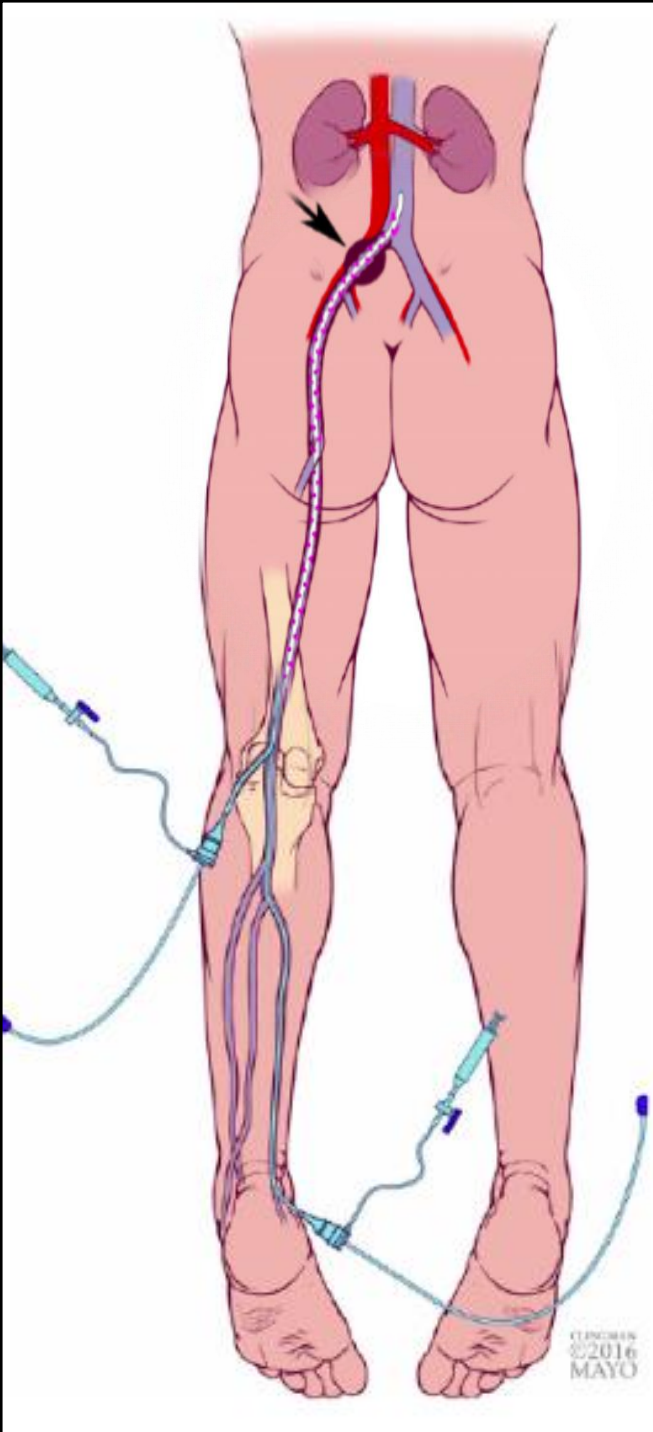
Ongoing inflammation / vein wall remodelling/ fibrosis

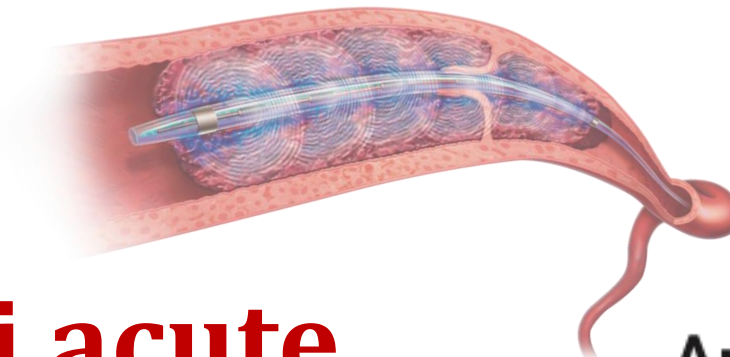
Adapted form Phillips II. J Vasc Surg 2007;45:116A-122A

The “open vein” hypothesis

- Fast removal of the thrombus prevents: reflux, venous obstruction (RVO) and PTS







Articles

Is trombolysen nuttig bij acute uitgebreide diepe veneuze trombose?

Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial

Pascale Notten, Arina J ten Cate-Hoek*, Carsten W K P Arnoldussen, Rob H W Strijkers, André A E A de Smet, Lidwine W Tick, Marlène H W van de Poel, Otmar R M Wikkeling, Louis-Jean Vleming, Ad Koster, Kon-Siong G Jie, Esther M G Jacobs, Harm P Ebben, Michiel Coppens, Irwin Toonder, Hugo ten Cate, Cees H A Wittens*



Lancet Haematol 2019

Published Online

November 27, 2019

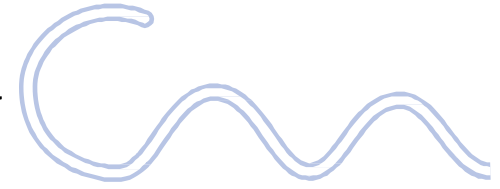
[https://doi.org/10.1016/S2352-3026\(19\)30209-1](https://doi.org/10.1016/S2352-3026(19)30209-1)

See Online/Comment

[https://doi.org/10.1016/S2352-3026\(19\)30205-4](https://doi.org/10.1016/S2352-3026(19)30205-4)

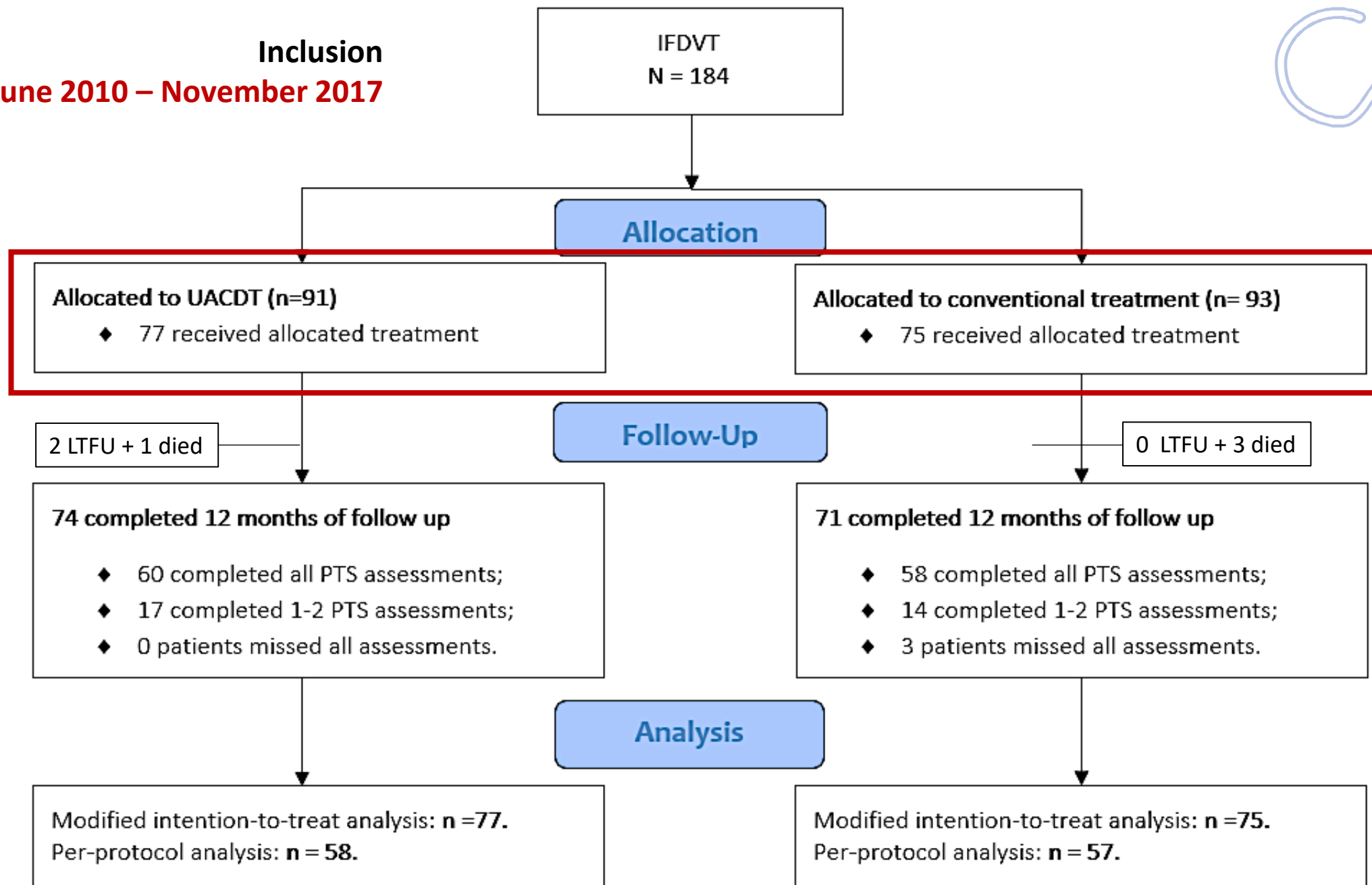
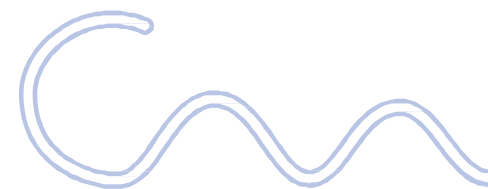
*Contributed equally

CAVA-trial INCLUSION & EXCLUSION

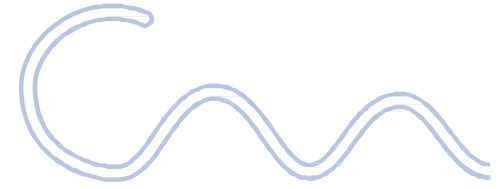


Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">• Age between 18-85 years• Objectively documented IFDVT• Acute stage IFDVT, complaints <14 days• Life expectancy longer than 6 months• First thrombus in the affected limb	<ul style="list-style-type: none">• Varicosities/venous insufficiency (\geqC3)• Severe hypertension ($>180/100$ mmHg)• Active malignancy• History of GI bleeding within 12 months• History of CVA/central nervous system disease within 12 months• Major surgery within 6 weeks• ALAT > 3 times normal range• eGFR < 30 ml/min• Pregnancy• Immobility (wheelchair dependent)

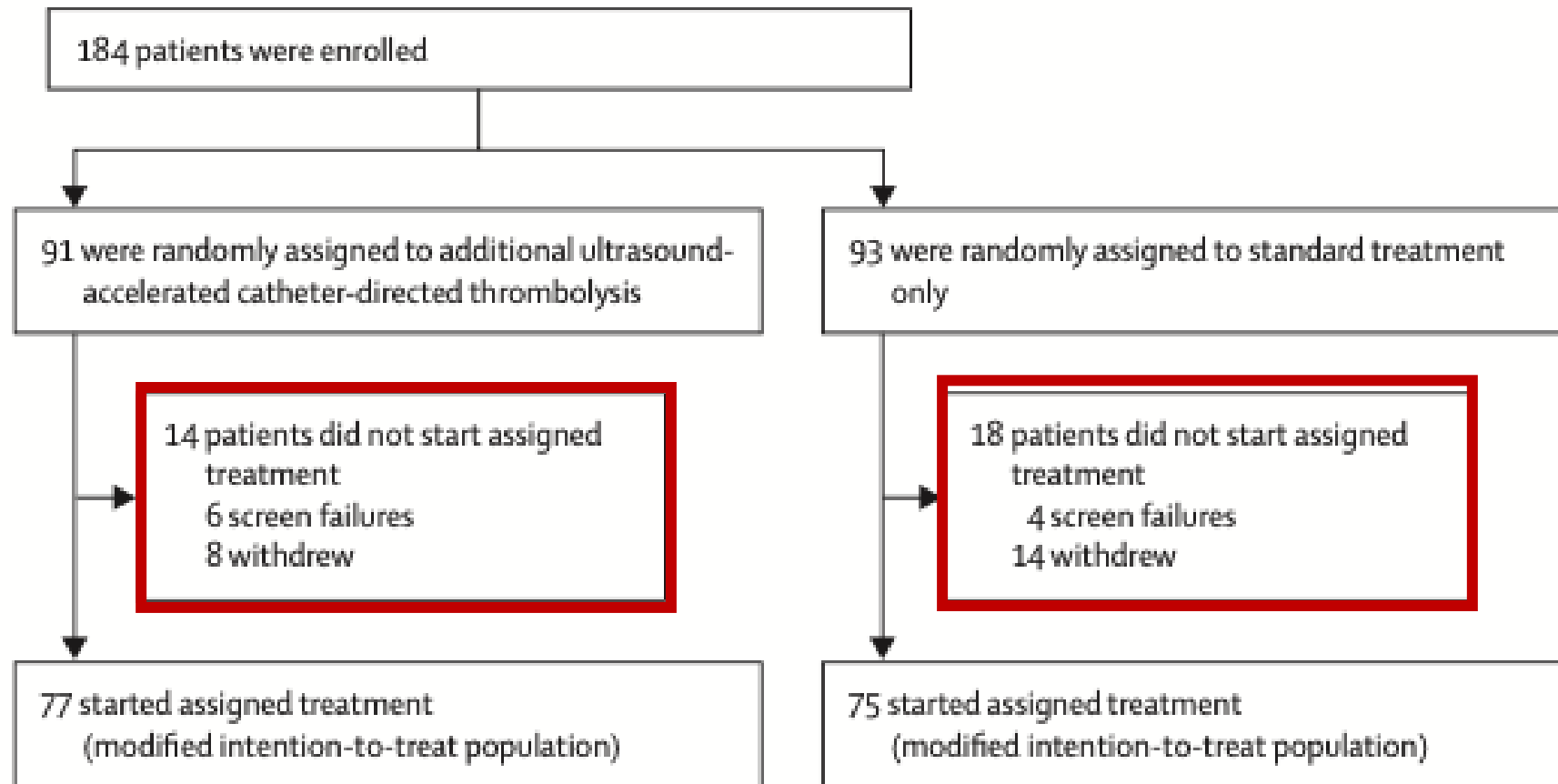
Inclusion
June 2010 – November 2017



CAVA-trial



Early withdrawal & exclusion



CAVA-trial

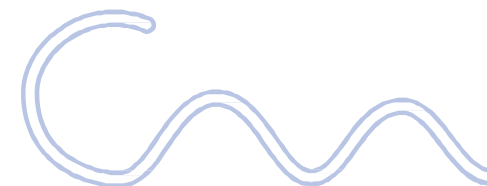


Table S1: Reasons for Exclusion or Withdrawal

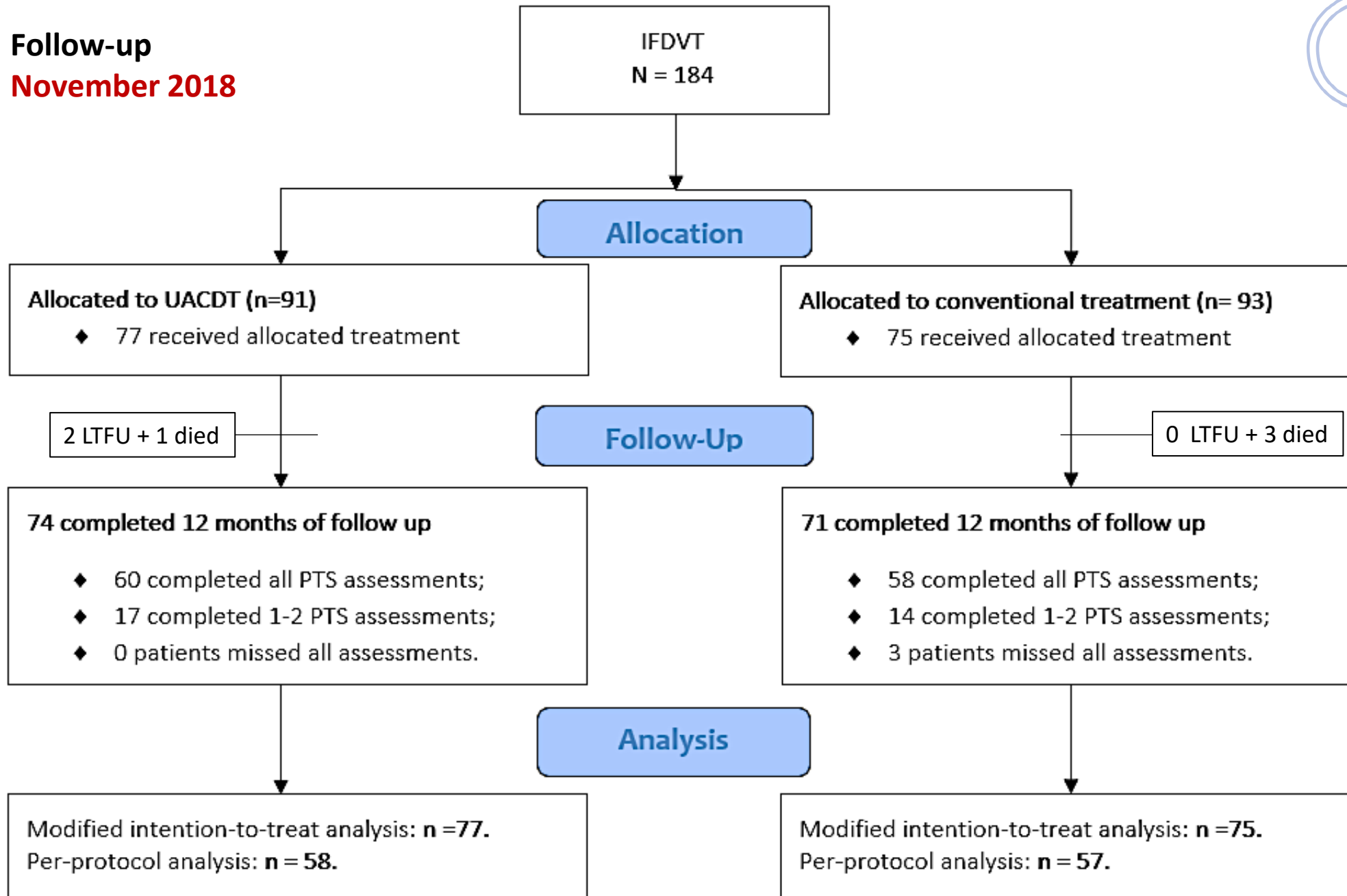
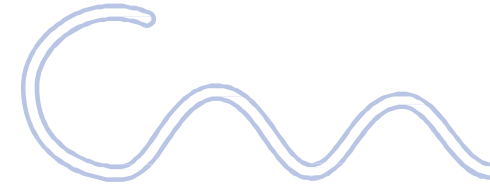
Reason for Exclusion or Withdrawal	Additional Thrombolysis N = 91	Standard treatment N = 93
Screen Failure	6 (6.6%)	4 (4.3%)
- No iliofemoral deep-vein thrombosis	5 (83.3%)	3 (75.0%)
- Previous deep-vein thrombosis of the index leg	1 (16.7%)	0 (0.0%)
- Hyperpigmentation (C4a) ³⁰ of the index leg	0 (0.0%)	1 (25.0%)
Withdrawal of Informed Consent *	8 (8.8%)	14 (15.1%)
- Unwilling to attend follow-up visits	5 (62.5%)	3 (21.4%)
- Discontent of assigned treatment	0 (0.0%)	10 (71.4%) [†]
- Personal reasons	0 (0.0%)	1 (7.2%)
- Incidental finding (tumour) at baseline assessments	1 (12.5%)	0 (0.0%)
- Fear of thrombolysis	1 (12.5%)	0 (0.0%)
- Aggressive behaviour of patient towards treating personnel	1 (12.5%)	0 (0.0%)

Data are n (%).

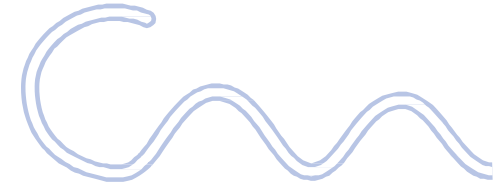
* Reasons for exclusion and withdrawal of patients after randomization and before start of assigned treatment.

† P=0.01

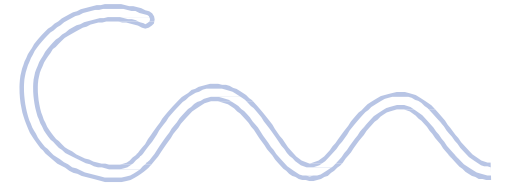
Follow-up
November 2018



CAVA-trial BASELINE



	Intervention (77)	Standard (75)
Age, mean – year	50.4	51.1
Male	39 (50.6)	38 (50.7)
Body Mass Index, mean ± SD	28.0 ± 5.6	27.4 ± 4.1
Previous contralateral DVT	9 (11.7)	5 (6.7)
Previous PE	3 (3.9)	5 (6.7)
Unprovoked DVT	35 (45.5)	43 (57.3)
Localization DVT		
Left	54 (70.1)	55 (73.3)
Bilateral	2 (2.6)	3 (4.0)
Duration symptoms at inclusion – days	7.2 ± 4.7	7.1 ± 4.9

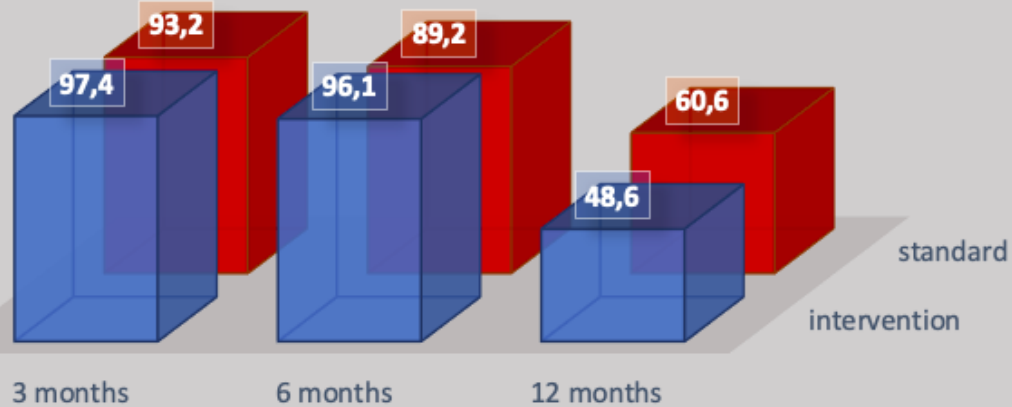


CAVA-trial RESULTS

Standard treatment

ON ANTICOAGULANT TREATMENT

■ intervention ■ standard

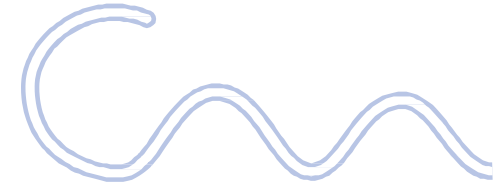


ADHERENCE STOCKINGS >80%



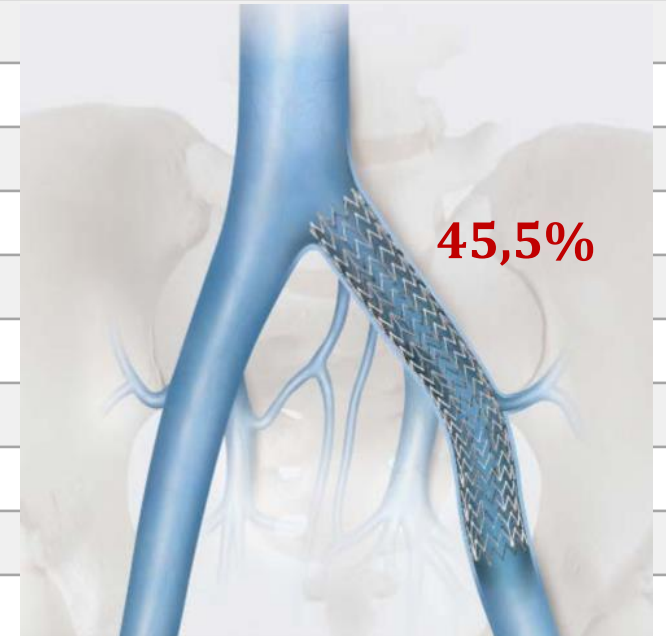
CAVA-trial RESULTS

Thrombolysis



Additional thrombolysis (77)

Duration symptoms at start UACDT-days		11.0 ± 5.3
	0-7	18 (24.3)
	7-14	31 (40.3)
	14-21	23 (29.9)
	>21	2 (2.6)
Duration of UACDT – days		2.2 ± 1.2
Adjunctive procedure		42 (54.5)
	Endovascular*	41 (53.2)
	Hybrid**	1 (1.3)
Stenting		35 (45.5)

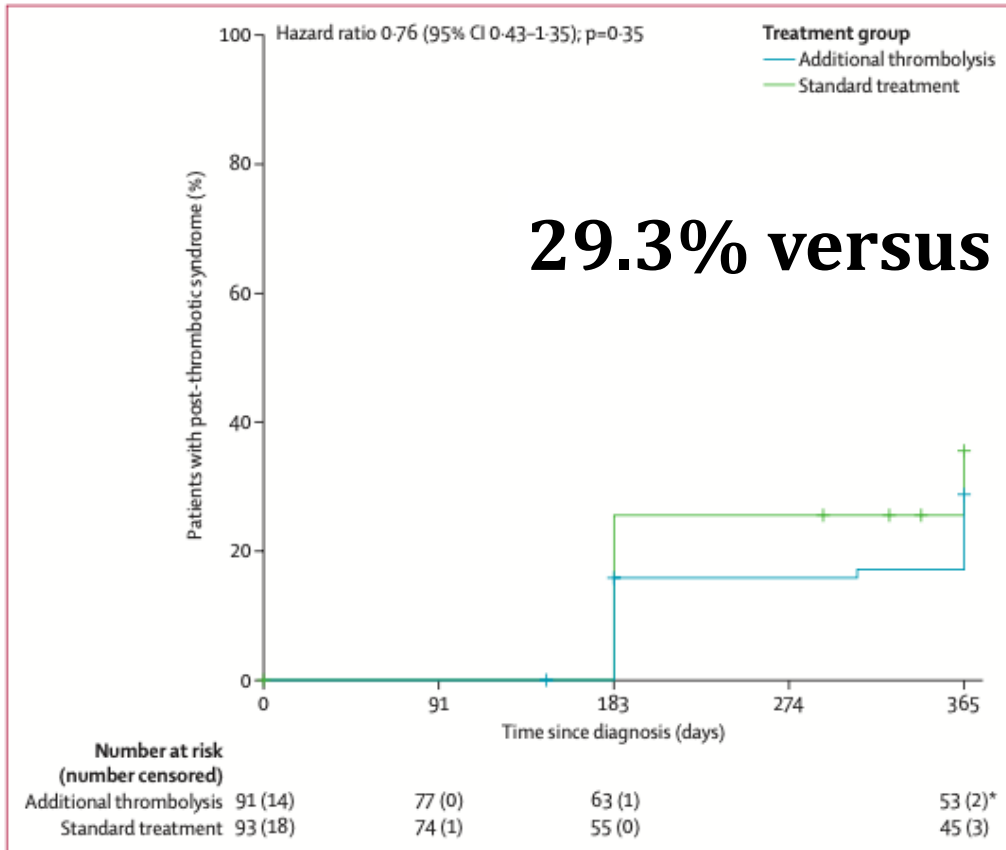
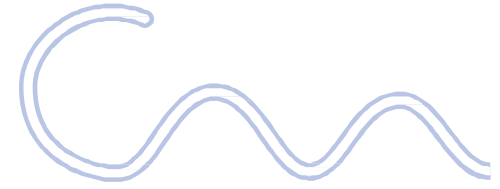


*Endovascular: angioplasty and stenting

**Hybrid procedure: endophlebectomy, stenting, creating an AV-fistula.

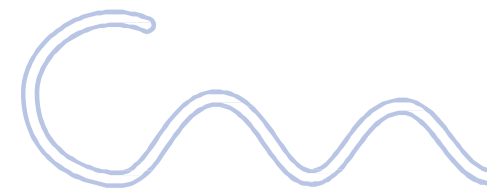
CAVA-trial RESULTS

Efficacy outcomes



29.3% versus 35.1% , OR 0.75(0.38-1.50), p0.42
-6.1% (95% CI -21.6 to 9.8).

CAVA-trial RESULTS



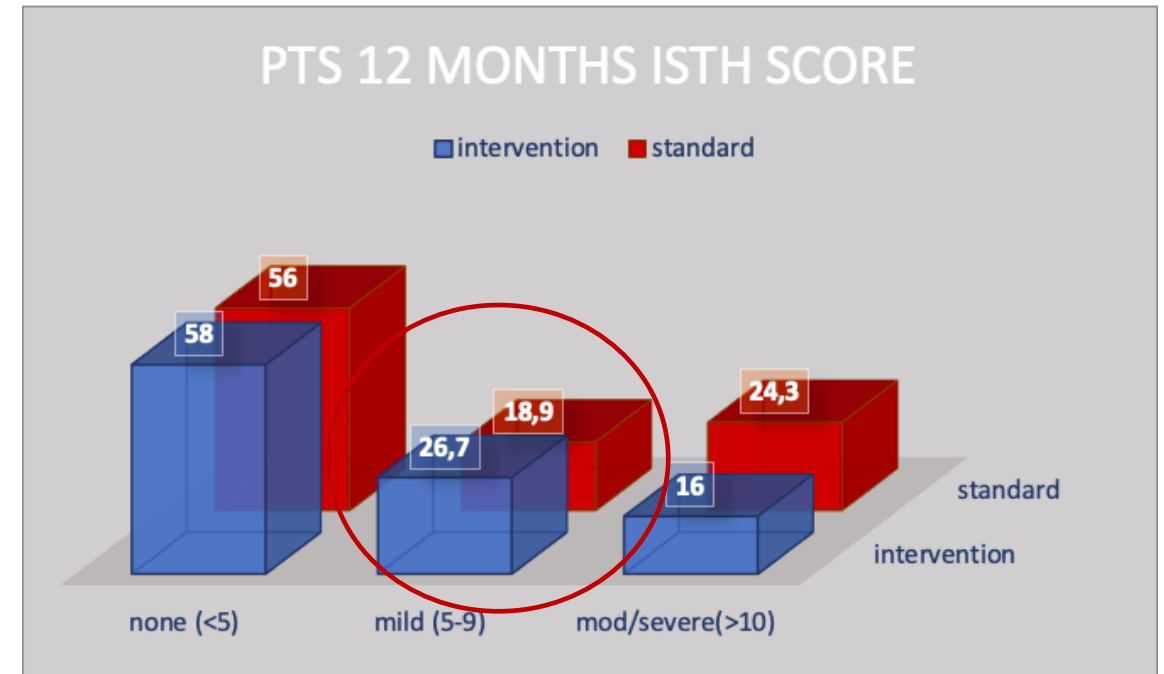
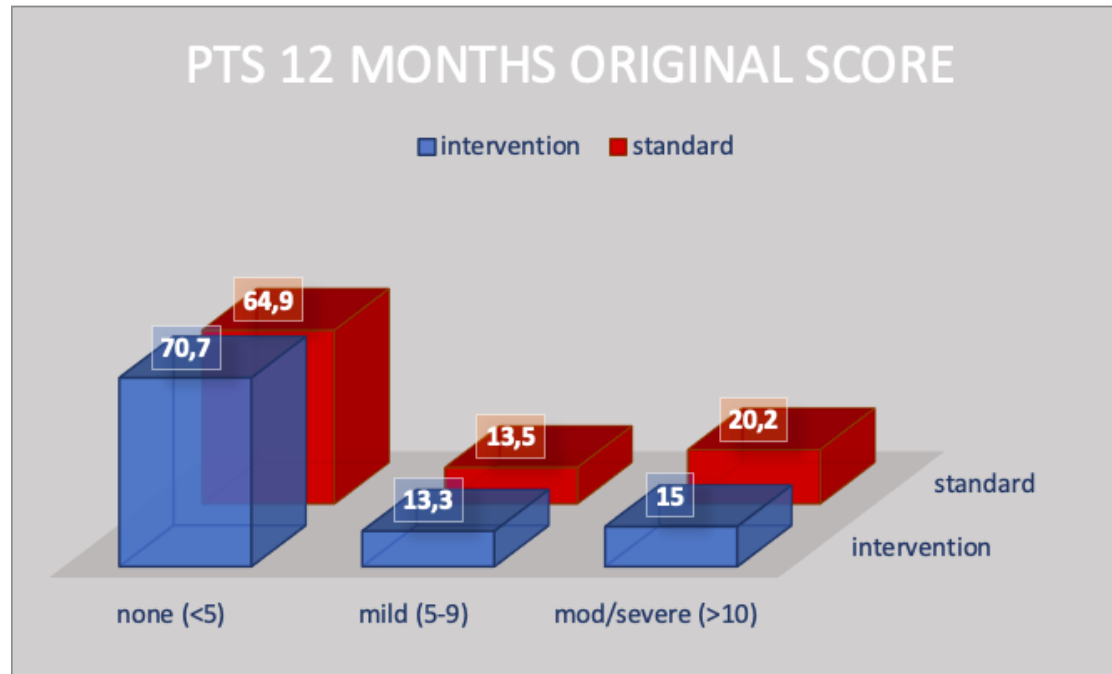
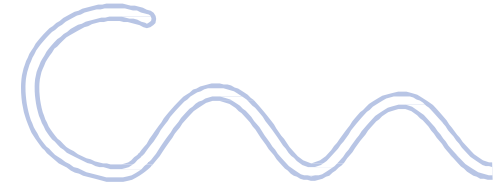
Efficacy outcomes

	Intervention (77)	Standard treatment (75)	Odds ratio (95%CI)
Villalta score at 12 months	4.0 ± 3.2	4.9 ± 4.2	n/a
Original definition¹	29%	35%	0.75 (0.38-1.50)
Mild (5-9)	13%	13%	0.97 (0.38-2.49)
Moderate (10-14)	14%	16%	0.88 (0.36-2.13)
Severe (≥ 15)	1%	4%	0.23 (0.03-2.14)
ISTH definition²	42.7%	44.6%	0.93 (0.46-1.86)
Mild (5-9)	26%	19%	1.53 (0.71-3.31)
Moderate (10-14)	14%	20%	0.67 (0.28-1.56)
Severe (≥ 15)	1%	4%	0.10 (0.01-1.94)

1. Villalta S, et al. Haemostasis 1994;24, 158a. 2. Kahn SR, et al. J Thromb Haemost. 2009 May;7(5):879-83.

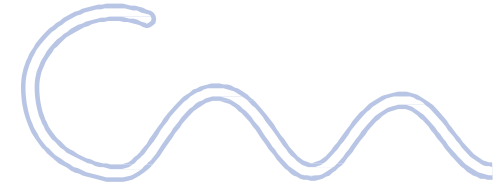
CAVA-trial RESULTS

Efficacy Outcomes



CAVA-trial RESULTS

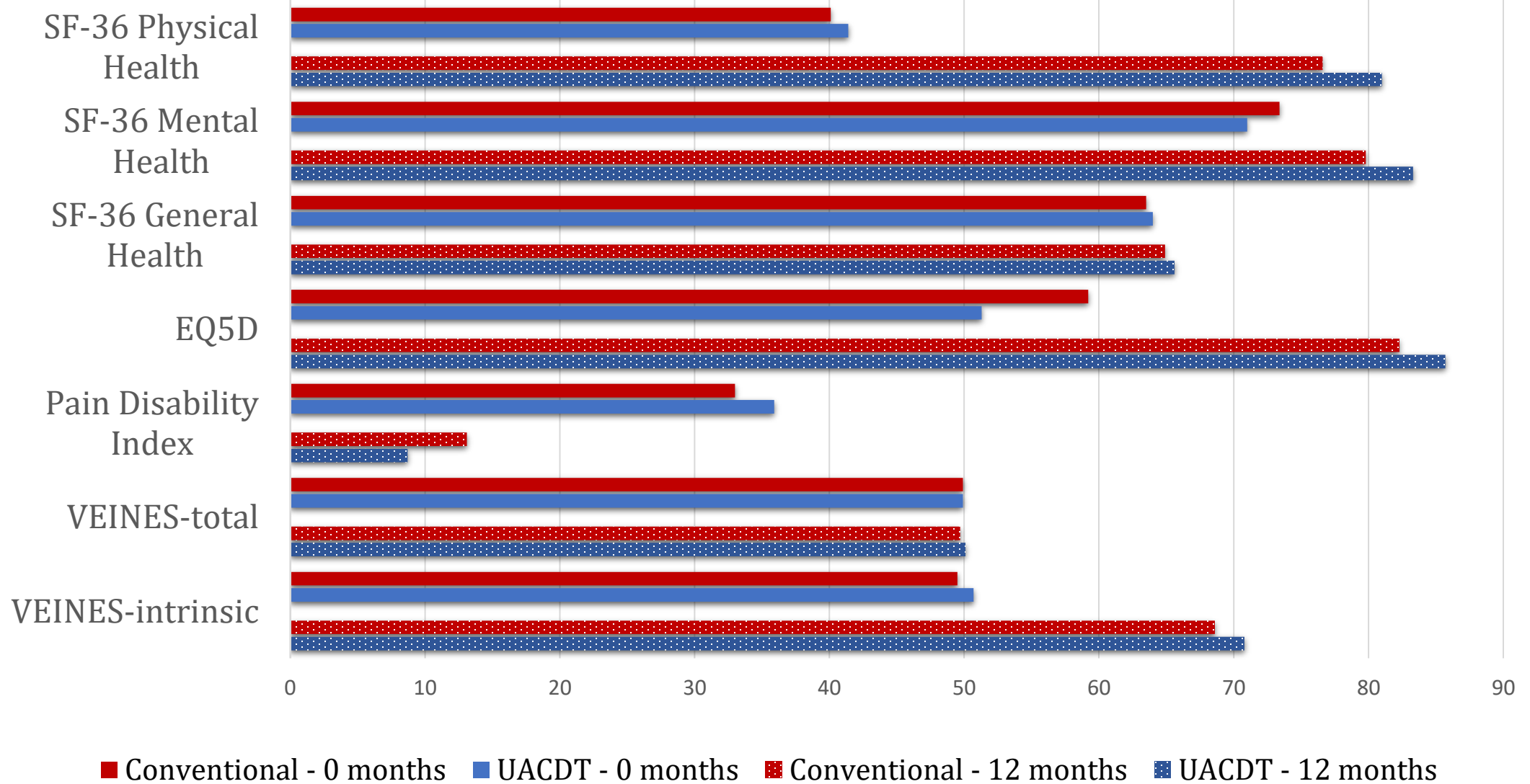
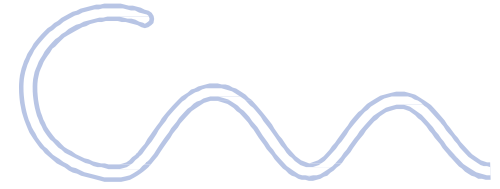
Safety Outcomes



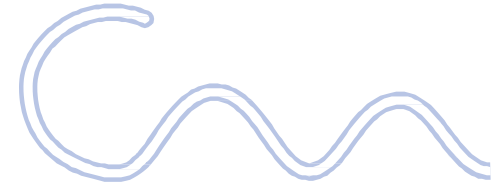
	Intervention (77)	Standard treatment(75)	Odds ratio(95%CI)
Major bleeding ¹	4 (5.2)	0	9.25 (0.49-174.7)
Recurrent DVT	5 (6.5)	4 (5.3)	1.23 (0.32-4.78)
Recurrent PE	0	2 (3.0)	0.19 (0.01- 4.02)
In-stent-thrombosis	10 (13.0)	n/a	n/a
Death	1 (1.3)	3 (3.9)	0.32 (0.03-3.11)

¹. Schulman S, et al. J Thromb Haemost. 2005 Apr;3(4):692-4.

CAVA-trial RESULTS



CAVA-trial Conclusions



- Additional UACDT did not significantly change the risk of PTS 1 year after an acute IFDVT compared with standard therapy alone.
- The outcome does however suggest the possibility of a moderately beneficial effect.
- Further research is therefore warranted to better understand our results in the context of previous trials, preferably by combining the available evidence in an individual patient data meta-analysis.



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Where does this leave us?

an unresolved clinical controversy

Where does the CAVA trial leave early thrombus removal for iliofemoral DVT?

8th January 2020 5316

We read with interest the long anticipated results of the CAVA trial that, unsurprisingly, did not show any benefit (eg, occurrence of post-thrombotic syndrome, recurrence of deep vein thrombosis, or quality of life).



CAVA-studie

Resultaten bekend van Nederlandse CAVA-studie

Geen bevestiging van preventief effect kathetergeleide trombolysie op PTS

straub MEDICAL

Straub Endovascular
Effective debulking of arteries and veins

straubmedical.com

vascular

Most read in past 7 days

Philips Interventional 2019
QuickClear
Published Online
November 27, 2019
[https://doi.org/10.1016/S2352-3026\(19\)30205-4](https://doi.org/10.1016/S2352-3026(19)30205-4)
See Online/Articles
[https://doi.org/10.1016/S2352-3026\(19\)30209-1](https://doi.org/10.1016/S2352-3026(19)30209-1)

Literature- Catheter directed thrombolysis



1085 patients !

Enden et al. Lancet. 2012 Jan 7;379(9810), Vedantham et al. N Engl J Med. 2017 Dec 7;377(23):2240-2252.
Notten et al. Lancet Haematol. 2020 Jan;7(1):e40-e49.

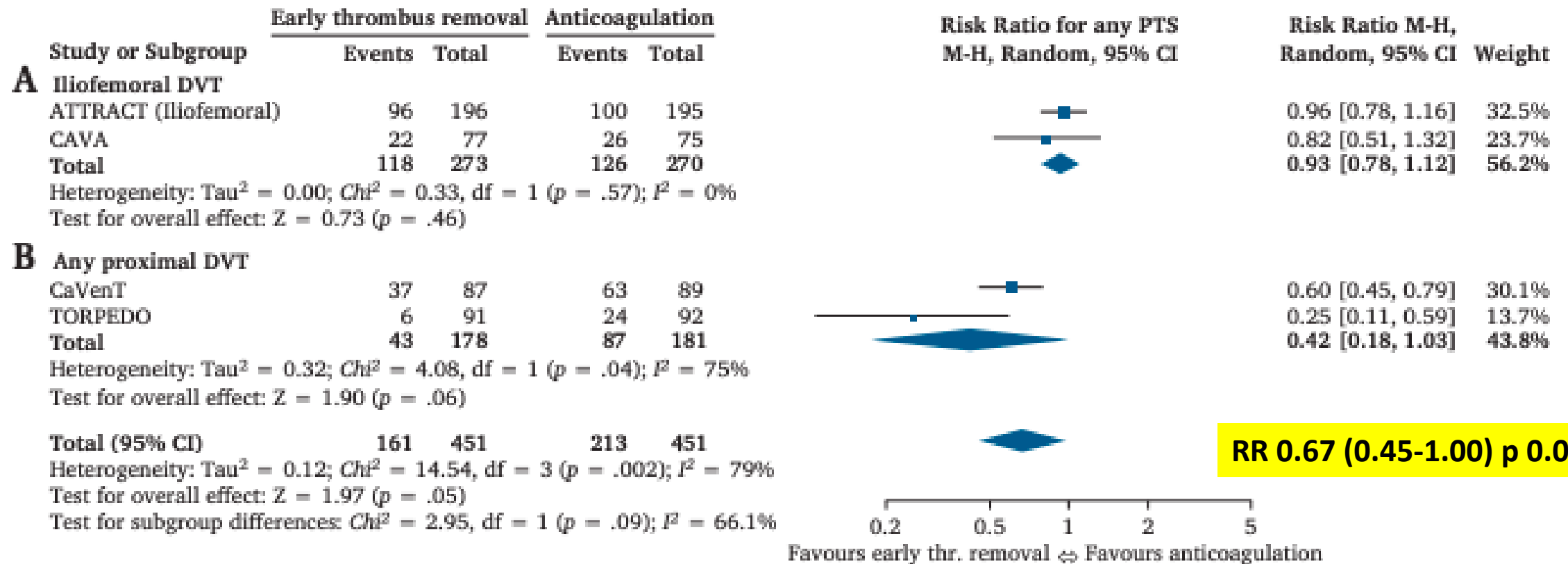
Literature- Catheter directed thrombolysis

Year, Study	N	Intervention	Outcome PTS		Bleed
2012 CaVenT	209	CDT(rtPA) + stenting (17%)	41.1% vs 55.6% -14.5%, p 0.047	RR 0.74 (0.53-1.02)	9.0 %vs. 0% p 0.002
2017 ATTRACT	692	CDT(rtPA)+ stenting (39%)	46.7% vs 48.2% -1.5%, NS	RR 0.96 (0.82-1.11)	1.7% vs. 0.3% p 0.049
2019 CAVA*	184	CDT(urokinase) stenting(45,5%)	41.6.% vs 44.0% -2.4%, NS	RR 0.94 (0.64-1.41)	5.2% vs. 0% p 0.06

*CAVA original scoring: 28.6% vs 34.7%, OR 0.75, 95% CI 0.38–1.50

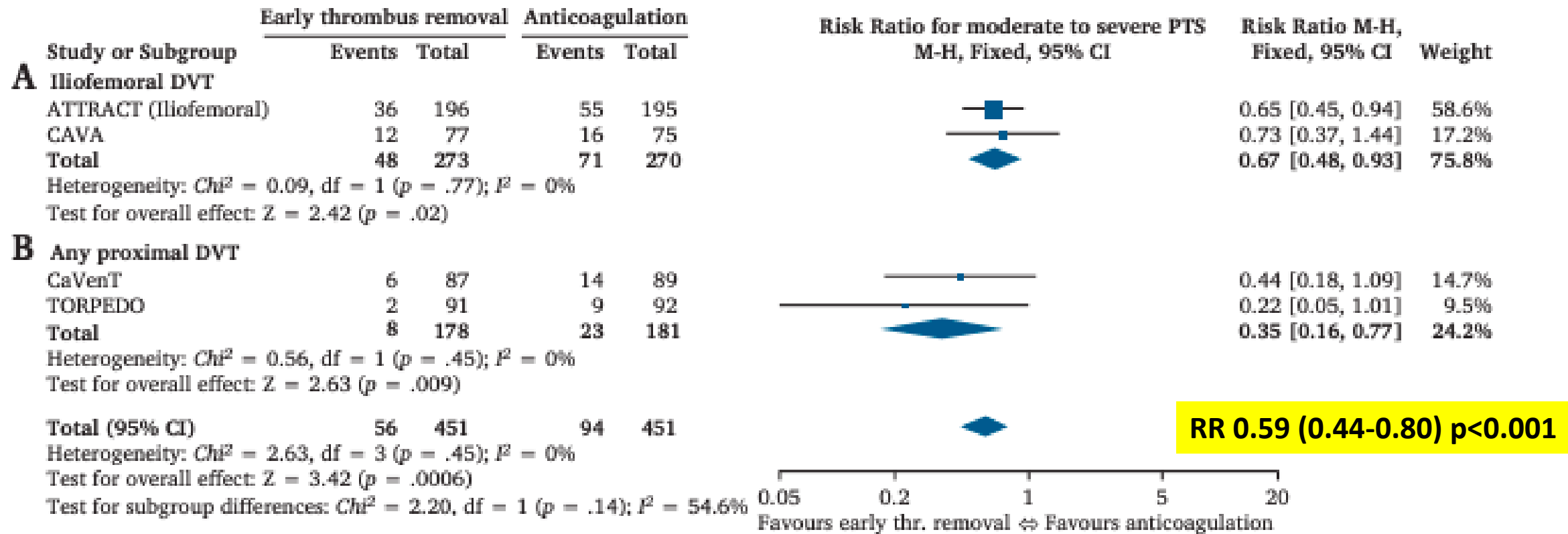
Thrombolysis vs. standard therapy

Any PTS



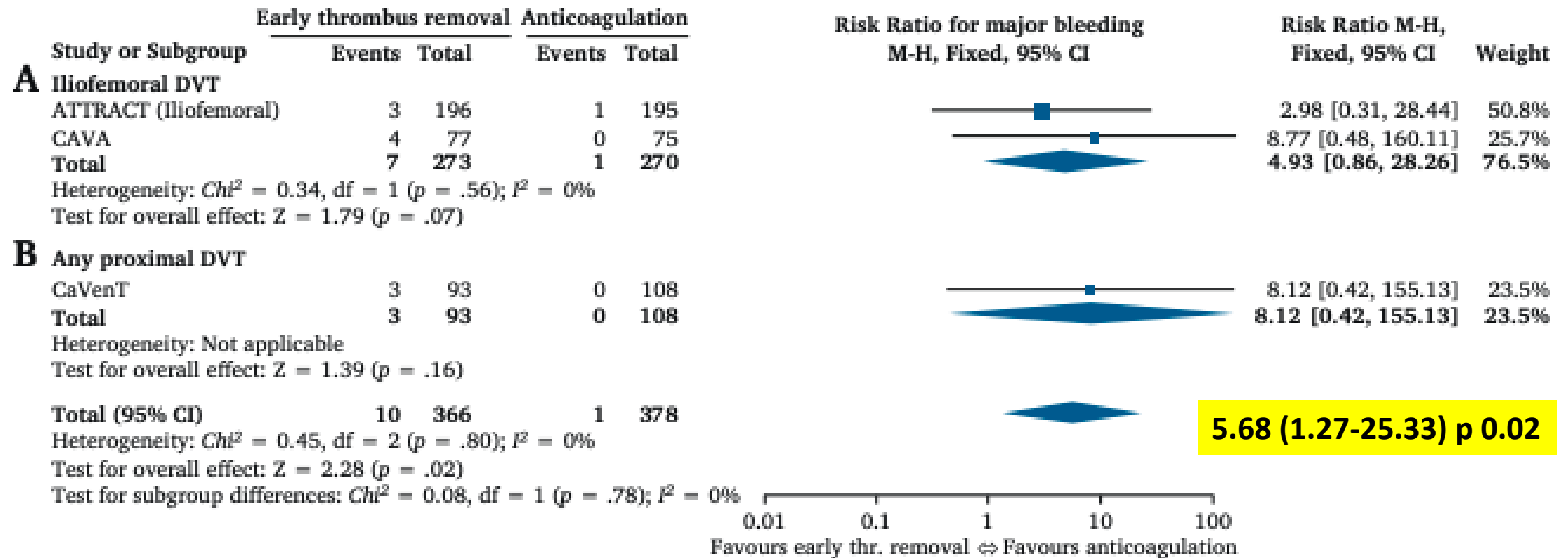
Thrombolysis vs. standard therapy

Moderate-Severe PTS



Thrombolysis vs. standard therapy

Bleeding risk



Upcomming guideline

Recommendations

Recommendation 34

In selected patients with symptomatic iliofemoral deep vein thrombosis, early thrombus removal strategies should be considered

Class	Level	References
IIa	A	[172, 222, 223, 226, 230, 233, 237]

Richtlijn Antitrombotisch Beleid

Aanbevelingen

- Geef **geen katheter-geleide trombolyse als standaardtherapie** aan patiënten met een acute DVT van het been.
- **Overweeg om in geselecteerde patiënten**, zoals jonge patiënten met zeer uitgebreide iliofemorale trombose met een bedreiging van het been, secundair aan de veneuze obstructie, katheter-geleide trombolyse uit te voeren.

ACCP guidelines

Recommendations

- **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, who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

Overall Conclusions

take HOME

- Standard management does not sufficiently prevent PTS.
- CDT in the acute phase may have the potential to lower the incidence of moderate-severe PTS in IFDVT patients.
- It is still unclear which patient characteristics are associated with favourable outcome – **who benefits most?**
- CDT is associated with a significantly increased risk of bleeding and in-stent thrombosis; new techniques and better periprocedural protocols might reduce these risks.



