Antistolling, toen, nu en straks

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Disclosures for Harry R. Büller

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Three Main Themes

Invasive strategies

Thrombolysis/catheter-directed, stents and filters

Antithrombotic strategies

Direct oral anticoagulants, heparin, reversal and novel agents

Extended-supportive strategies

Direct oral anticoagulants, aspirin, sulodexide, stockings and duration/prediction

For each theme

- Where do we have convincing clinical evidence?
- Where are we uncertain?
- Which improvements can we expect?

Where do we have convincing clinical evidence?

- Thrombolysis in sub-massive PE (with RVD)
- Thrombolysis in hemodynamic unstable PE
- Filters in addition to anticoagulation

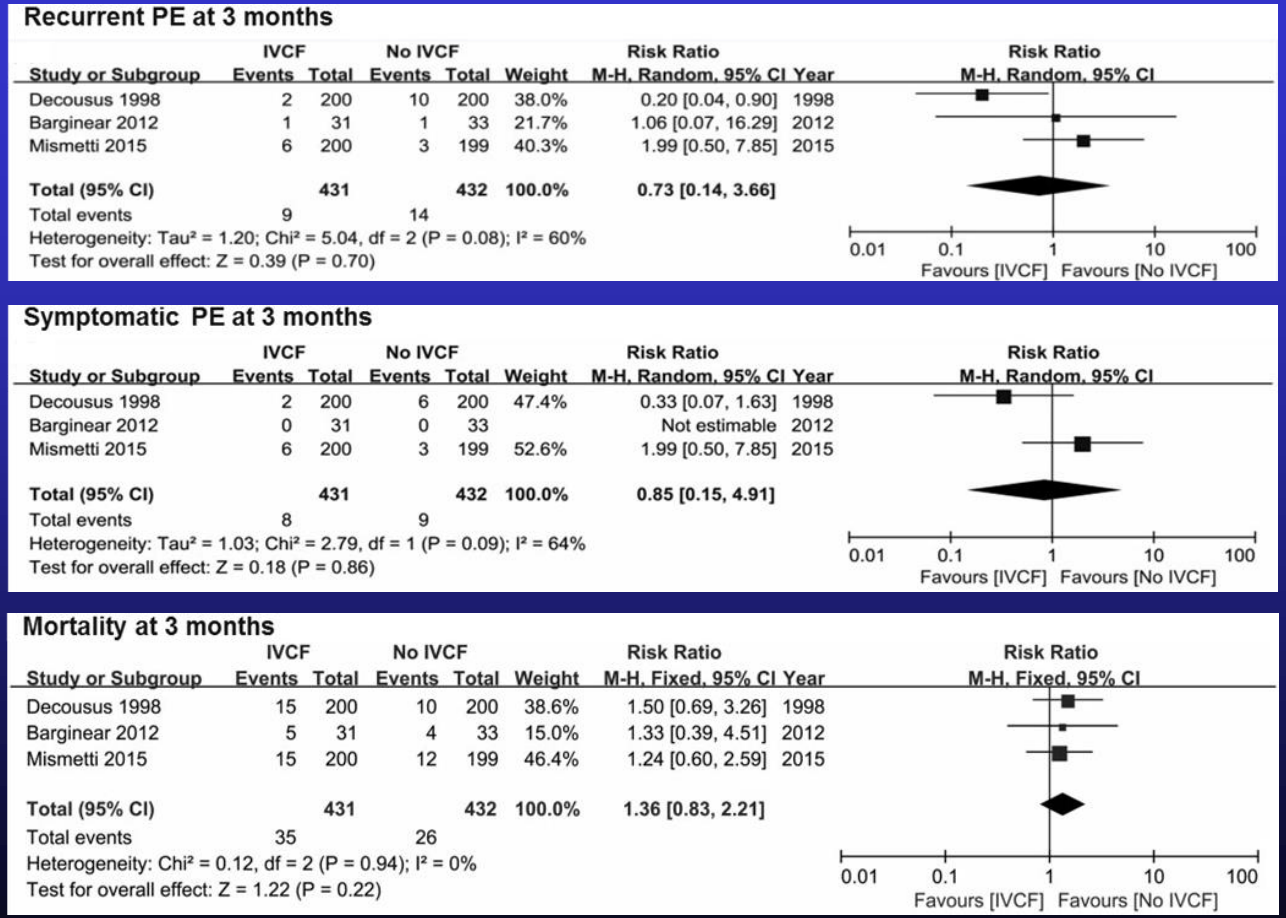
Submassive PE

- Number needed to prevent one recurrence 59
- Number needed to harm (major bleed) 17

- Longterm outcome (mortality, RV dysfunction and dyspnea) not different[1]

1. S. Konstantinides et al, JACC, 2017

Vena Cava Filters in addition to Anticoagulation in VTE Patients



J. Jiang et al. Phlebology, 2016

Invasive strategies; thrombolysis/catheter directed, stents and filters

Where are we uncertain?

Catheter directed thrombolysis/stents	
DVT	CaVenT & ATTRACT
PE	no RCT

The CaVenT study

	Control	Catheter-directed thrombolysis	P-value
Original no. of pts.	108	101	
PTS at 24 months (villalta ≥ 5)	55/99 (55.6%)	37/90 (41.1%)	p=0.047
Severe PTS (≥ 15)	1/99	0/90	
Bleeding complication	0/99	20/90	
Severe PTS at 5 years	1/63 (1.6%)	4/37 (10.8%)	

T. Enden et al. Lancet, 2012 and Y. Haig et al. Lancet Haem, 2016

ATTRACT Study

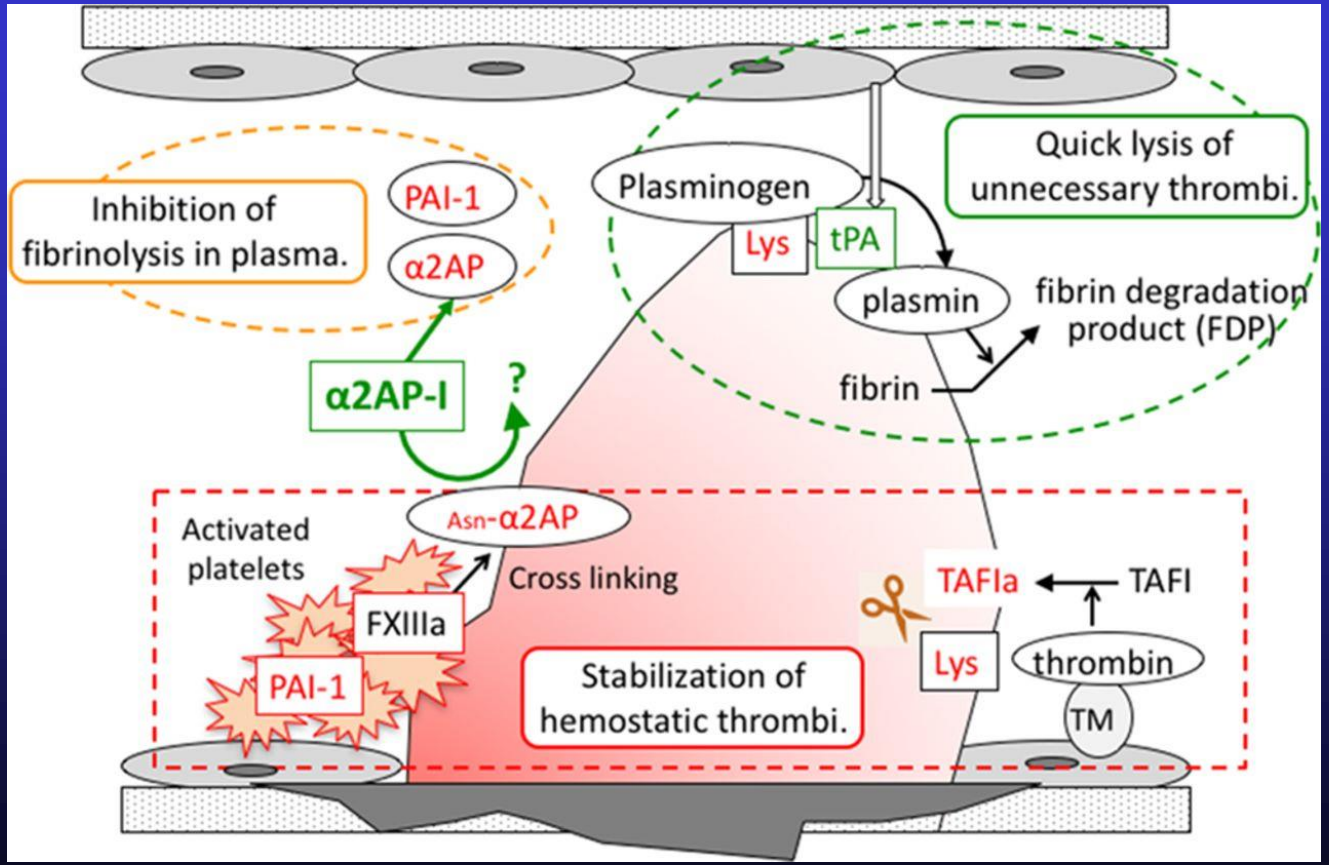
	Control	Pharmacomechenical catheter directed thrombolysis	P-value
Original no. of patients	355	337	-
PTS at 24 months (Villalta ≥5)	48.2%	46.7%	N.S.
Major Bleeding (10 days)	0.3%	1.7%	P=0.049
Recurrent VTE	8.5%	12.5%	N.S.
Quality of life	Comparable		N.S.
Severe PTS	23.7%	17.9%	N.S.

S. Vedantham et al. Endovascular Today, 2017

Which improvements can we expect?

- Novel (endogeneous) fibrinolysis enhancers
- Bleeding risk stratification in hemodynamic stable PE with RVD

Fibrinolytic System



T. Urano et al. Circulation. 2017

Novel endogeneous fibrinolysis enhancers

- LMW imidazole derivative that inhibits TAFIa (DS-1040)[1]
- Heterodimer diabody against TAFI and PAI-1[2]
- α 2-antiplasmin – inactivating antibody (both circulating and firbrin bound; TS23; DS-9231)[3]
- PAI-1 inhibitors (PAI trap (H37R)-HSA, and others)[4]

1. J. Zhou et al. JTH, 2017; 2. T. Wyseure et al, Blood 2015; 3. S. Singh et al. Circulation, 2017; 4. S. Peng et al. TH, 2017

Invasive strategies

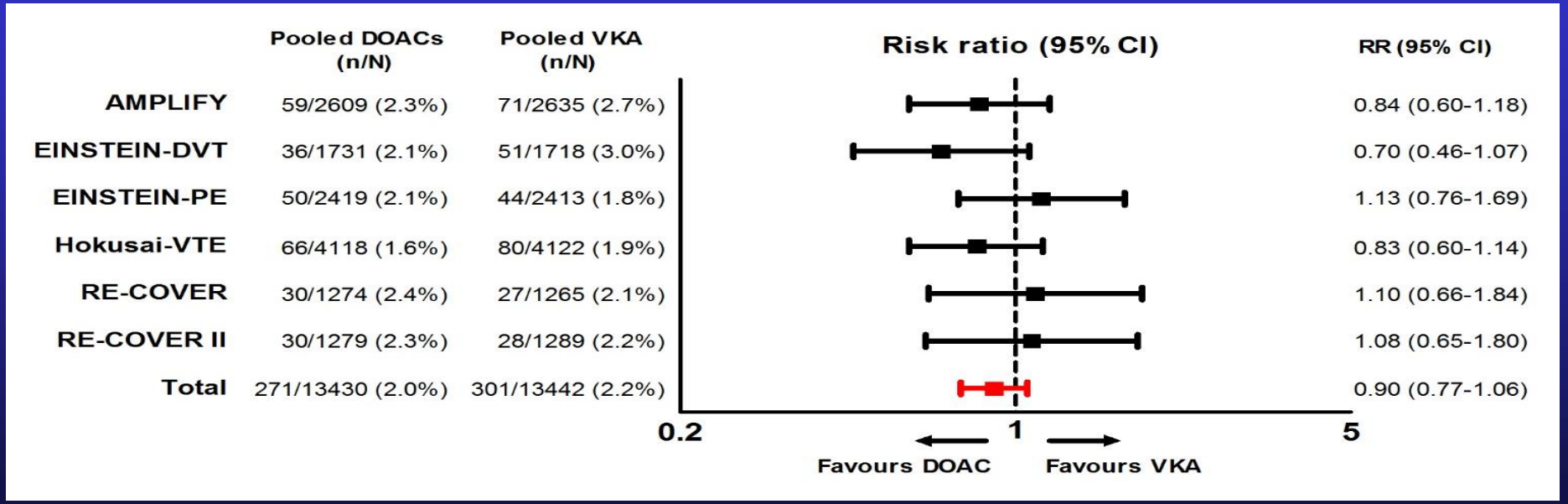
- No routine thrombolysis in hemo-dynamic stable PE with RVD; better stratification needed
- In hemodynamic-unstable PE, thrombolysis should be considered
- No role for IVC filters in addition to anticoagulants
- Catheter directed thrombolysis/stents in DVT not indicated
- Endogeneous fibrinolysis enhancers deserve thorough clinical evaluation

Antithrombotic strategies; direct oral anti-coagulants, heparin, reversal and novel agents

Where do we have convincing clinical evidence?

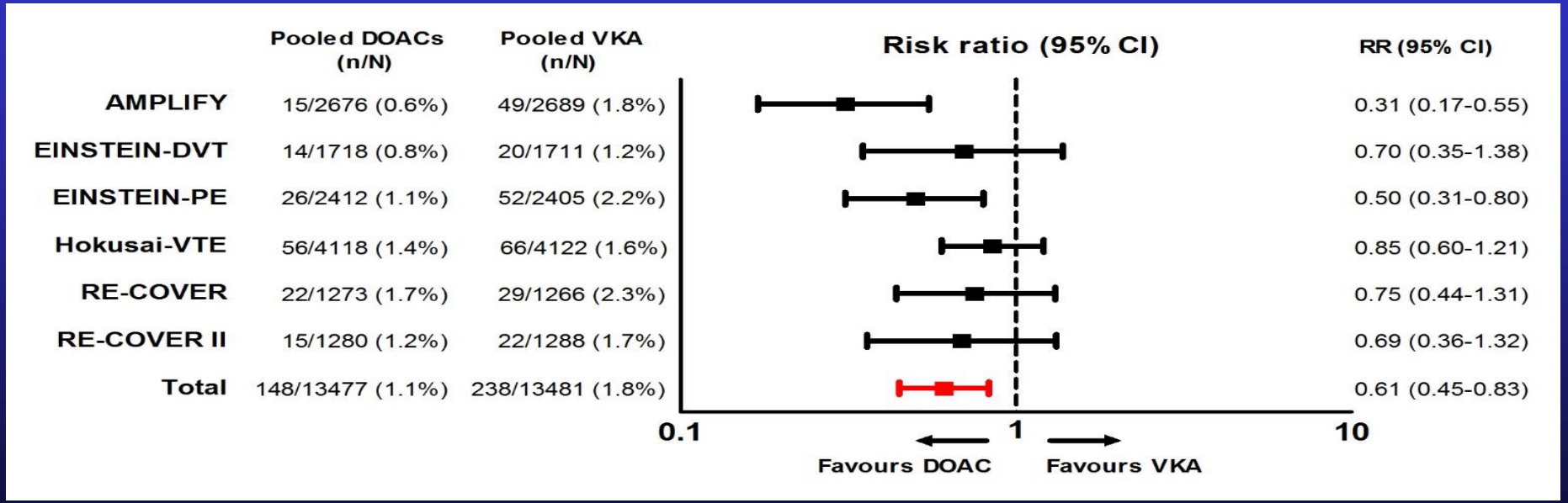
- DOACs for most VTE patients
- Change in bleeding pattern
- Idarucizumab for reversal dabigatran

Efficacy



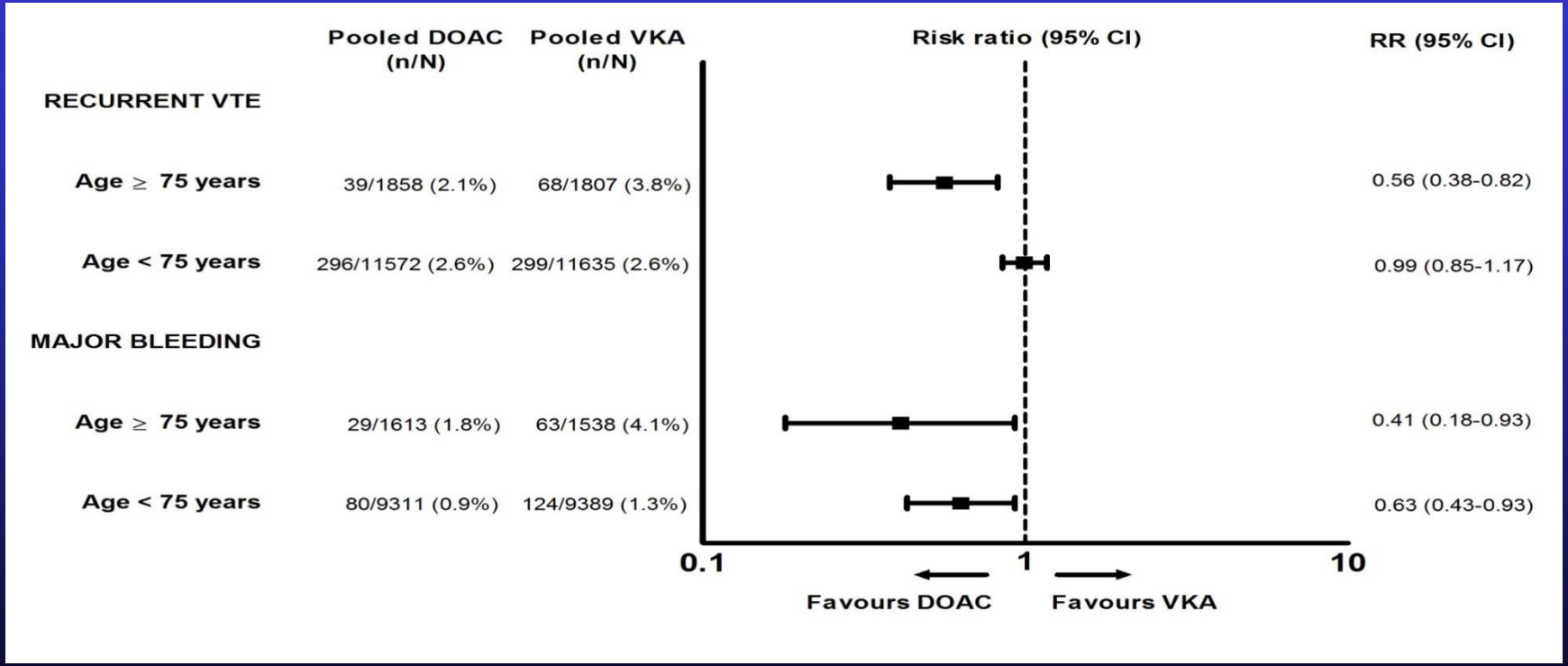
N. van Es et al. Blood 2014

Major bleeding



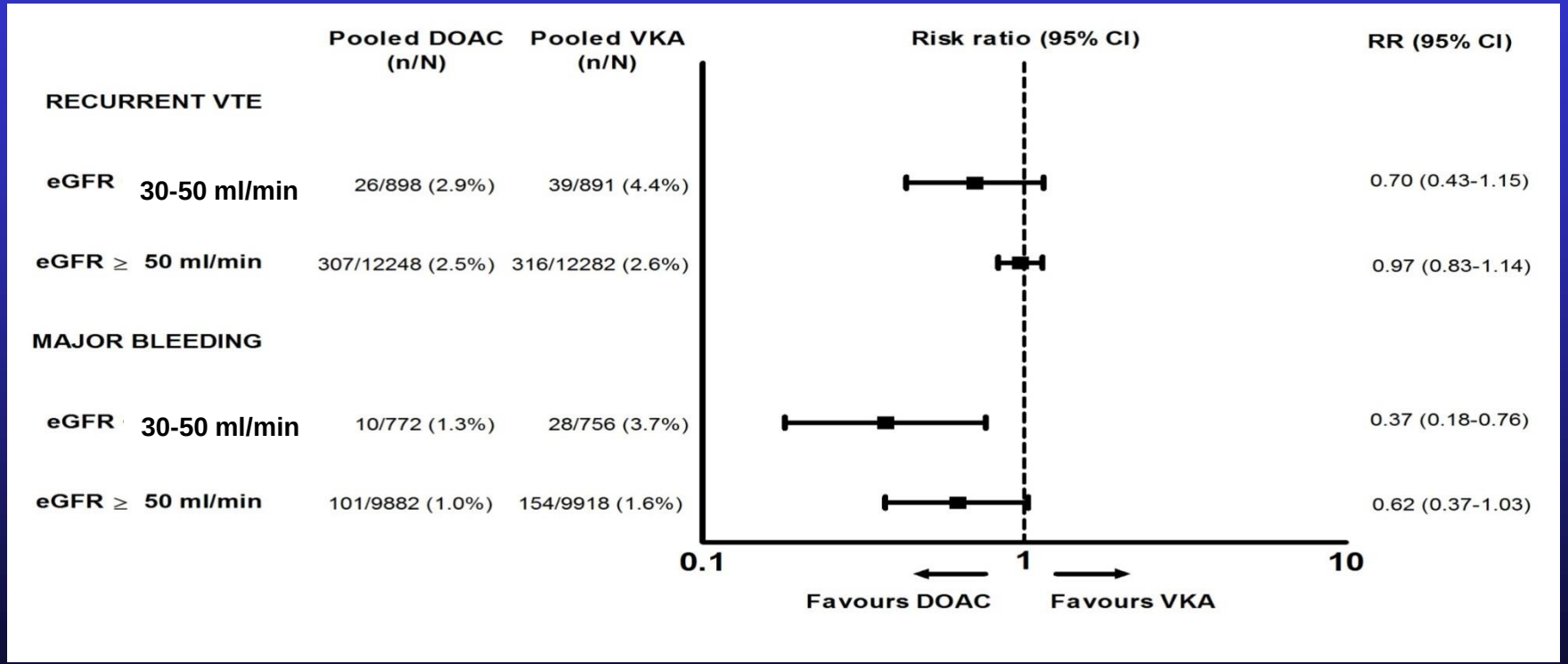
N. van Es et al. Blood 2014

Elderly



N. van Es et al. Blood 2014

Renal function



N. van Es et al. Blood 2014

Abnormal uterine bleeding

- Rivaroxaban vs VKA:

  HR 2.13 (1.6-2.9)[1]

- Rivaroxaban vs VKA:

  prolonged (>8 days) menstrual bleeding (27% vs 8.3%; P0.017)

  need for medical intervention (2.5% vs 7.7% P0.032)[2]

- Comparable findings for apixaban and edoxaban[3,4]

1. Martinelli et al. Blood, 2016; 2. De Crem et al., TR, 2015; 3. Brekelmans et al., TH, 2017; 4. Brekelmans et al. TH, 2016

Where are we uncertain?

- Need for heparin lead-in
- DOACs in special patient populations (cancer; APS and HIT)
- Other reversal agents (andexanet alpha and ciraparantag)

Which improvements can we expect?

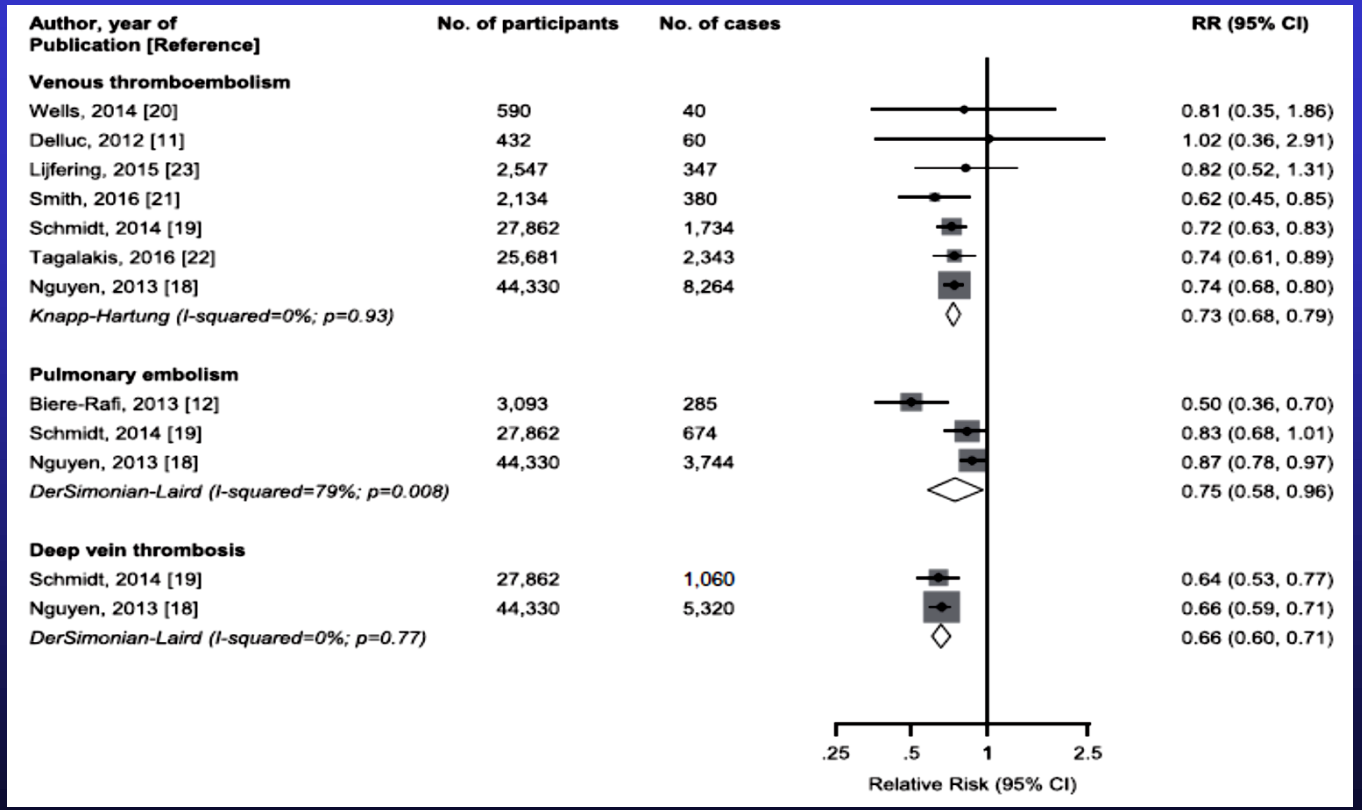
- Confirmation of efficacy/safety DOACs in practice based data
- Novel anticoagulants
- Anti inflammatory agents

Mode of Action of Factor XII or Factor XI Directed Anticoagulants.

	Target	
Agent	Factor XII	Factor XI
Antisense oligonucleotides	Reduce hepatic synthesis of factor XII	Reduce hepatic synthesis of factor XI
Antibodies	Bind factor XII and block its activation	Bind factors XI and block its activation and its capacity to activate factor IX. Bind factor XIa and block its activity
Small molecule inhibitors	Not reported	Bind to the active site of factor XIa and block its activity
Allosteric inhibitors	Not reported	Bind to charged residues on factor XI and modulate factor XIa activity
Aptamer	Binds to factor XII and blocks autoactivation and factor XIIa activity	Not reported

J. Weitz, TR, 2016

Association of statin use with recurrent VTE



S. Kunutsor et al. E Heart J, 2017

Antithrombotic strategies

- DOACs drug of choice in most VTE patients, for those with cancer, APS or HIT: wait and see
- Clear change in bleeding pattern, i.e. less intracranial more uterine bleeding
- Dabigatran has approved reversal agent, for Xa inhibitors: wait and see
- Heparin lead-in requires studies
- Good practice based studies useful
- Factor XI and XII inhibition promising but real clinical studies urgently needed
- Statins deserve evaluation in RCT in addition to anticoagulants