New areas of development for the direct oral anticoagulants

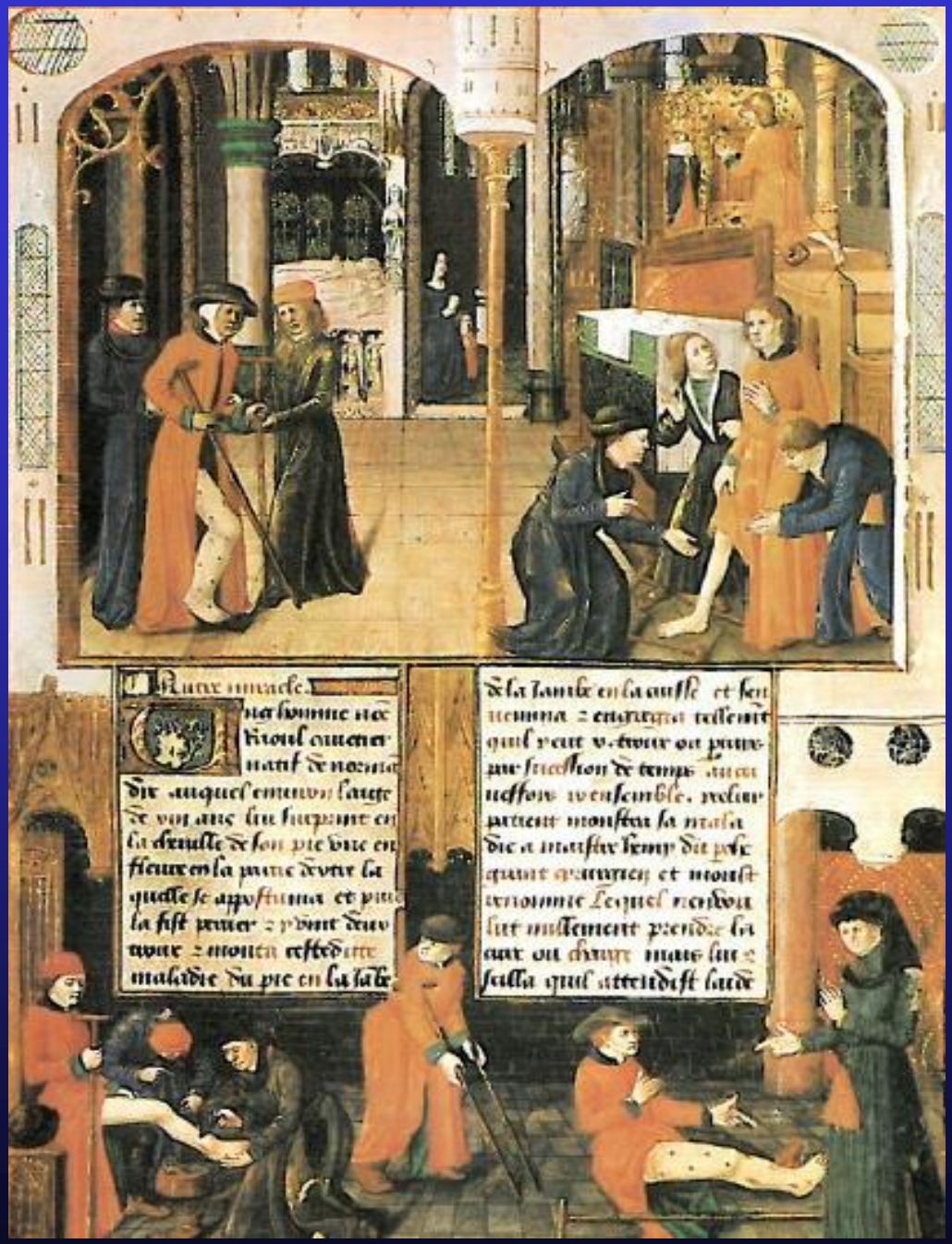
Varese
March 2016

Disclosures for Harry R Büller

Research Support/P.I.	Sanofi-aventis, Bayer HealthCare, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Pfizer, Roche, Isis, Thrombogenics
Employee	No relevant conflicts of interest to declare
Consultant	Sanofi-aventis, Bayer HealthCare, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Pfizer, Roche, Isis, Thrombogenics
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Scientific Advisory Board	Sanofi-aventis, Bayer HealthCare, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Pfizer, Roche, Isis, Thrombogenics

History and future of anticoagulant treatment in VTE

- Heparin and vitamin K antagonists 1938 – 2005
- Direct oral anticoagulants 2005 – 2020
- Intrinsic Pathway Inhibitors 2020 –

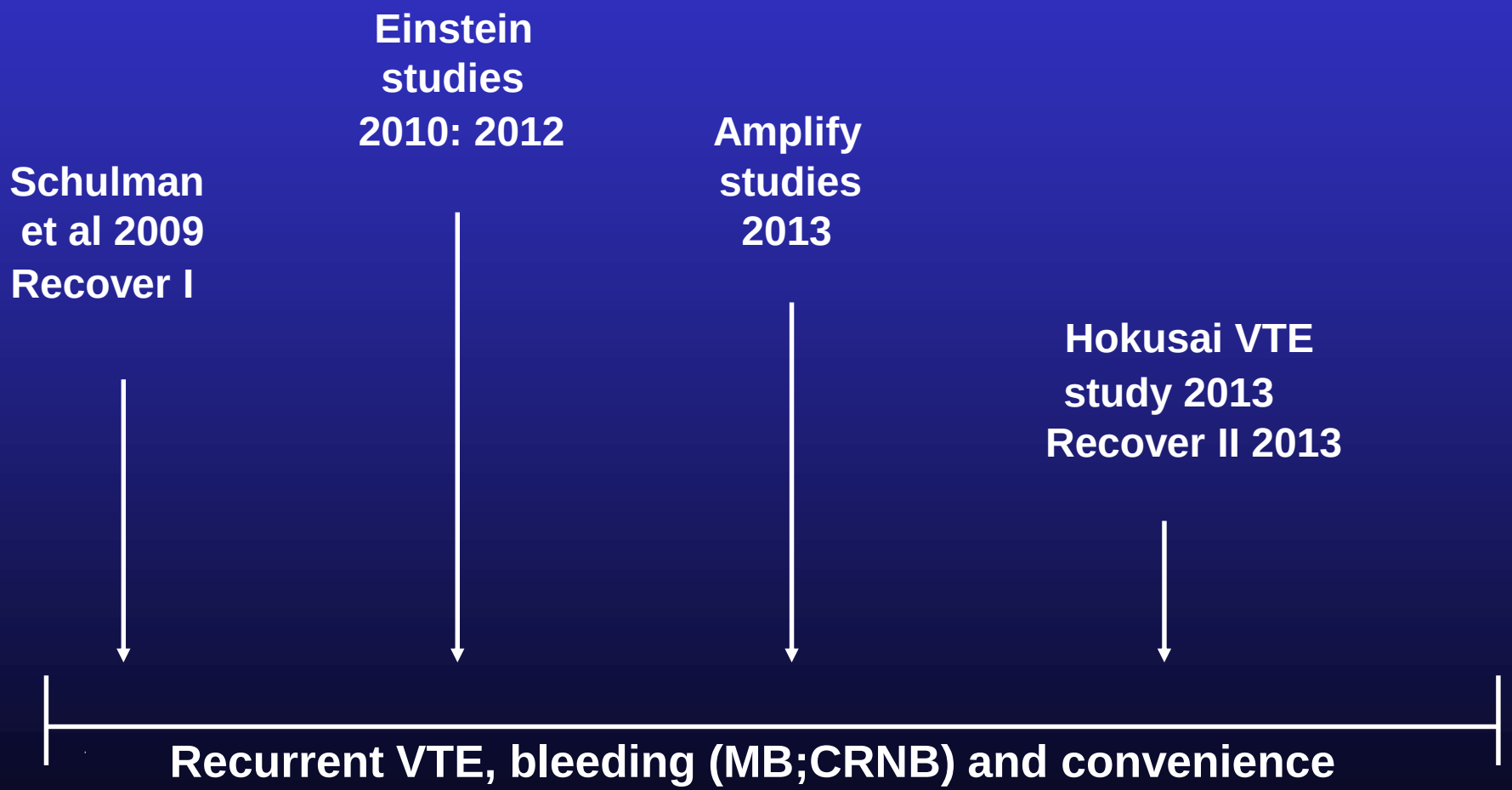


VTE treatment studies - new oral anticoagulants

	Hokusai-VTE	EINSTEIN-DVT EINSTEIN-PE	AMPLIFY	RE-COVER I RE-COVER II
Drug	Edoxaban	Rivaroxaban	Apixaban	Dabigatran
Study design	Double-blind	Open-label	Double-blind	Double-blind
Heparin lead-in	At least 5 days	None	None	At least 5 days
Dose	60 mg qd 30 mg qd (CrCl, bw, P-gp)	15 mg bid x 3 wk then 20 mg qd	10 mg bid x 7 days then 5 mg bid	150 mg bid
Non-inferiority margin	1.5	2.0	1.8	2.75
Sample size	8,292	**EINSTEIN-DVT** 3,449 **EINSTEIN-PE** 4,832	5,400	**RE-COVER I** 2,564 **RE-COVER II** 2,568
Treatment duration	Flexible 3 to 12 months	Pre-specified 3, 6, or 12 months	6 months	6 months

Adapted from Raskob et al. J Thromb Haemost 2013. doi:10.1111/jth.12230

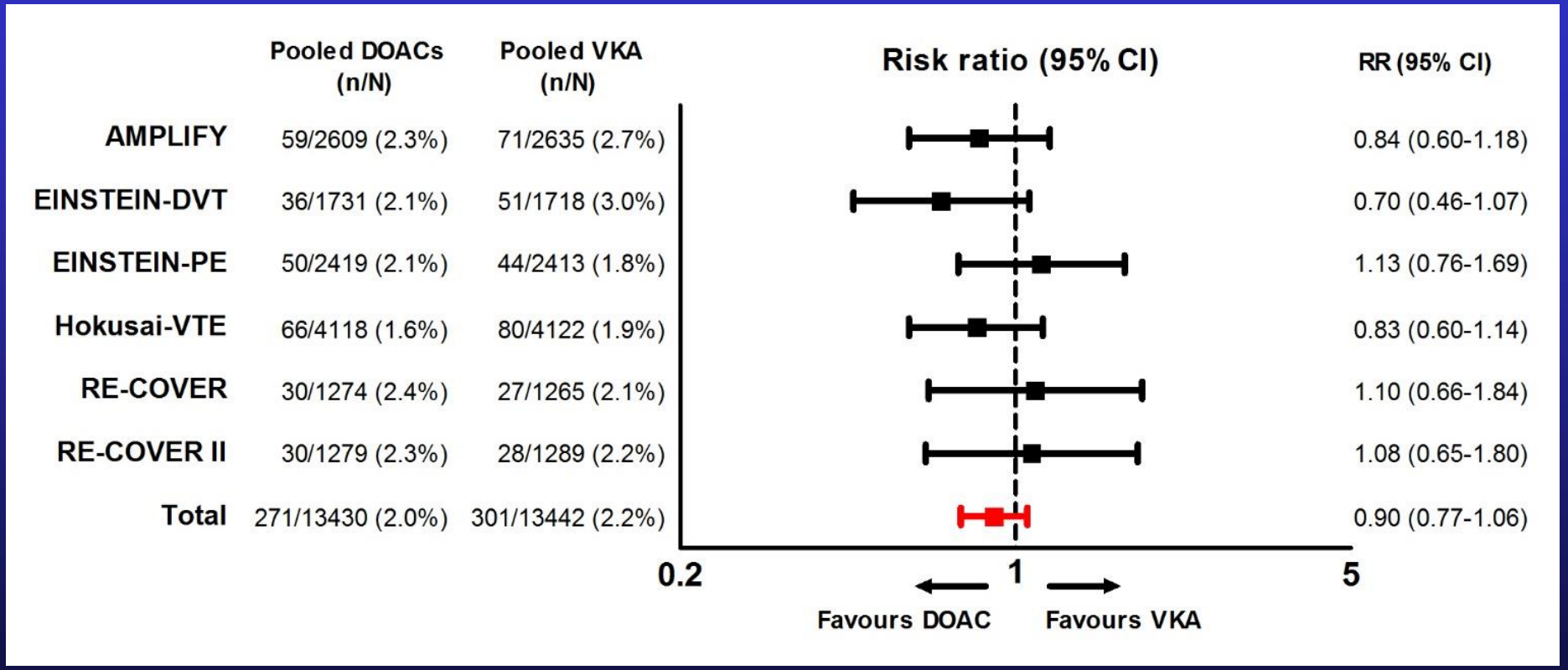
DOAC Revolution



Differences and similarities

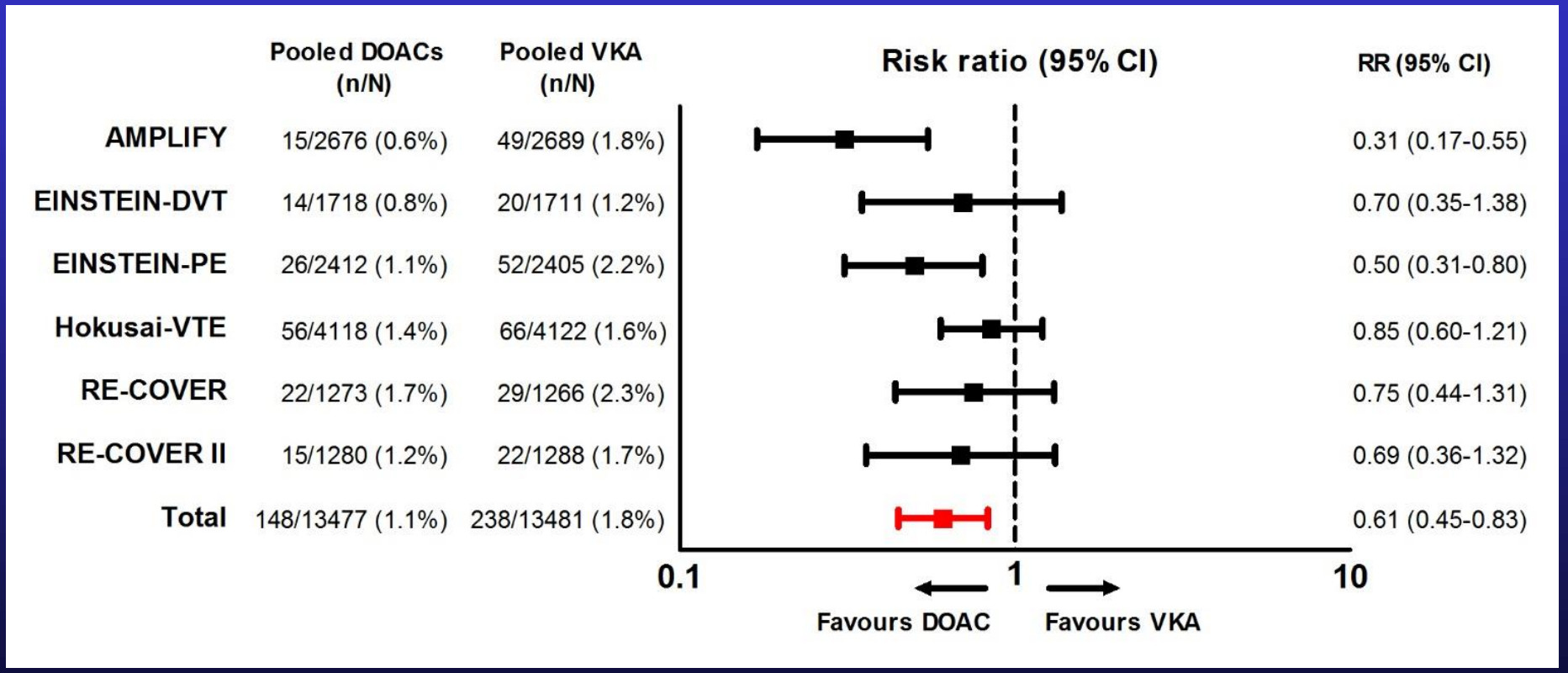
- Hokusai / Recover I/II used initial heparin
- Mostly DVT and PE combined
- Duration of treatment / follow-up variable
- Identical definition of efficacy and safety outcomes
- The same adjudication committee

Overall efficacy



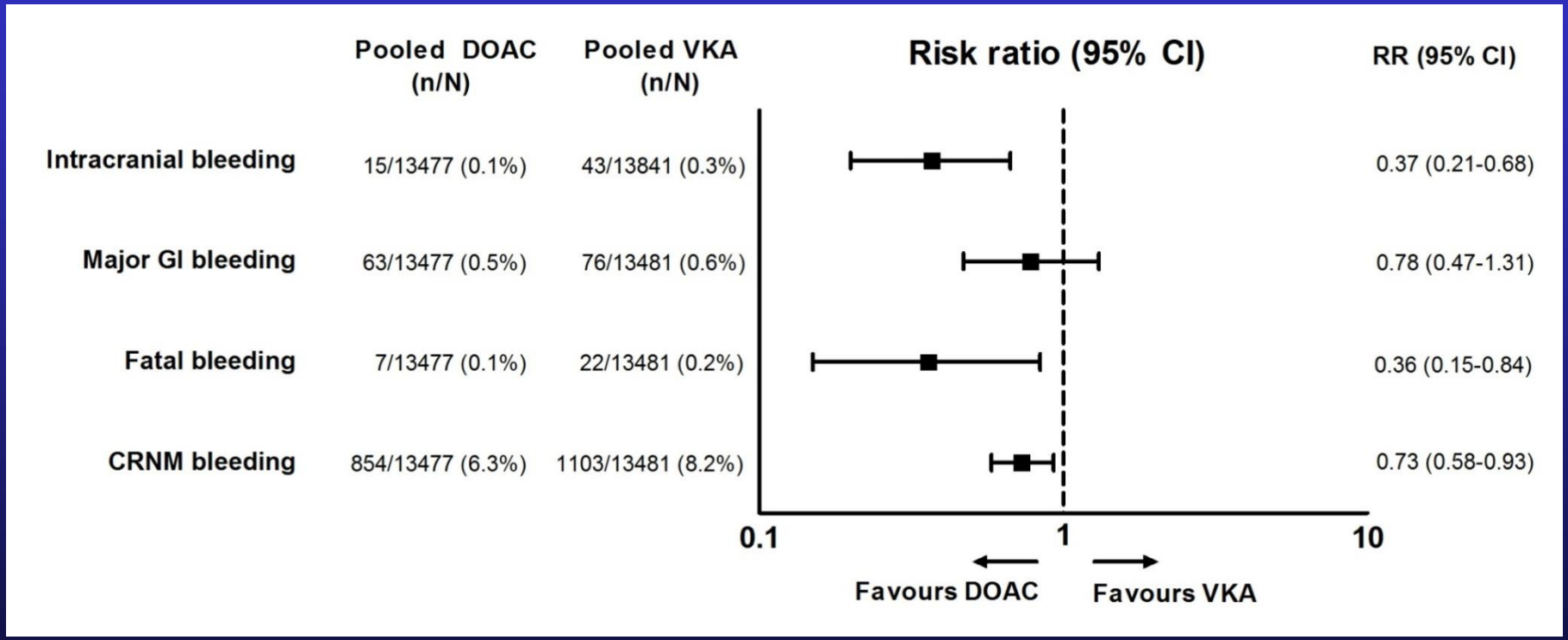
Van Es et al. Blood 2014

Overall major bleeding



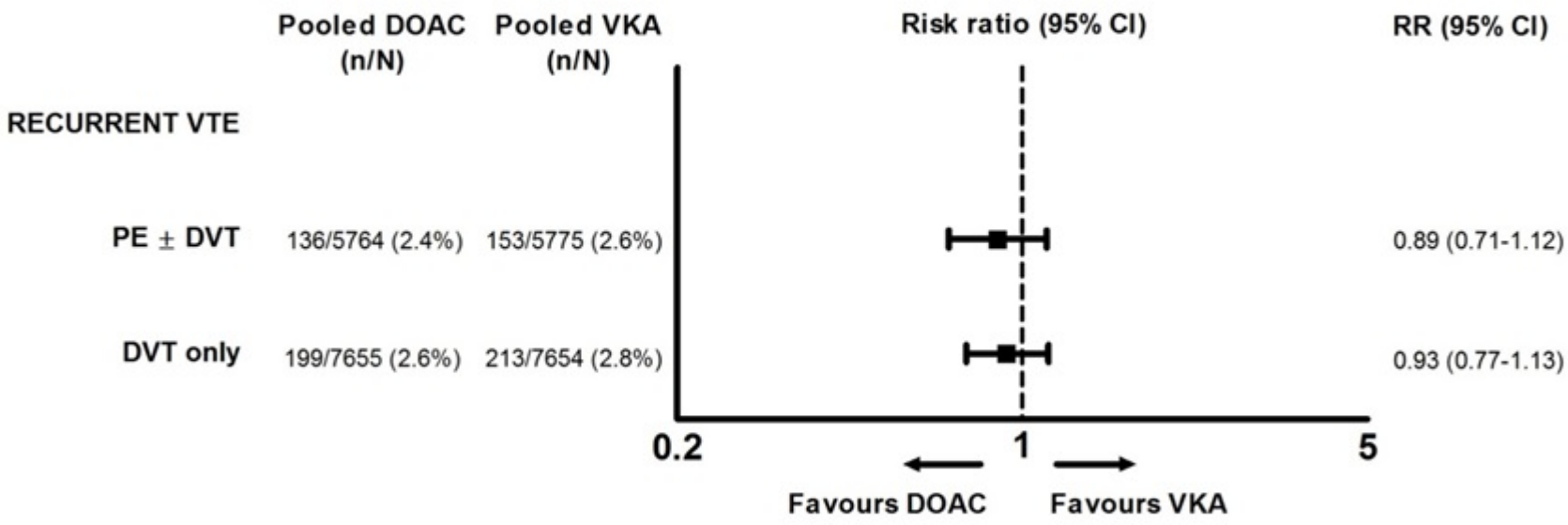
Van Es et al. Blood 2014

Bleeding components

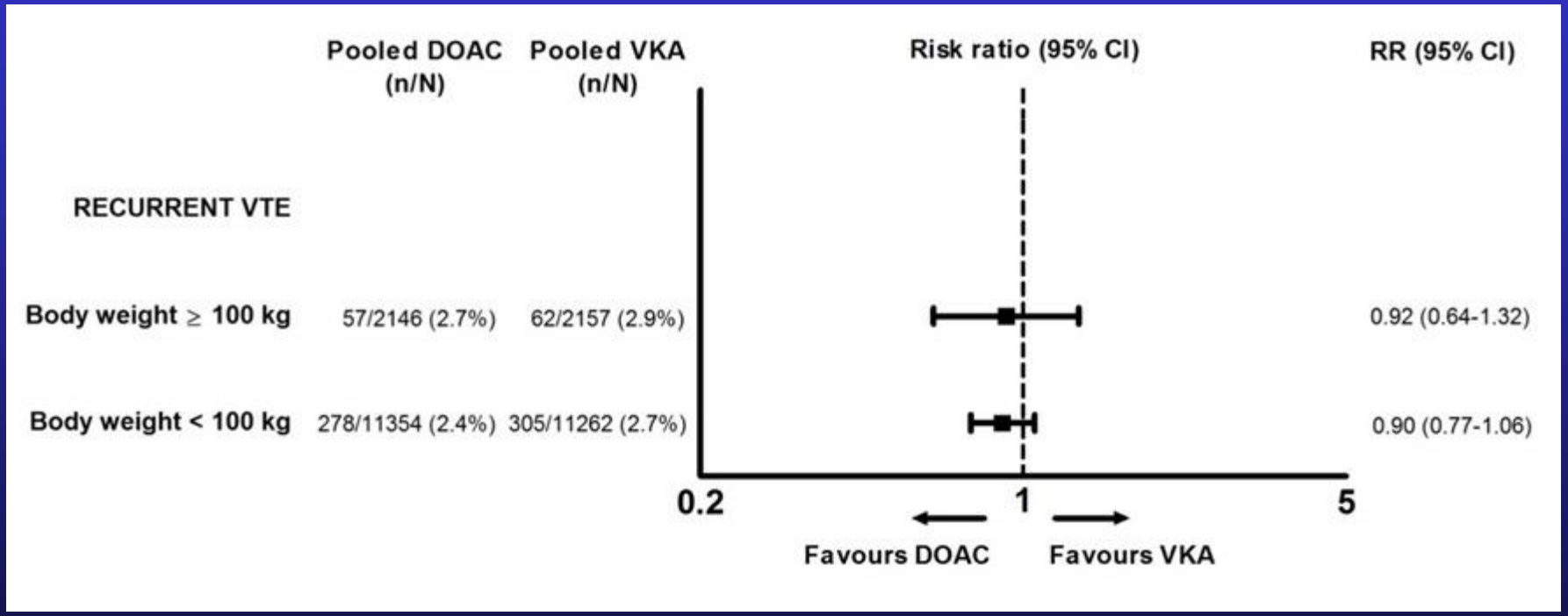


Van Es et al. Blood 2014

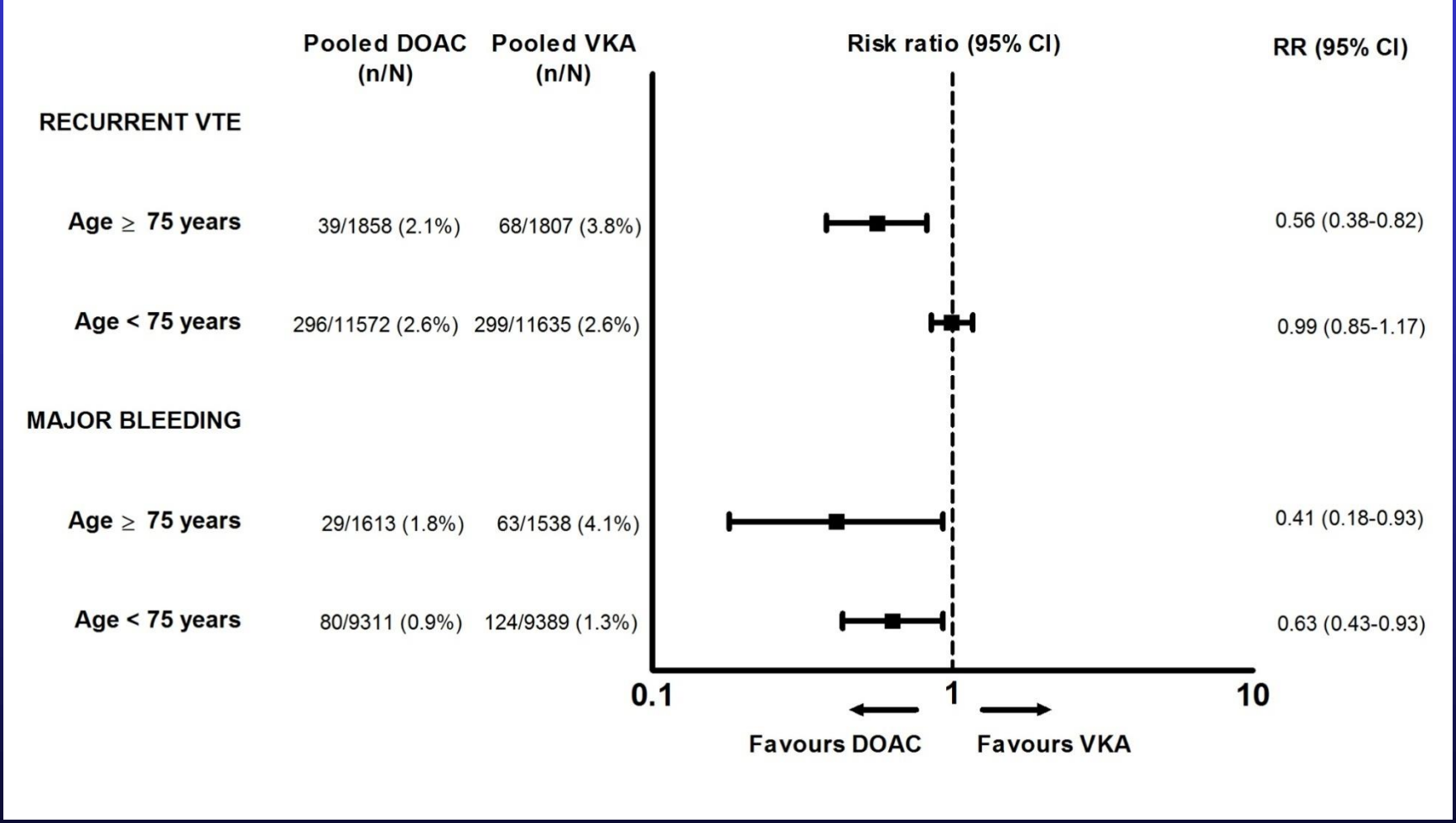
PE / DVT


Pooled DOAC (n/N)
Pooled VKA (n/N)
Risk ratio (95% CI)
RR (95% CI)
RECURRENT VTE
PE ± DVT
136/5764 (2.4%)
153/5775 (2.6%)
0.89 (0.71-1.12)
DVT only
199/7655 (2.6%)
213/7654 (2.8%)
0.93 (0.77-1.13)
0.2
1
5
Favours DOAC
Favours VKA

Body weight

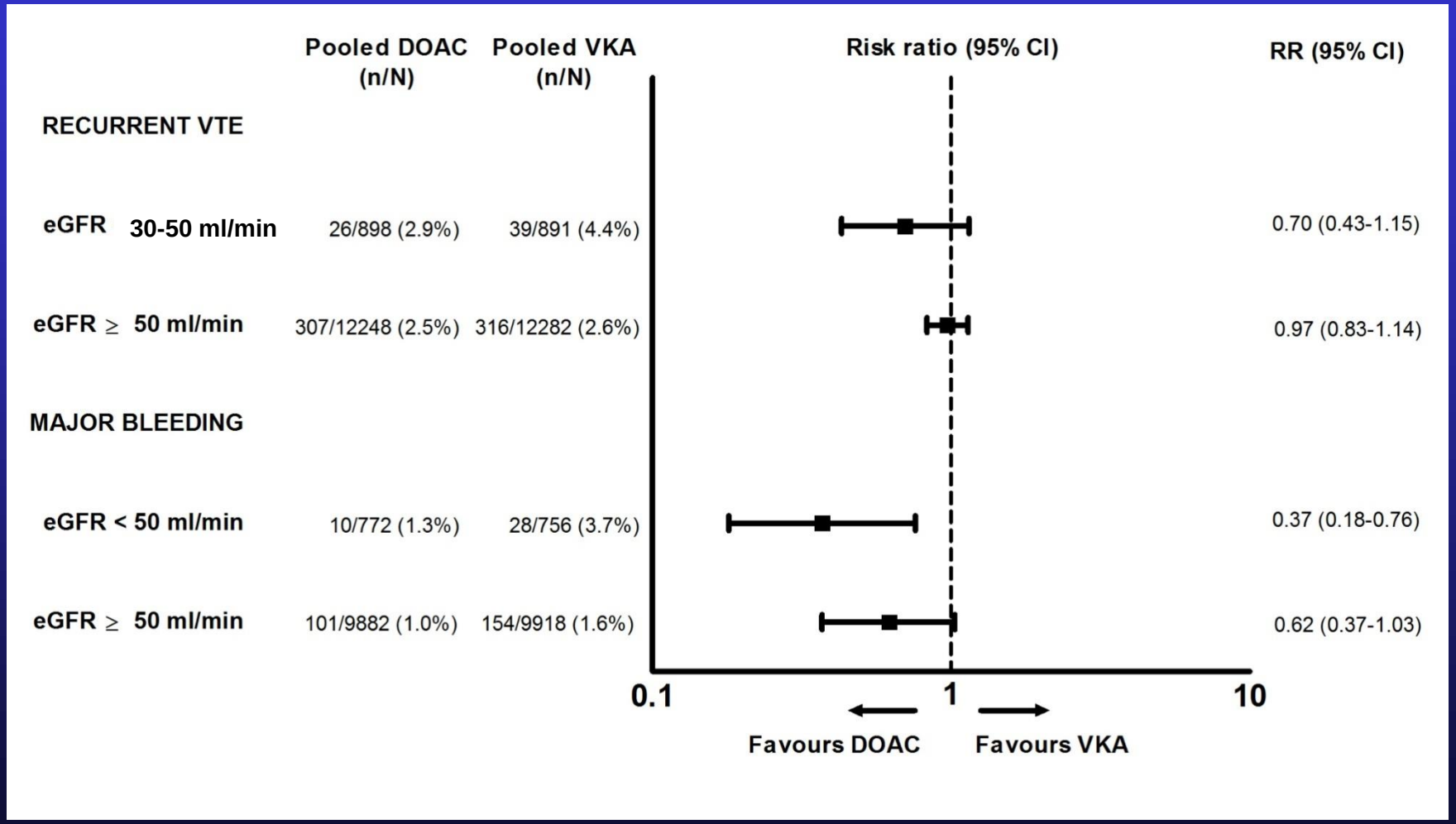

Pooled DOAC (n/N)
Pooled VKA (n/N)
Risk ratio (95% CI)
RR (95% CI)
RECURRENT VTE
Body weight ≥ 100 kg
57/2146 (2.7%)
62/2157 (2.9%)
0.92 (0.64-1.32)
Body weight < 100 kg
278/11354 (2.4%)
305/11262 (2.7%)
0.90 (0.77-1.06)
0.2
1
5
Favours DOAC
Favours VKA

Elderly



Van Es et al. Blood 2014

Renal function

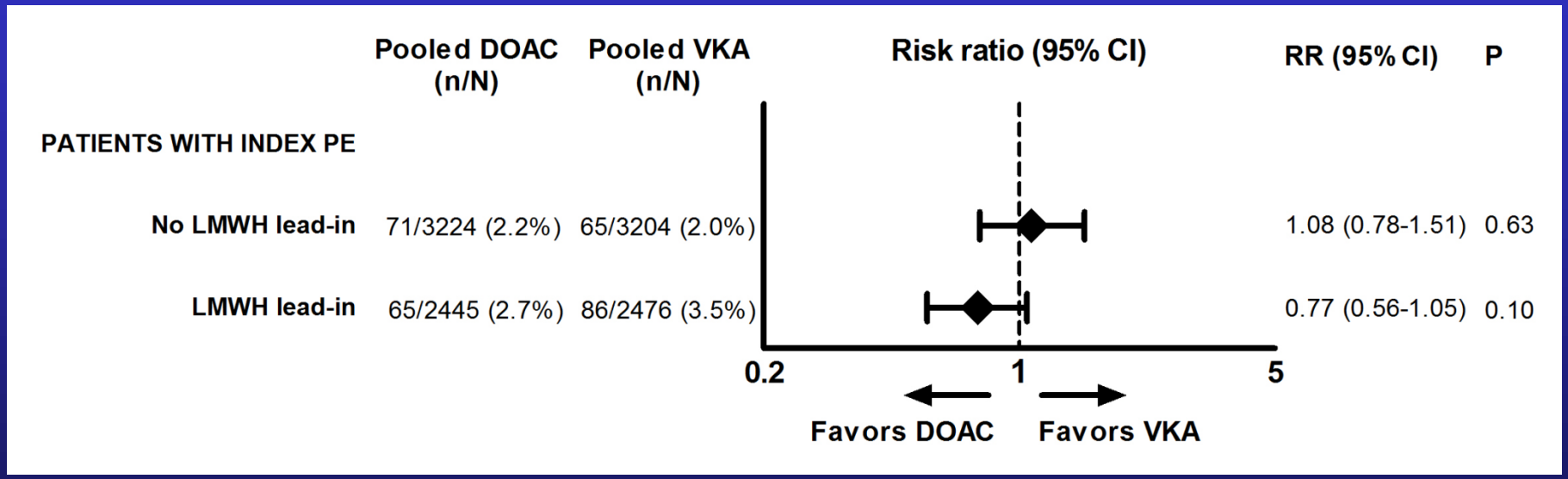


Van Es et al. Blood 2014

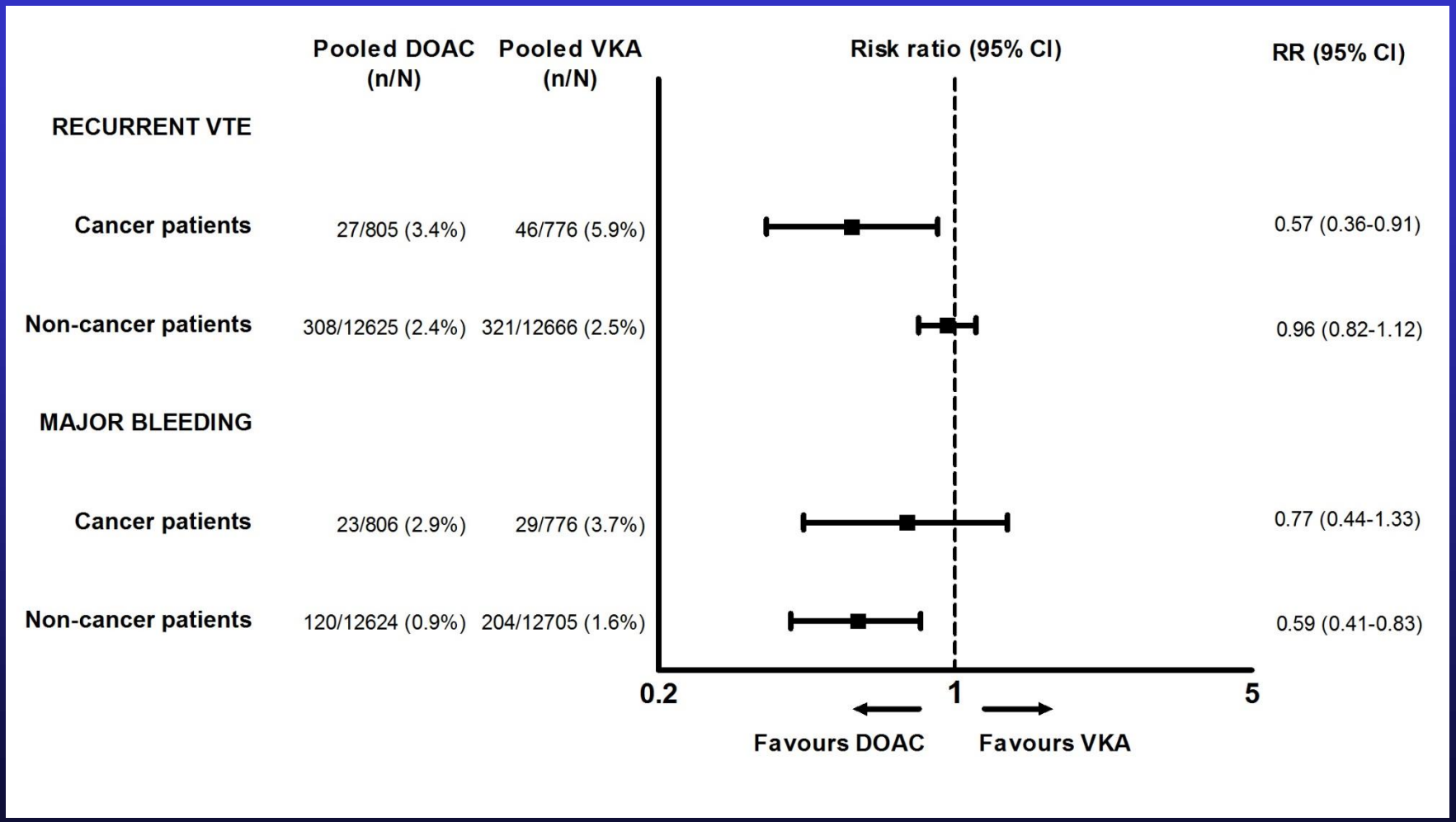
DOAC uncertainties

- Heparin lead in
- Cancer
- APS/HIT

Heparin / no Heparin



Cancer



Van Es et al. Blood 2014

Hokusai VTE-cancer Study
- Design features -

- Prospective, randomized, open label, blind evaluation study
- LMWH/Edoxaban vs LMWH (Clot)
- Primary objective: non inferiority for combined outcome of recurrent VTE and major bleeding
- Follow up: 12 months; 1000 pts
- Patients: active or within 2 years

APS

- APS
  - Retrospective cohort[1]; 26 pts with thrombotic APS (7 all 3 types of APLA; 12 lupus anticoagulant); 6 Riva / Dabi as firstline, others switchers
  - Median follow up 1.5 year
    - 1 recurrent VTE (3.8%)
    - 2 bleeding (7.7%)

Noel et al. Autoimmun. Rev. 2015

APS

- APS
  - Case series[2]; 12 pts with thrombotic APS (5 all 3 types; 3 lupus); all switchers; Riva
  - Follow up 2-16 months
    - 2 recurrent VTE
- Several Case series with failures

Son et al, Thromb Res. 2015

APS

- Rivaroxaban in Anti Phospholipid Syndrome (RAPS)
  - RCT; riva vs. VKA; ETP outcome
  - 156 pts; completed; no recurrences
- The Rivaroxaban in Thrombotic APS (TRAPS)
  - RCT, open; riva vs. VKA; combined outcome (thrombosis, major bleeding, death)
  - 4 yr fu, N=536, dec. 2018
- Rivaroxaban in APS Pilot Study
  - Cohort, 150 pts, riva 20mg/dd
  - Fu. 1 yr; venous/arterial and bleeding

HIT

- Laboratory studies
  - No cross-reaction of DOACs with HIT antibodies and no platelet activation
- Clinical data
  - 6 case reports (5 Riva; 1 Dabi)
    - no thrombotic events; full platelet recovery
  - Retrospective cohort (N=22); dabi, apix and riva
    - no thrombotic events

HIT

- Rivaroxaban for HIT Study
  - Cohort, (high/intermediate probability; 4 T's score); Riva
  - Planned N=219; vs. historical argatroban outcome thromboembolic rate

Conclusions

- DOAC's are effective, but safer, both in DVT and PE
- Also in important subgroups; elderly, clearance 30-50, and cancer
- APS and HIT promising, but wait
- Direct comparison of DOAC versus LMWH in cancer warranted
- Unresolved is whether to give initial heparin