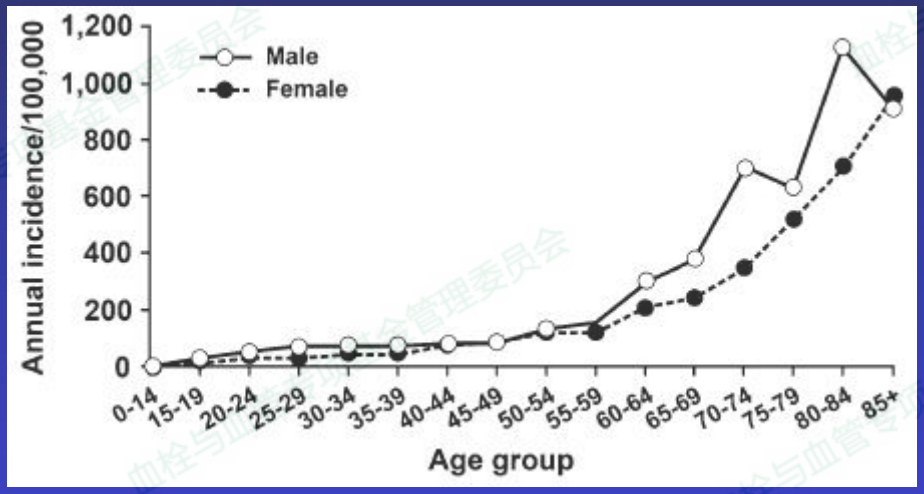
新型口服抗凝药在VTE治疗中的地位

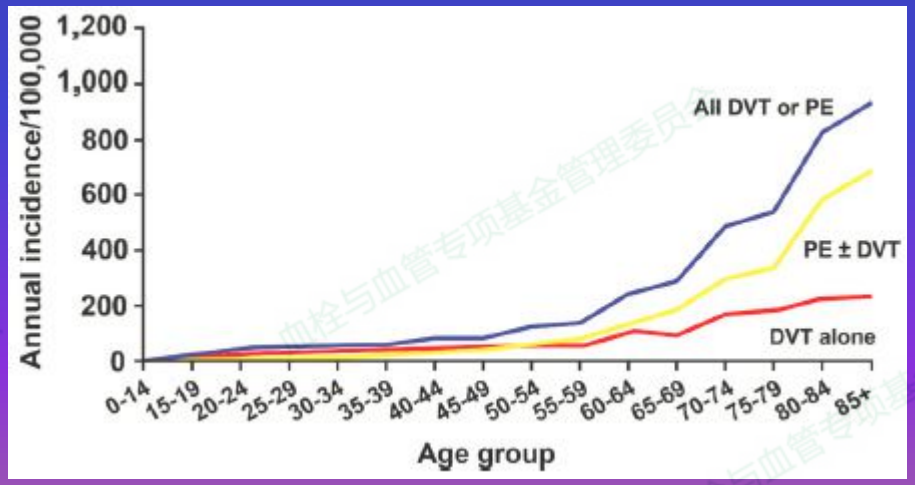
马壮

沈阳军区总医院呼吸与重症医学科

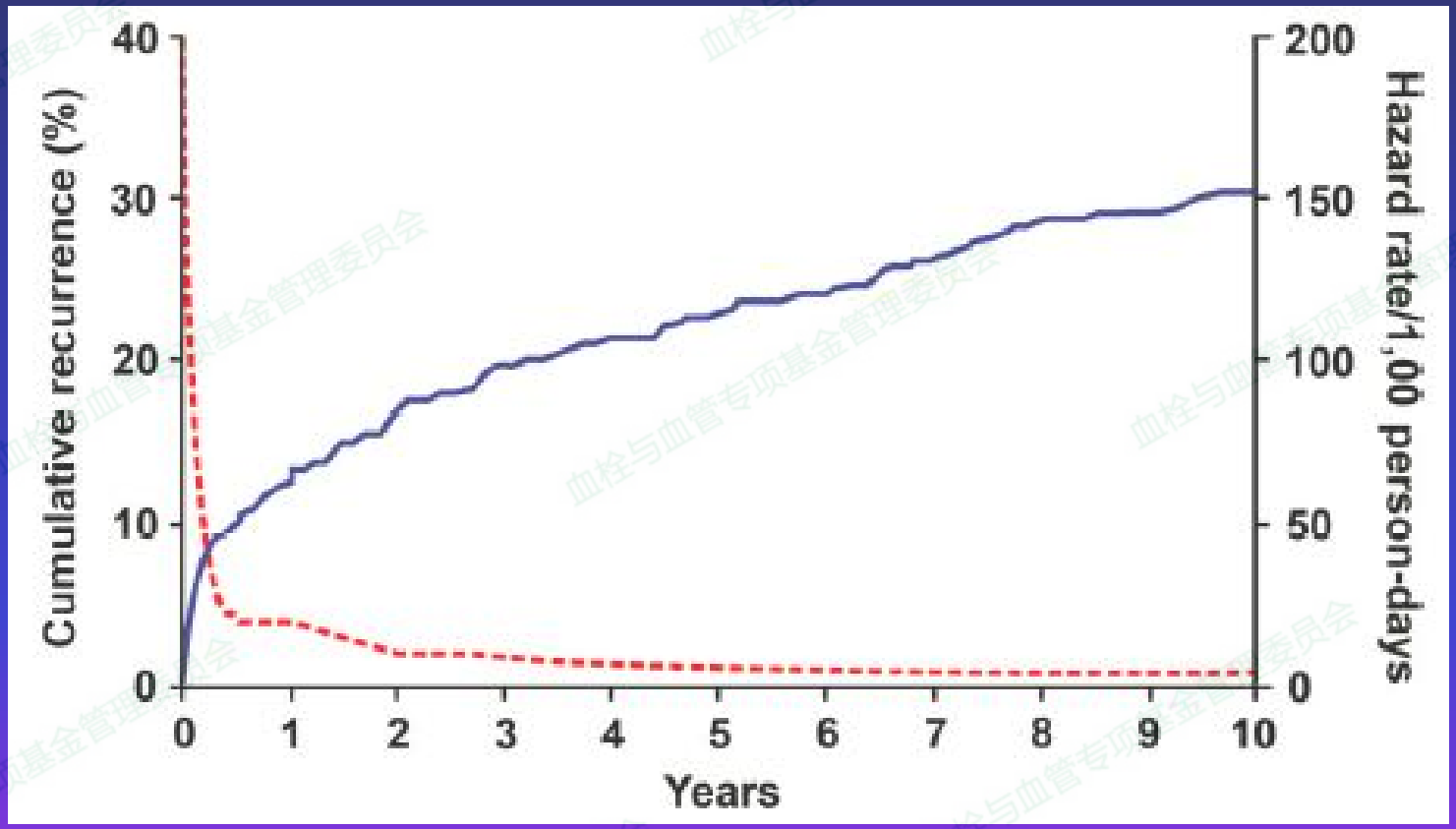
VTE的年龄相关流行病学



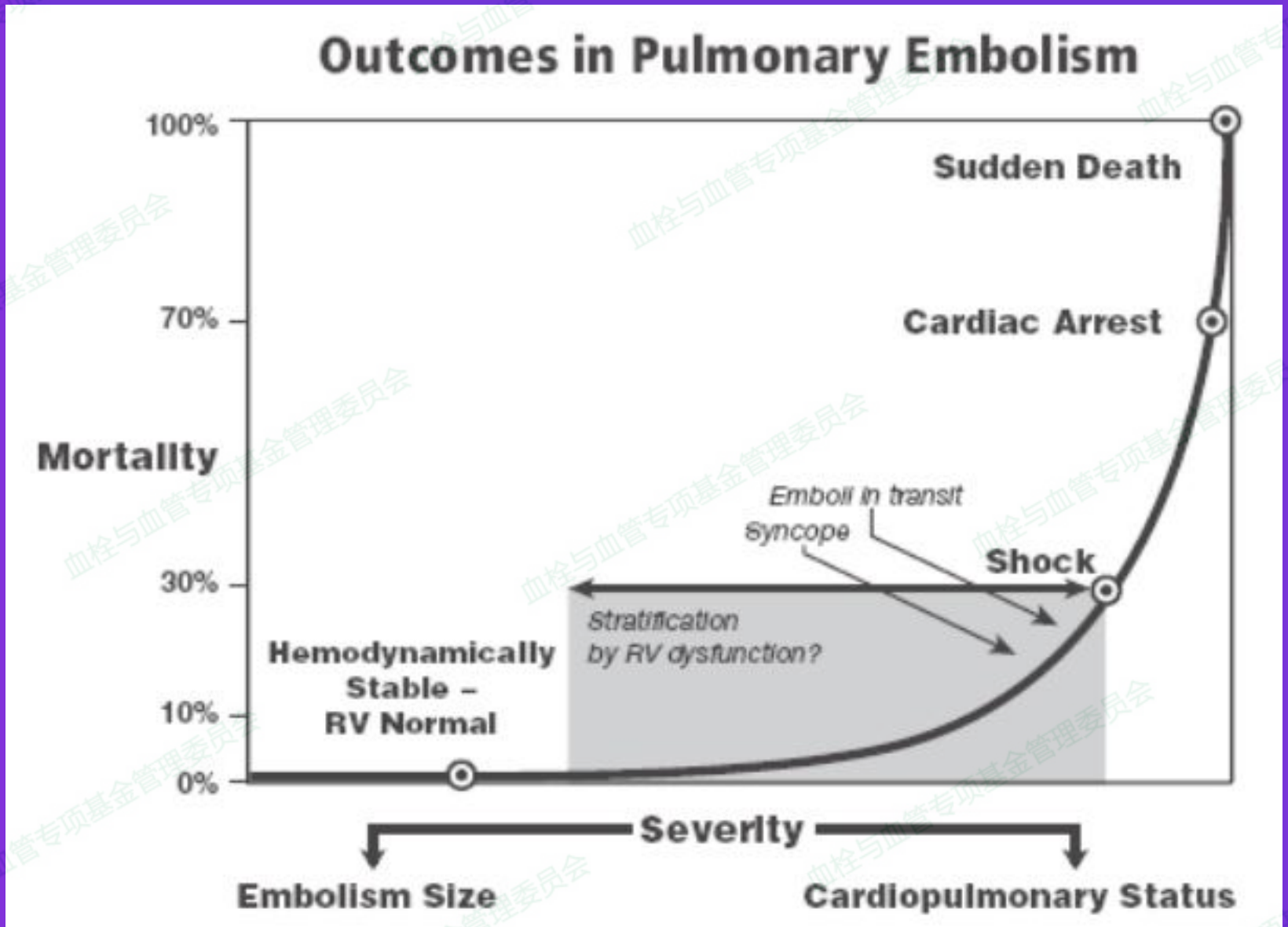
J. A. Heit et al.
J Thromb Thrombolysis
(2016) 41:3–14



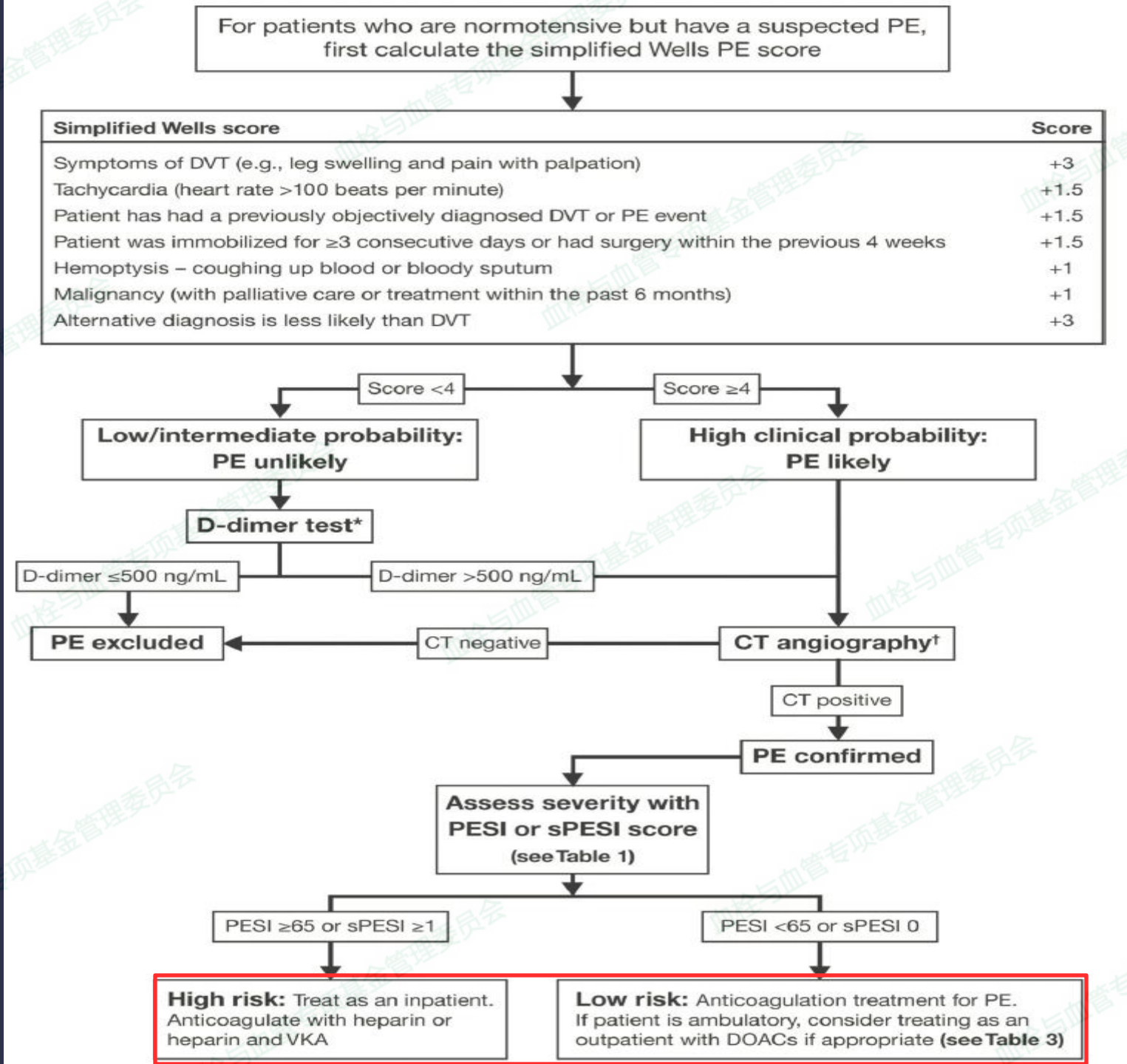
VTE复发累计发病率



J. A. Heit et al. J Thromb Thrombolysis (2016) 41:3–14

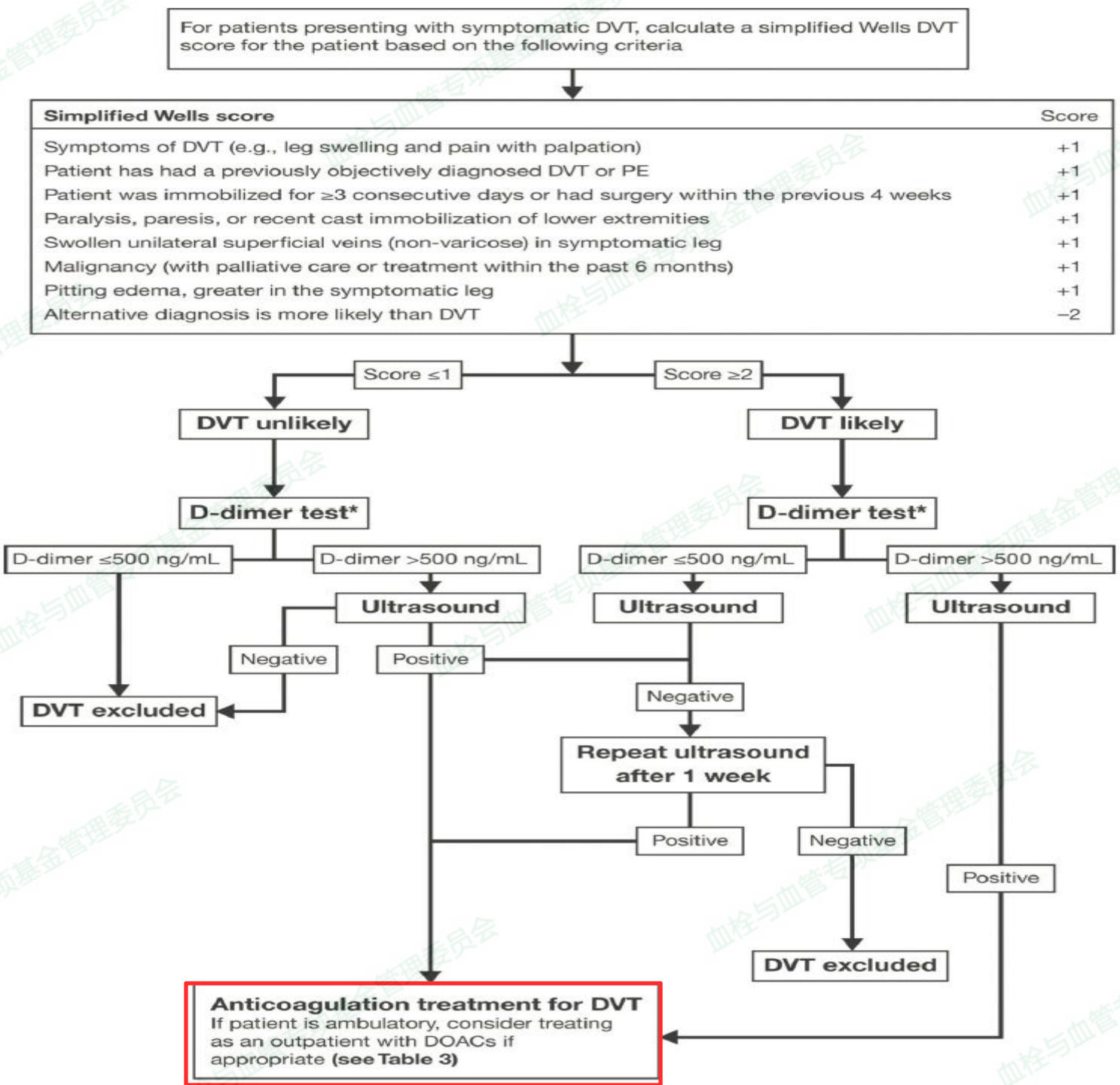

Outcomes in Pulmonary Embolism
100%
70%
30%
10%
0%
Mortality
Sudden Death
Cardiac Arrest
Shock
Emboli in transit
Syncope
Stratification
by RV dysfunction?
Hemodynamically
Stable –
RV Normal
Severity
Embolism Size
Cardiopulmonary Status

血流动力学稳定的有症状肺栓塞诊治流程



Ceresetto JM. CLINICS 2016;71(1):36-46

有症状DVT的诊治流程

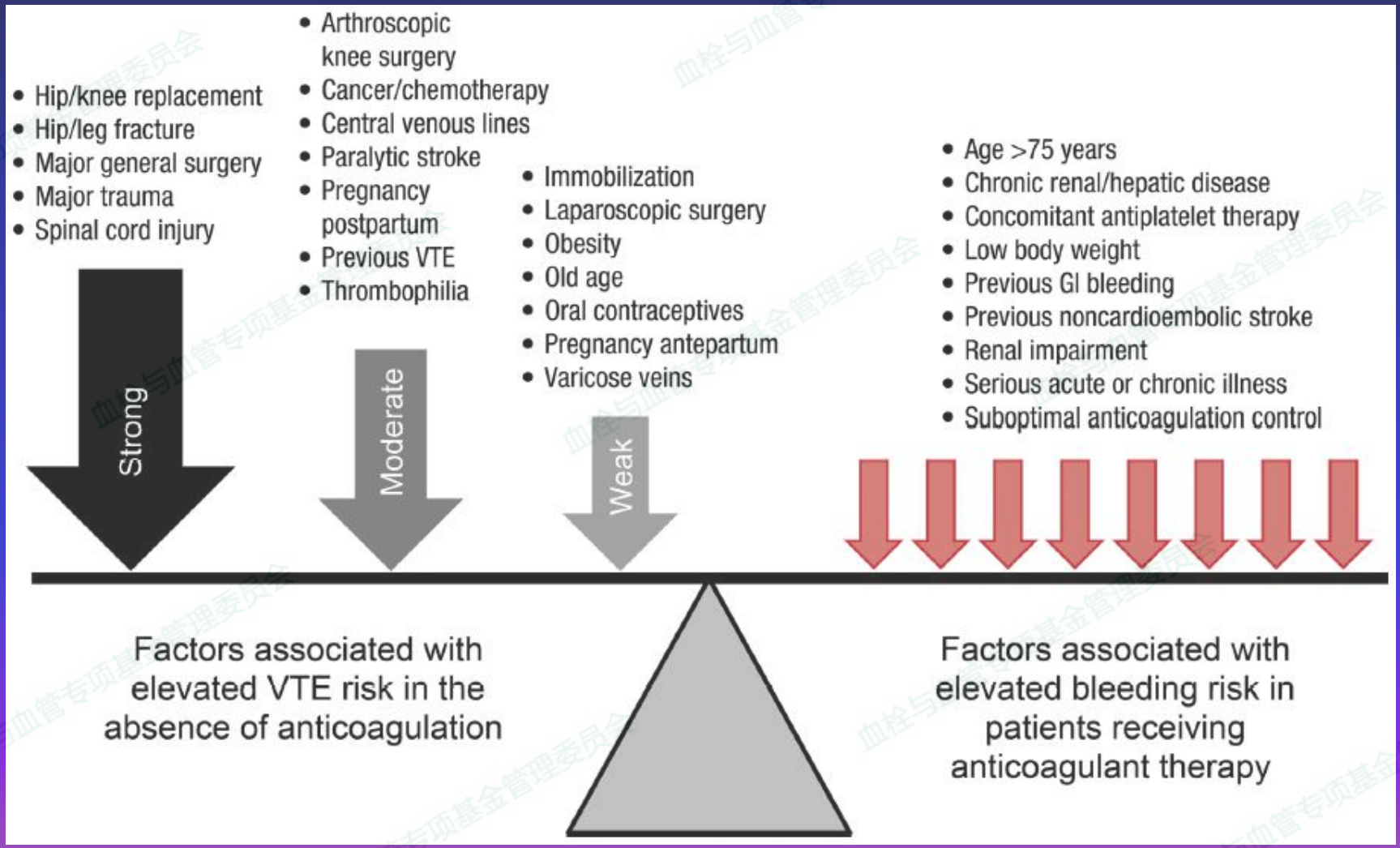


Ceresetto JM. CLINICS 2016;71(1):36-46

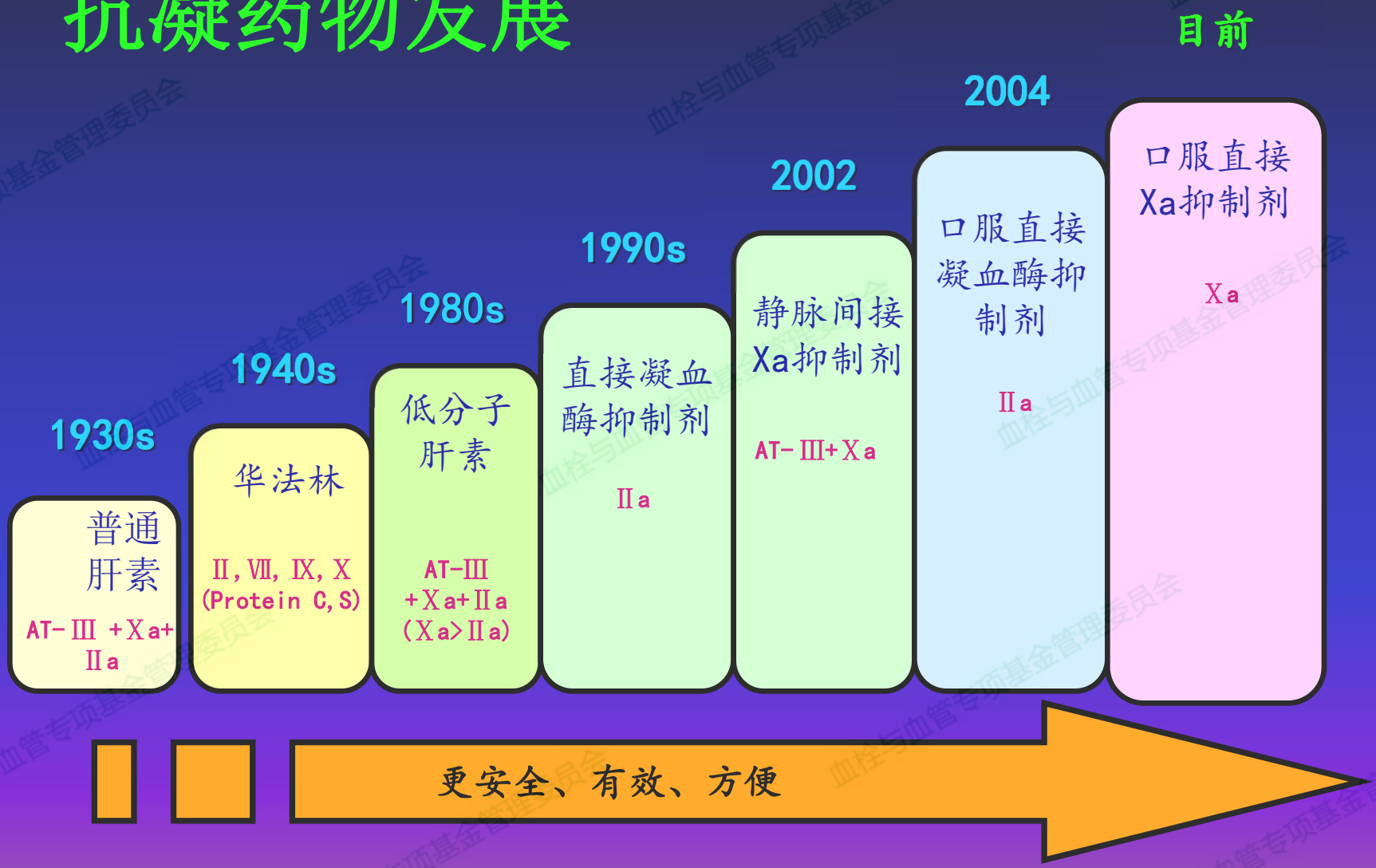
抗凝治疗的目的

- 早期及时的抗凝治疗
  - 防止肺栓塞的发生
  - 防止血栓扩展到大静脉中
- 后续持续的抗凝治疗
  - 防止复发
  - 预防慢性并发症

VTE复发与出血风险的平衡



抗凝药物发展


1930s
普通肝素
AT-Ⅲ +Xa+ Ⅱa
1940s
华法林
Ⅱ,Ⅶ, Ⅸ, Ⅹ (Protein C,S)
1980s
低分子肝素
AT-Ⅲ +Xa+Ⅱa (Xa>Ⅱa)
1990s
直接凝血酶抑制剂
Ⅱa
2002
静脉间接Xa抑制剂
AT-Ⅲ+Xa
2004
口服直接凝血酶抑制剂
Ⅱa
目前
口服直接Xa抑制剂
Xa
更安全、有效、方便

临床需要的理想抗凝药物

- 口服
- 起效迅速
- 治疗窗宽
- 固定剂量
- 不需要凝血功能的监测
- 与食物和其他药物之间相互作用少

新型口服抗凝药的药理特点

Table 3
Pharmacologic properties of the new oral anticoagulants

Properties	Dabigatran	Rivaroxaban	Apixaban
Target	FIIa	FXa	FXa
Peak plasma concentrations	~1.5 h	~3 h	~1–3 h
Half-life (normal Cr)	12–14 h	4–13 h	8–15 h
Clearance	80% renal	60% renal	Multiple mechanisms
Antidote	No	No	No
Laboratory monitoring	Not required, TT/TCT or aPTT	Not required, anti-Xa assay	Not required, anti-Xa assay
Involvement of CYP	Minor	Minor	Minor
FDA indications	(1) Stroke and systemic embolism prophylaxis in nonvalvular atrial fibrillation	(1) VTE prophylaxis after TKR/THR (2) Stroke and systemic embolism prophylaxis in nonvalvular atrial fibrillation	None

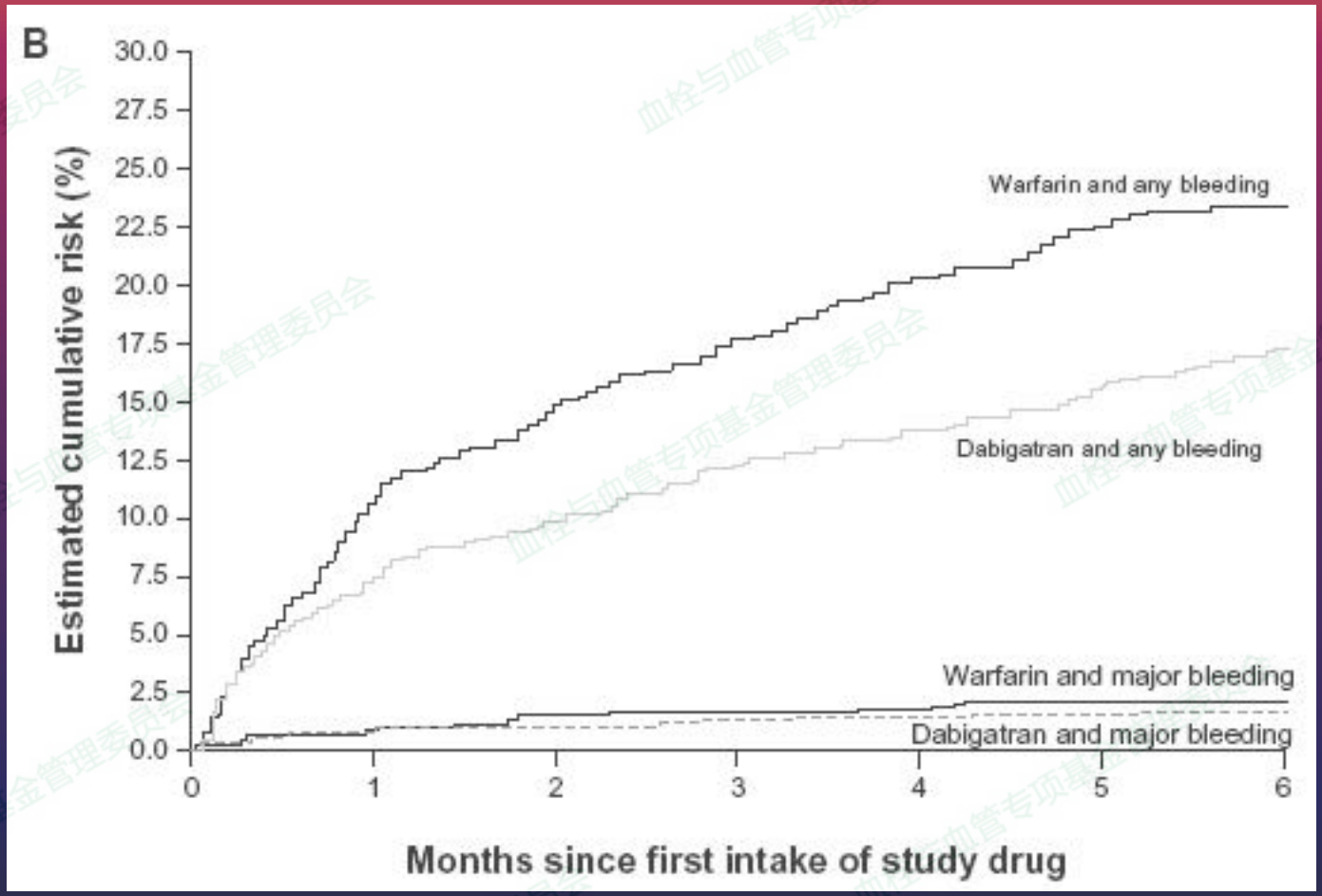
Rajasekhar A, et al. Crit Care Clin 28 (2012) 427–451

新型口服抗凝药的研究汇总

Clinical Trial	RE-MEDY	ADOPT	AMPLIFY	MAGELLAN	EINSTEIN Extension
Patients	Previously treated VTE (at least 3 mo)	Medically ill	VTE previously treated (for 6–12 mo)	Medically ill	Medically ill after 3 mo treatment for VTE
Study design	International multicenter randomized double-blind controlled trial	International multicenter randomized double-blind controlled trial	Randomized, double-blind	International, randomized, blinded, controlled trial	Randomized controlled trial
Participants	2,866	6,524	2,486	8,101	1,197
Follow-up	3 cohorts: <18 mo, 18 mo, and >18 mo	90 d	13 mo	90 d	12 mo
Primary efficacy end point	Composite of recurrent symptomatic VTE and related mortality	Composite of recurrent total VTE incidence and related mortality	Composite of recurrent symptomatic VTE and related mortality	Composite of recurrent total VTE incidence and related mortality	Recurrent VTE incidence
Safety end points	Major and nonmajor clinically significant bleeding	Major and nonmajor clinically significant bleeding	Major bleeding Composite of major and nonmajor clinically significant bleeding	Major and nonmajor clinically significant bleeding	Major bleeding
Drugs	Dabigatran 150 mg BID 36 mo Warfarin 36 mo	Apixaban 2.5 mg BID for 30 d Enoxaparin 40 mg SC OD	Apixaban 2.5 mg BID Apixaban 5 mg BID Placebo	Rivaroxaban 10 mg OD Enoxaparin 40 mg SC OD	Rivaroxaban 10 mg OD 6 mo Rivaroxaban 10 mg OD 12 mo Placebo
Results	Lower rate of recurrent VTE with dabigatran Significant more acute coronary syndrome with dabigatran	Lower rates of VTE and related mortality Higher rates of bleeding at Day 30	Both apixaban doses were superior with respect to efficacy ($P < 0.001$) Similar rates of bleeding in the 3 groups	Lower rates of VTE and mortality Increased bleeding rates Nonsignificant net clinical benefit	Lower rates of VTE incidence (rivaroxaban superior to placebo, $P < 0.001$) No significant differences regarding bleeding

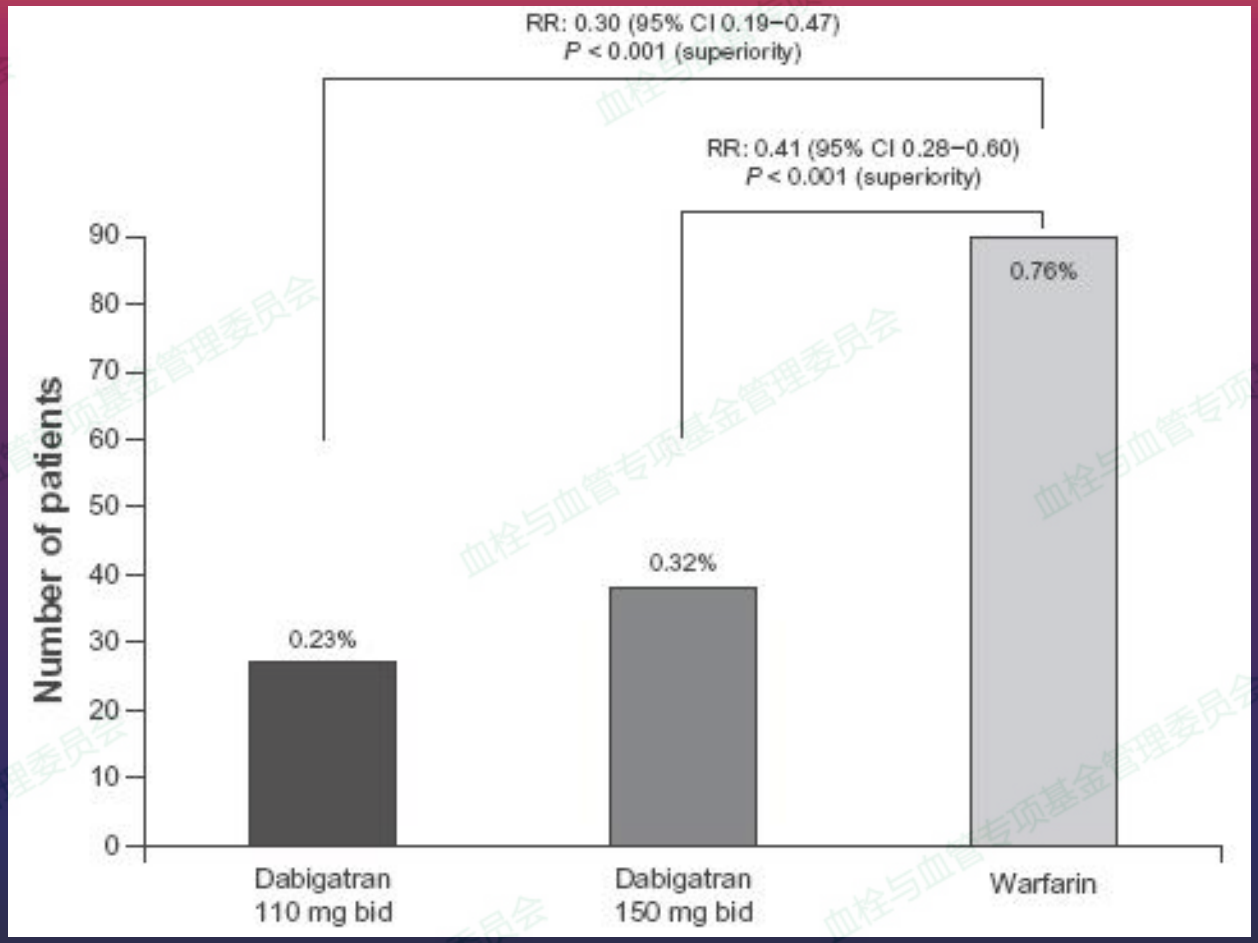
Gallego P, et al. Am J Respir Crit Care Med 2013, 188(4): 413–421

达比加群与华法令出血风险比较



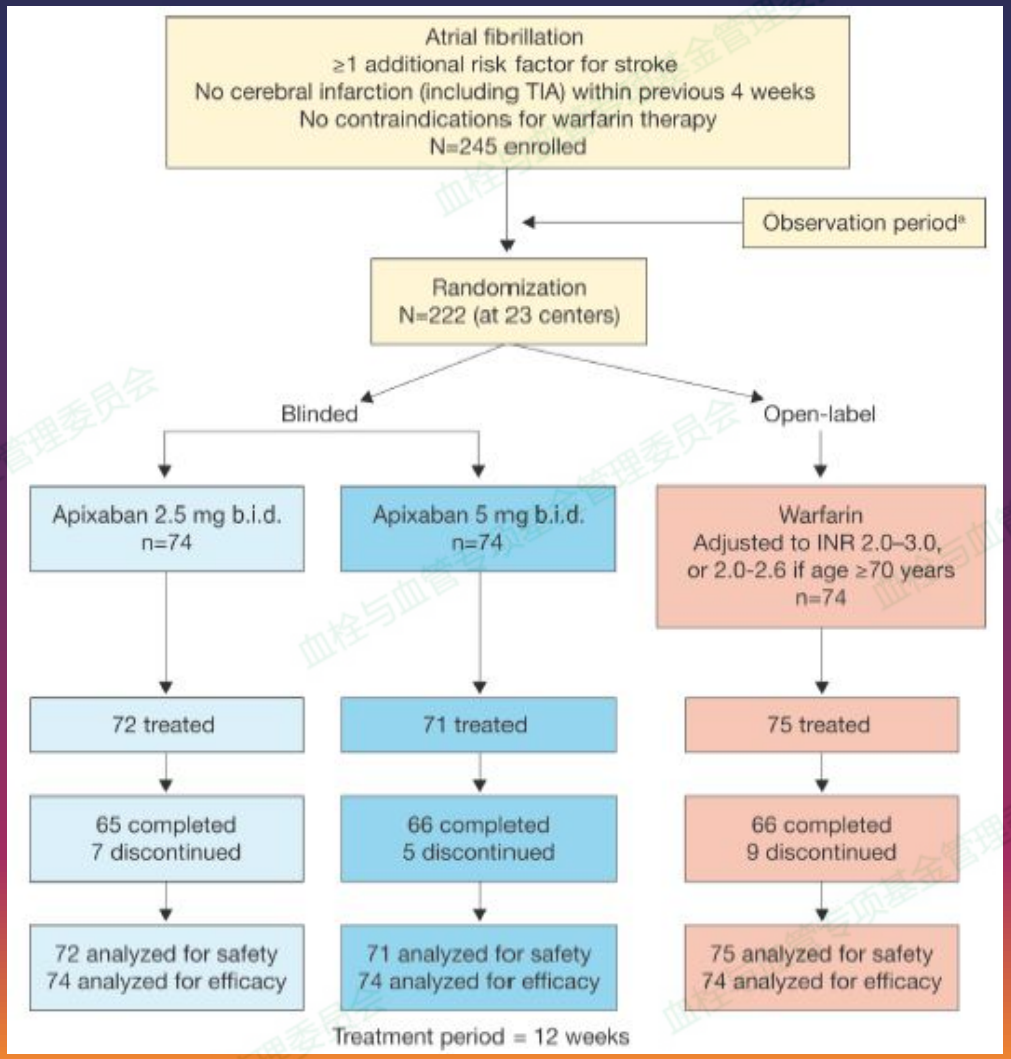
Dahl OE. Vascular Health and Risk Management 2012:8 45–57

达比加群与华法令颅内出血比较



Dahl OE. Vascular Health and Risk Management 2012:8 45–57

口服直接X因子抑制剂阿哌沙班的疗效和安全性



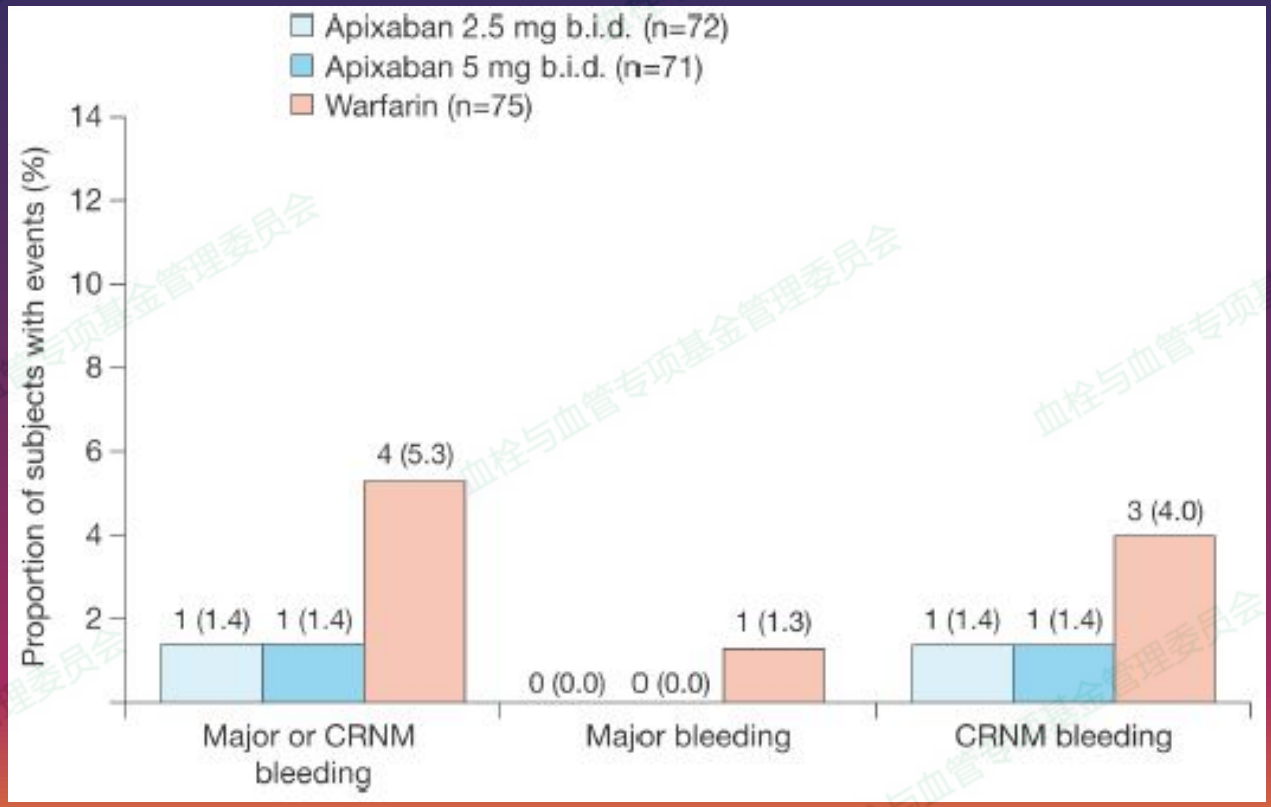
Ogawa S, et al. Circulation Journal doi: 10.1253/circj.CJ-10-1183

口服直接X因子抑制剂阿哌沙班的疗效和安全性

- 阿哌沙班组未发生中风、系统性栓塞、心肌梗塞或所有死因
- 华法令组3例(4.1%)患者发生中风，1例出现蛛网膜下腔出血
- 尽管INR控制良好，华法令组有2例缺血性卒中、无心肌梗塞或所有死因

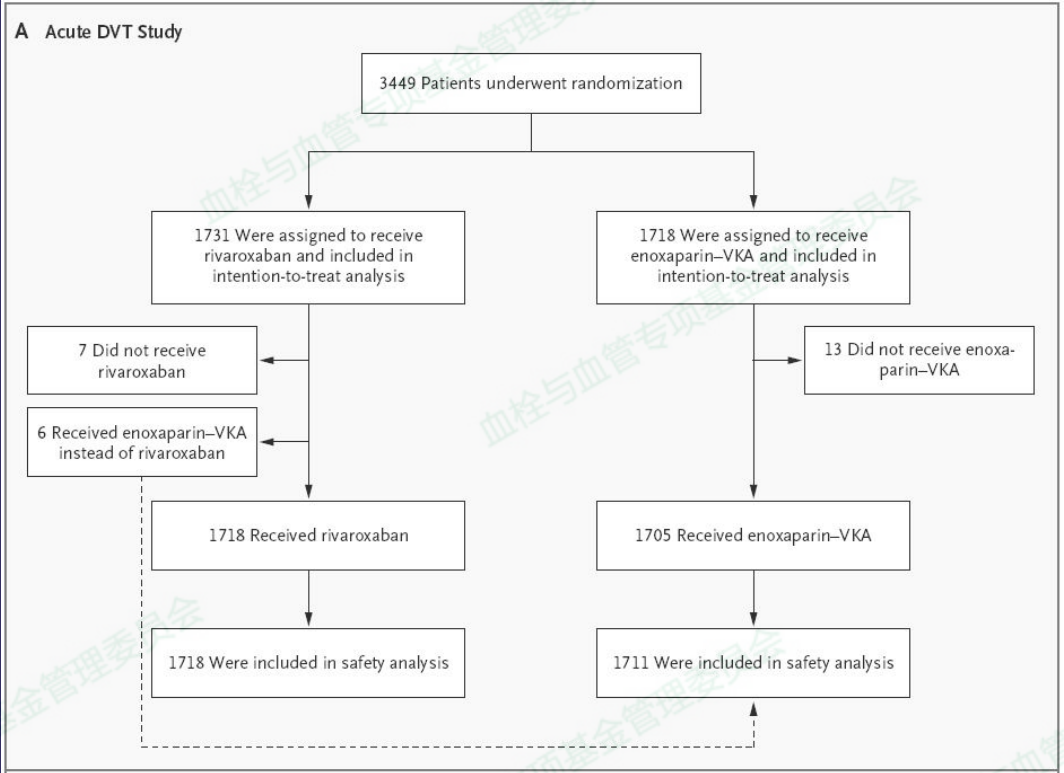
Ogawa S, et al. Circulation Journal doi: 10.1253/circj.CJ-10-1183

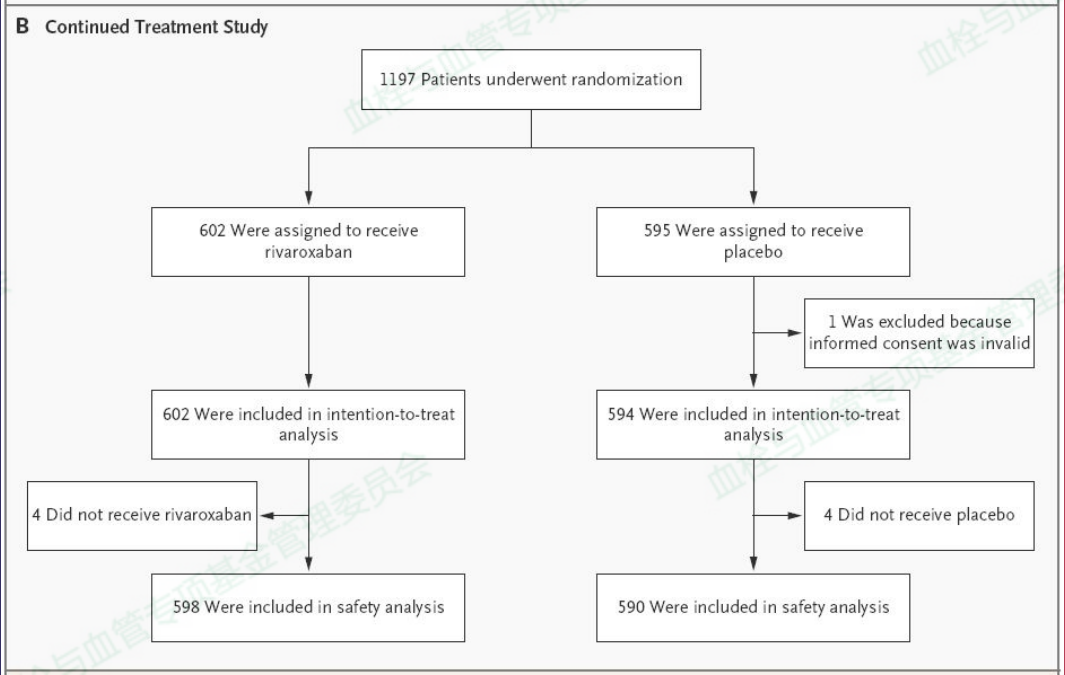
口服直接X因子抑制剂阿哌沙班的疗效和安全性



Ogawa S, et al. Circulation Journal doi: 10.1253/circj.CJ-10-1183

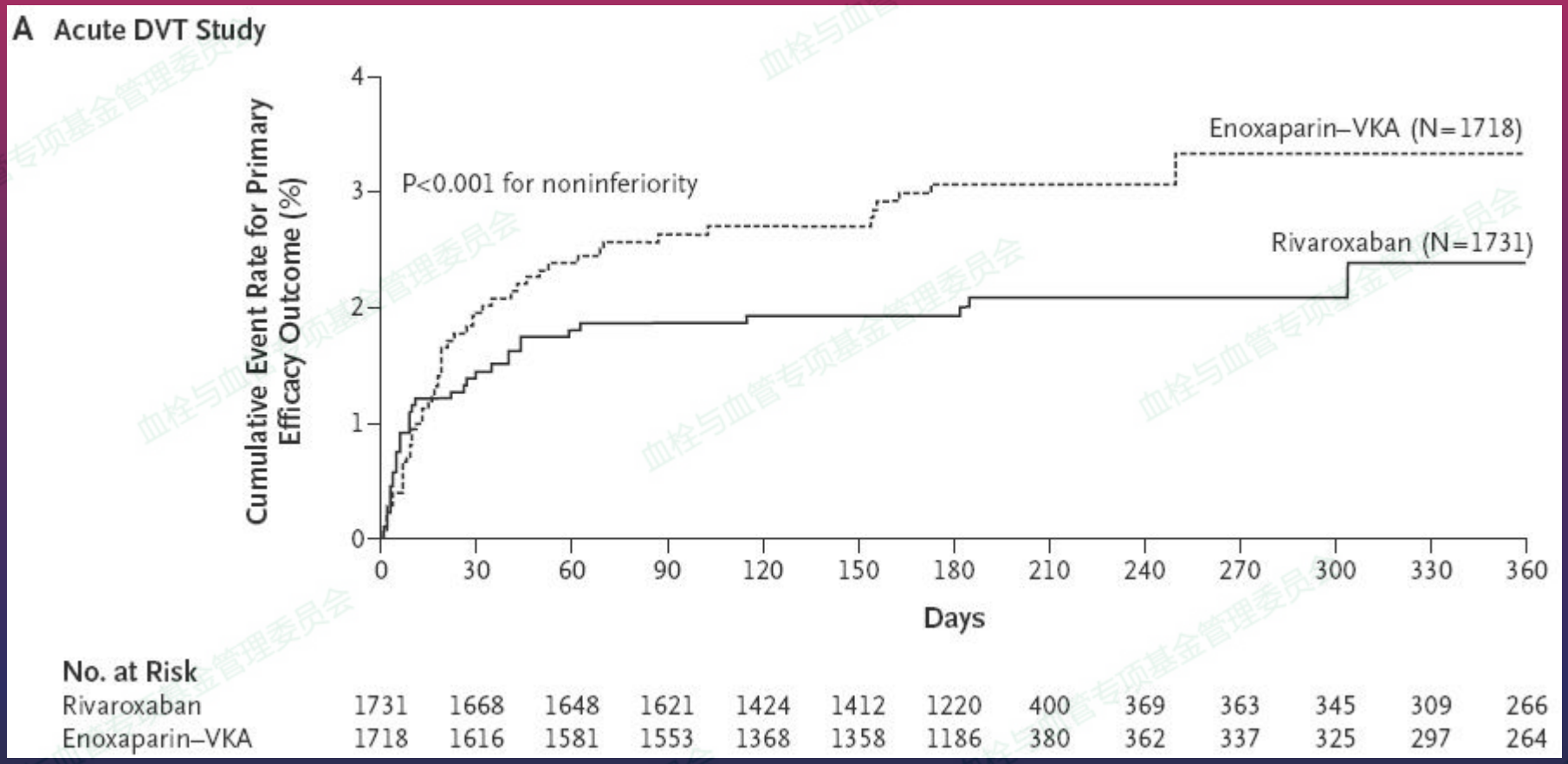
N Engl J Med 2010;363:2499-2510





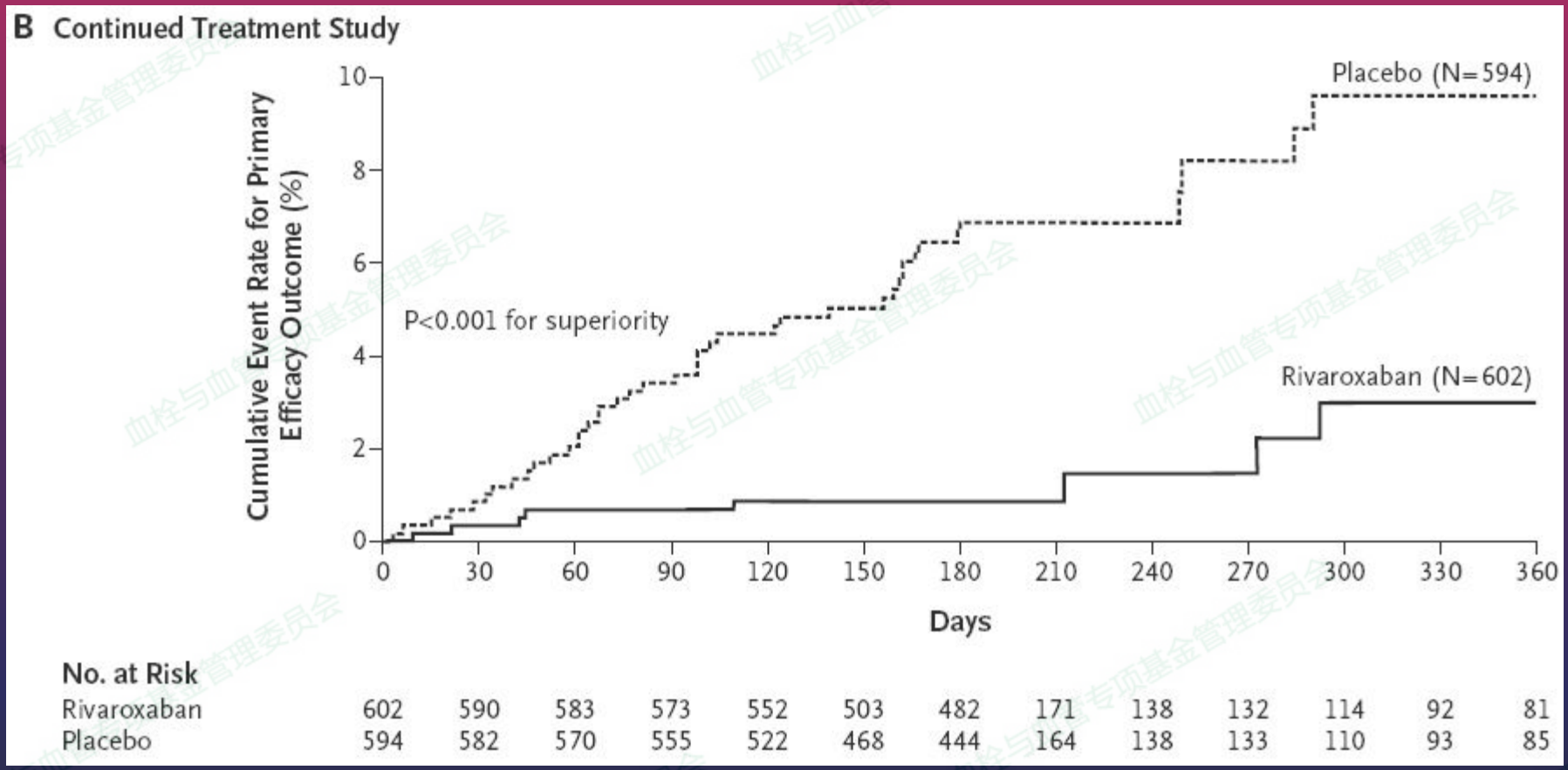
EINSTEIN研究

EINSTEIN研究



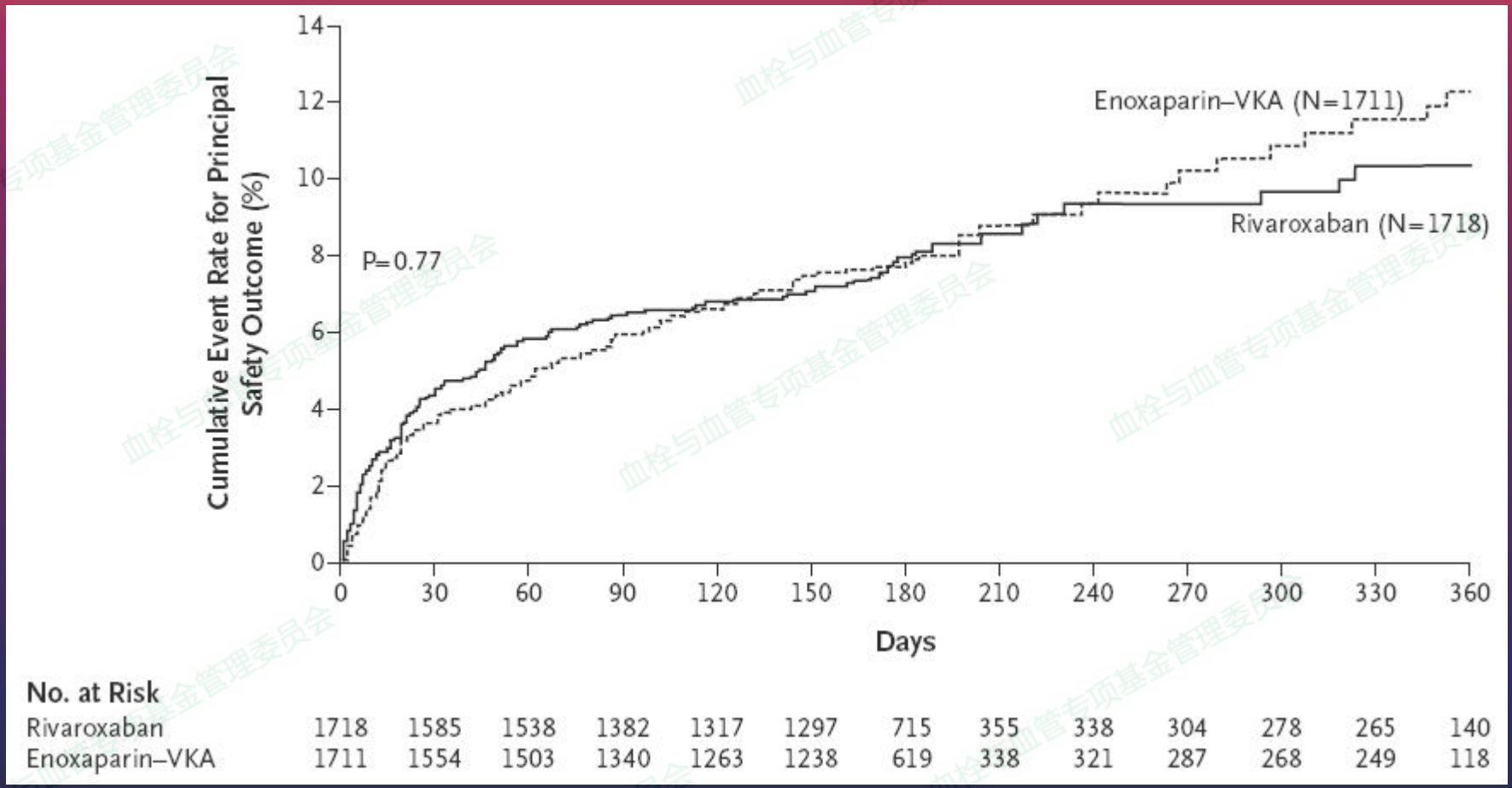
N Engl J Med 2010;363:2499-2510

EINSTEIN研究



N Engl J Med 2010;363:2499-2510

安全性评价



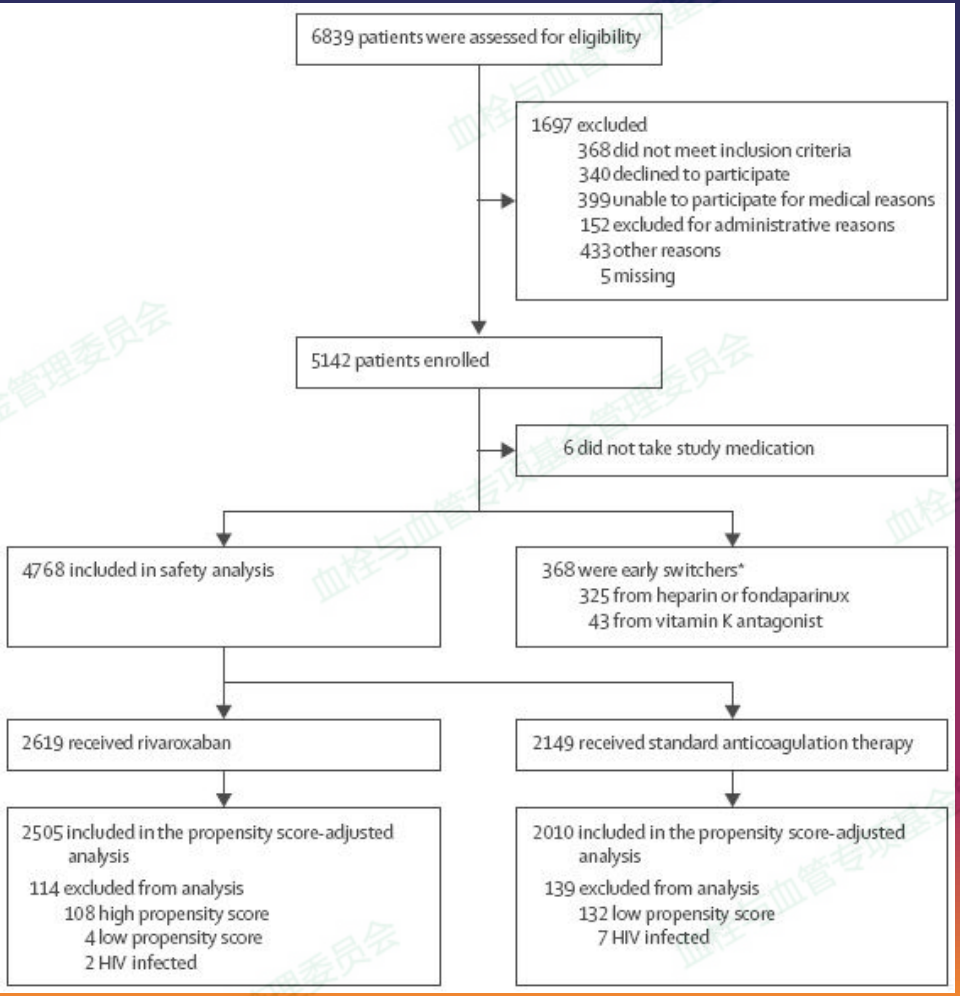
N Engl J Med 2010;363:2499-2510

安全性评价

Outcome	Rivaroxaban	Placebo	Hazard Ratio (95% CI)	P Value
	no. (%)			
Efficacy				
Intention-to-treat population	602	594		
Recurrent VTE	8 (1.3)	42 (7.1)†	0.18 (0.09–0.39)	<0.001
Type of recurrent VTE				
Fatal PE	0	1		
PE cannot be ruled out	1	0		
Nonfatal PE	2	13		
Recurrent DVT	5	31		
Safety				
Safety population	598	590		
First major or clinically relevant nonmajor bleeding	36 (6.0)	7 (1.2)	5.19 (2.3–11.7)	<0.001
Major bleeding†	4 (0.7)‡	0	NA	0.11

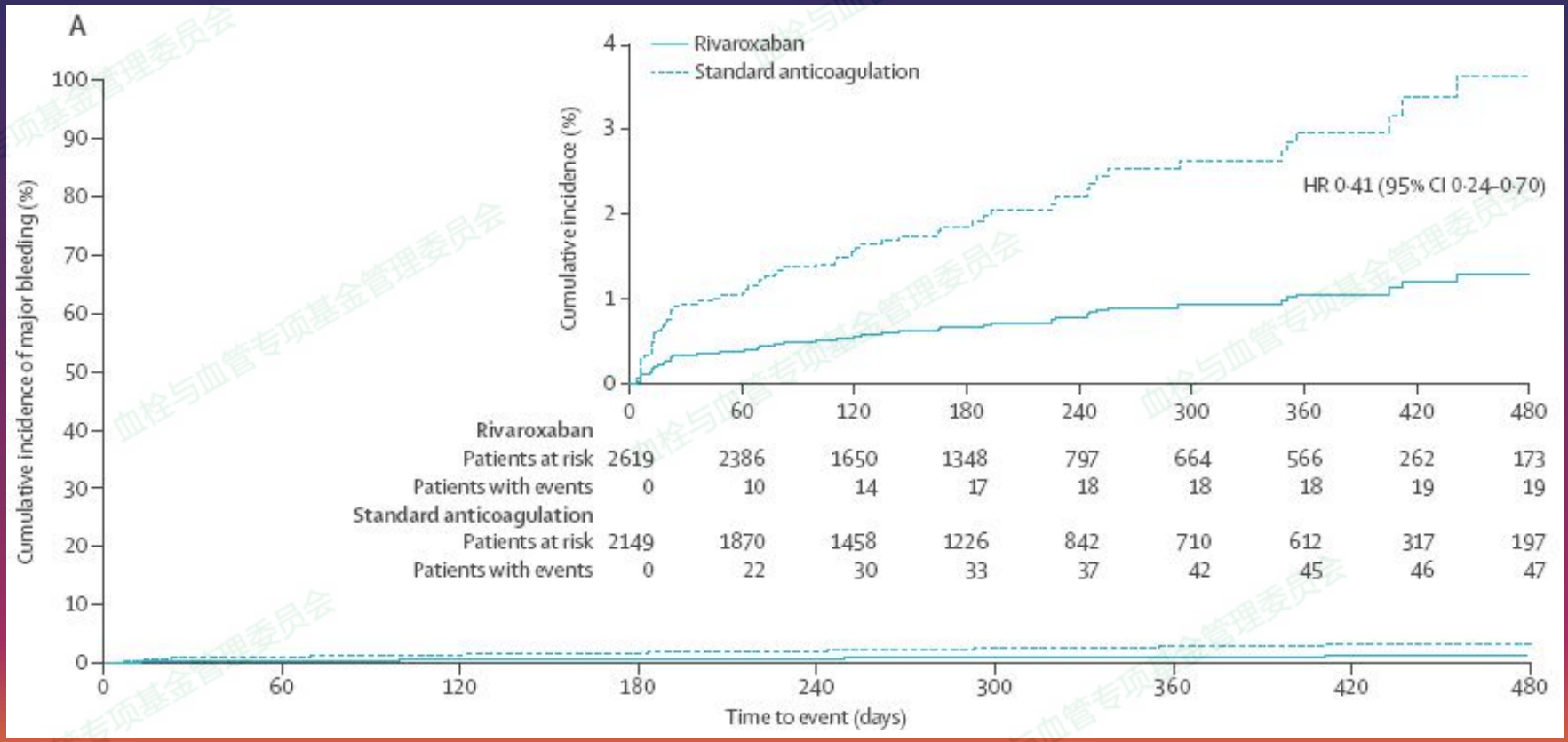
N Engl J Med 2010;363:2499-2510

XALIA研究设计



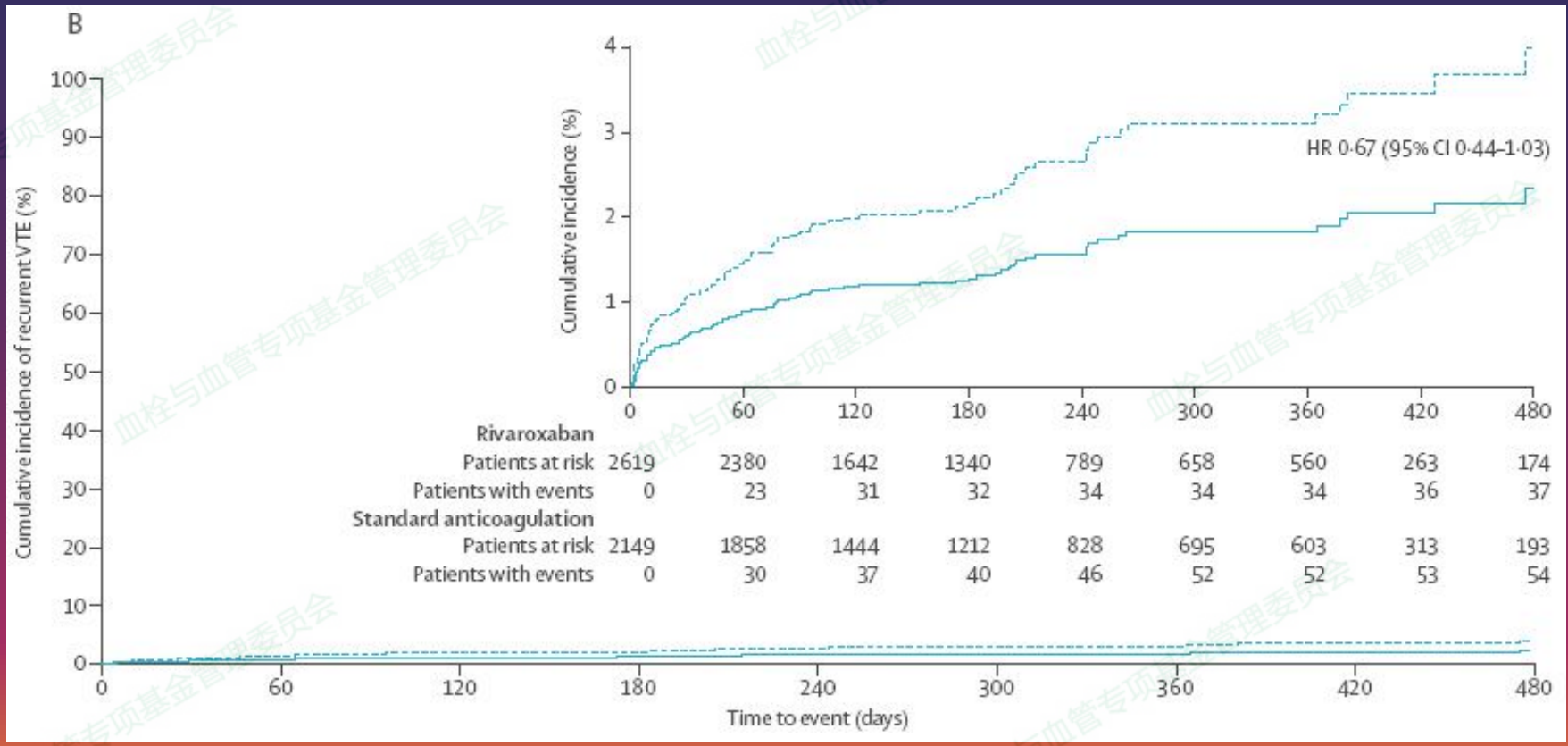
Ageno W, et al. Lancet Haematol 2016; 3: e12–21

累计大出血的发生率



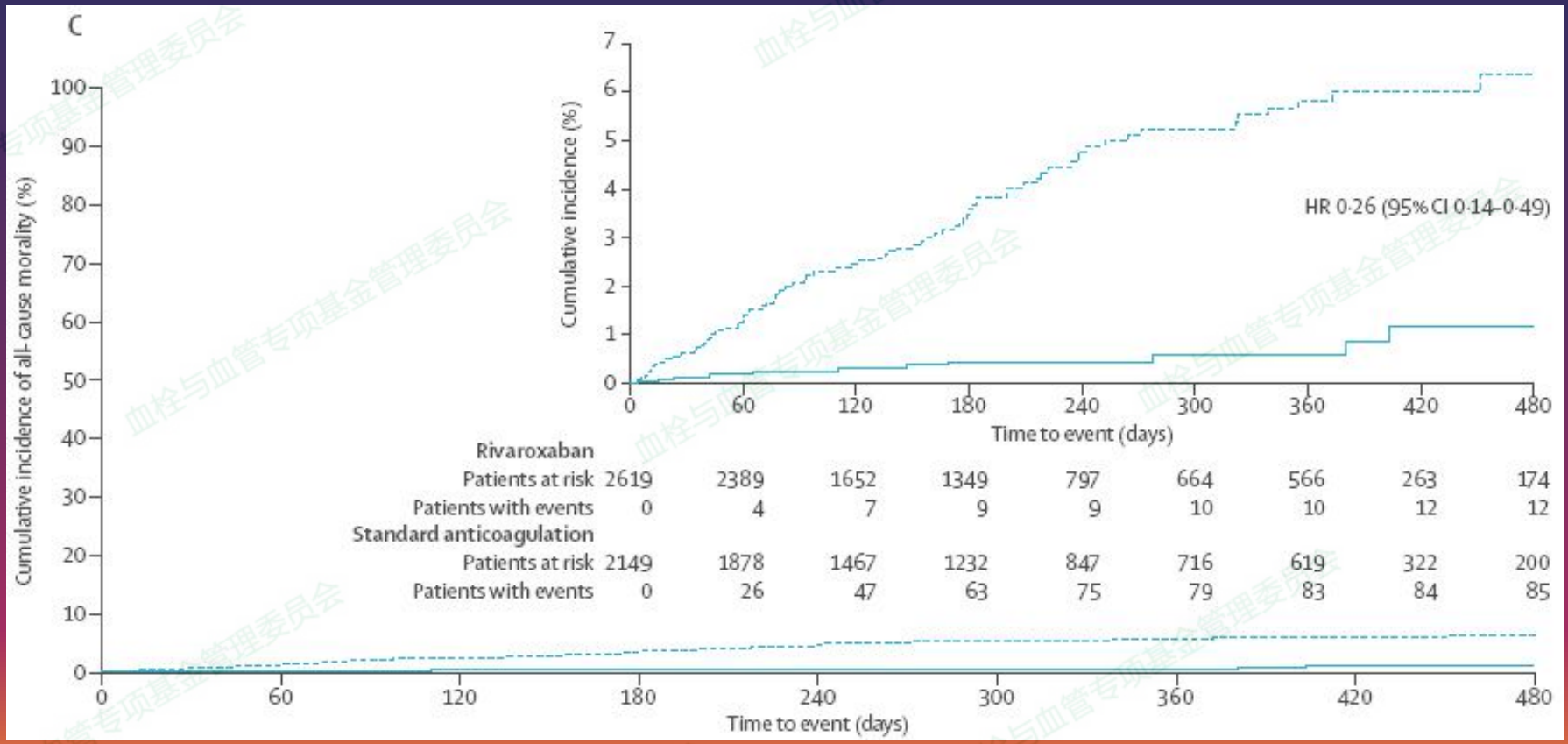
Ageno W, et al. Lancet Haematol 2016; 3: e12–21

累计VTE复发率



Ageno W, et al. Lancet Haematol 2016; 3: e12–21

累计全因病死率



Ageno W, et al. Lancet Haematol 2016; 3: e12–21

影响抗凝药物选择的因素

Factor	Preferred anticoagulant	Qualifying remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised due to liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 ml/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of gastrointestinal bleeding	VKA, apixaban,	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban and edoxaban may be associated with more gastrointestinal bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	Unfractionated heparin infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, unfractionated heparin	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

抗凝治疗的总体原则

- 近端DVT 或肺栓塞患者，推荐3个月的长疗程抗凝治疗。 (Grade 1B)
- 非癌症的下肢DVT 或肺栓塞 ，当使用3个月长疗程抗凝治疗时，建议给予达比加群、利伐沙班、阿哌沙班、艾多沙班，而不是华法林。 (Grade 2B)
- 如果不用上述药物，建议给予华法林，而不是低分子肝素。 (Grade 2C)

ACCP10，2016

癌症VTE患者抗凝药物种类的选择

- 癌症的下肢DVT 或肺栓塞 患者，进行头3个月长疗程抗凝治疗时，推荐低分子肝素，而不是华法林、达比加群、利伐沙班、阿哌沙班、艾多沙班。 (Grade 2C)
- 3个月后进行延长治疗时，不建议更换抗凝药。 (Grade 2C)

ACCP10，2016

抗凝治疗中反复出现VTE的处理原则

- 华法林、达比加群、利伐沙班、阿哌沙班、艾多沙班治疗患者反复发生VTE，若依从性良好，推荐至少暂时改为低分子肝素治疗。 (Grade 2C)
- 长期使用低分子肝素、且反复发生VTE的患者，若依从性良好，建议增加1/4至1/3剂量。 (Grade 2C)

ACCP10，2016

新型口服抗凝药的缺陷

- 大出血或急诊手术时缺乏逆转的特异性拮抗剂
- 正在开发的达比加群和口服Xa 因子特异性拮抗剂尚未获批临床应用。
- aDabi-Fab 是人的抗体片段，可特异性结合达比加群，逆转抗凝作用。
- r-拮抗剂 (PRT064445) 可催化灭活重组蛋白，对阿哌沙班、利伐沙班和低分子肝素激活的抗凝血酶III均有作用。

Gallego P, et al. Am J Respir Crit Care Med 2013, 188(4): 413–421

抗凝药所致出血的处置

Table 5
Suggested recommendations for reversal of major bleeding on newer anticoagulants

Anticoagulant	Reversal Agent	Dose/Timing	Laboratory Monitoring of Reversal	Special Considerations
LMWH • Enoxaparin • Dalteparin • Tinzaparin	(1) Protamine (2) rVIIa for life-threatening bleeding	(1) 1 mg protamine IV for each 1 mg of enoxaparin or 100 U of dalteparin tinzaparin given over prior 8 h. (2) rVIIa 50–90 μg/kg IV.	Anti-Xa activity	Only partially reversed by protamine and may require repeated doses given half-life of LMWHs. Protamine dose should be maintained <100 mg and administered slowly (≤5 mg/min).
Factor Xa inhibitor • Fondaparinux • Rivaroxaban • Apixaban	(1) rVIIa	(1) No effective antidote. Poor quality evidence supports use of rVIIa in the case of truly life-threatening bleeding at a dose of 90 μg/kg IV.	Anti-Xa activity	Immediate effect. Duration of effect 2–6 h. Rivaroxaban: can use 50 U/kg IV PCC-based on 1 RCT in healthy subjects.[98]
Parenteral direct thrombin inhibitors • Argatroban • Lepirudin • Bivalirudin • Desirudin	(1) DDAVP (2) Cryoprecipitate (3) Antifibrinolytics	(1) DDAVP: .3 μg/kg. (2) ≥10 U cryoppt. (3) ε-aminocaproic acid (Amicar) .1–.15 g/kg IV over 30 min then infusion .5–1 g/h OR TXA 10 mg/kg IV q 6–8 h.		DDAVP can be repeated q 8–12 h. Can develop tachyphylaxis, hyponatremia, and seizures. No more than two doses should be administered.
Oral direct thrombin inhibitor • Dabigatran	(1) Oral charcoal (2) rVIIa (3) PCC	(1) Given within 2 h of last dose. (2) rVIIa 60–90 μg/kg IV. (3) PCC 25–100 U/kg IV depending on product used.	aPTT, TT/TCT	Consider HD especially if renal impairment.

Rajasekhar A, et al. Crit Care Clin 28 (2012) 427–451

临床使用新型口服抗凝药的禁忌证与注意事项

- 以下情况下不能使用新型口服抗凝药

  机械性心脏瓣膜、瓣膜性房颤、妊娠/哺乳、

  活动性出血、严重肾衰竭、肝功能障碍的凝血病
- 若具备以下合并症出血风险增加

  肝肾功能均受损、血小板减少症、酗酒
- 依从性差的患者避免给药
- 用药前应常规检查血红蛋白、血小板、转氨酶、胆红素、肌酐、**INR**

临床使用新型口服抗凝药的注意事项

- 药物相互作用
- 使用抑制或诱导P-gp或CYP3A4的患者避免使用新型口服抗凝药
- 抑制剂导致出血风险增加：胺碘酮、维拉帕米、奎尼丁、酮康唑、氟立康唑、克拉霉素/红霉素、抗HIV药物
- 诱导剂可降低疗效：利福平、卡马西平、苯妥英
- 除非有指征，不能与抗血小板、非甾体类抗炎药、其他抗凝药联合应用

从肠外给药改为口服抗凝药的方法

	To warfarin	To dabigatran or edoxaban	To rivaroxaban or apixaban
Initial parenteral therapy	Required	Required	Not required
From heparin	Start warfarin and heparin concurrently	Start heparin alone	Stop heparin
	Continue heparin for a minimum of 5 days AND until INR > 2.0	After a minimum of 5 days of heparin, start dabigatran or edoxaban and stop heparin	Give first dose of rivaroxaban or apixaban
From LMWH or fondaparinux	Start warfarin and LMWH/fondaparinux concurrently	Start LMWH/fondaparinux alone After a minimum of 5 days, stop LMWH/fondaparinux	Stop LMWH/fondaparinux
	Continue LMWH/fondaparinux for a minimum of 5 days AND until INR > 2.0	Give first dose of dabigatran or edoxaban at the time the next dose of LMWH/fondaparinux would have been given	Give first dose of rivaroxaban or apixaban at the time the next dose of LMWH/fondaparinux would have been given

Smythe MA, et al. J Thromb Thrombolysis (2016) 41:165–186

直接口服抗凝药向华法令过渡

DOAC to warfarin	
Dabigatran[a]	Start warfarin & overlap with dabigatran; CrCl ≥ 50 mL/min, overlap 3 days CrCl 30-50 mL/min, overlap 2 days CrCl 15-30 mL/min, overlap 1 day
Rivaroxaban[a] Apixaban[a]	Stop DOAC; start warfarin & LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0
Edoxaban[a]	For 60 mg dose reduce dose to 30 mg & start warfarin concomitantly. For 30 mg dose reduce dose to 15 mg and start warfarin concomitantly. Stop edoxaban when INR ≥ 2.0

D. M. Witt et al. J Thromb Thrombolysis (2016) 41:187–205

肝素类和华法令向直接口服抗凝药过渡

Warfarin to DOAC	
Dabigatran[a]	Start when INR < 2.0
Rivaroxaban[a]	Start when INR < 3.0
Apixaban[a]	Start when INR < 2.0
Edoxaban[a]	Start when INR ≤ 2.5
LMWH to DOAC	
Dabigatran	Start DOAC within 0–2 h of the time of next scheduled dose of LMWH
Rivaroxaban	
Apixaban	
Edoxaban	
(iv) UFH to DOAC	
Dabigatran[a]	Start DOAC immediately after stopping iv UFH
Rivaroxaban[a]	
Apixaban[a]	
Edoxaban[a]	Start Edoxaban 4 h after stopping iv UFH

D. M. Witt et al. J Thromb Thrombolysis (2016) 41:187–205

小结

- VTE是临床常见疾病，且为易复发疾病
- 抗凝治疗是VTE的主要治疗方法
- 治疗获益和出血风险是临床需要平衡的问题
- 选择恰当的抗凝药物可能改变临床结局
- 新型抗凝药物的应用将越来越广泛

谢谢