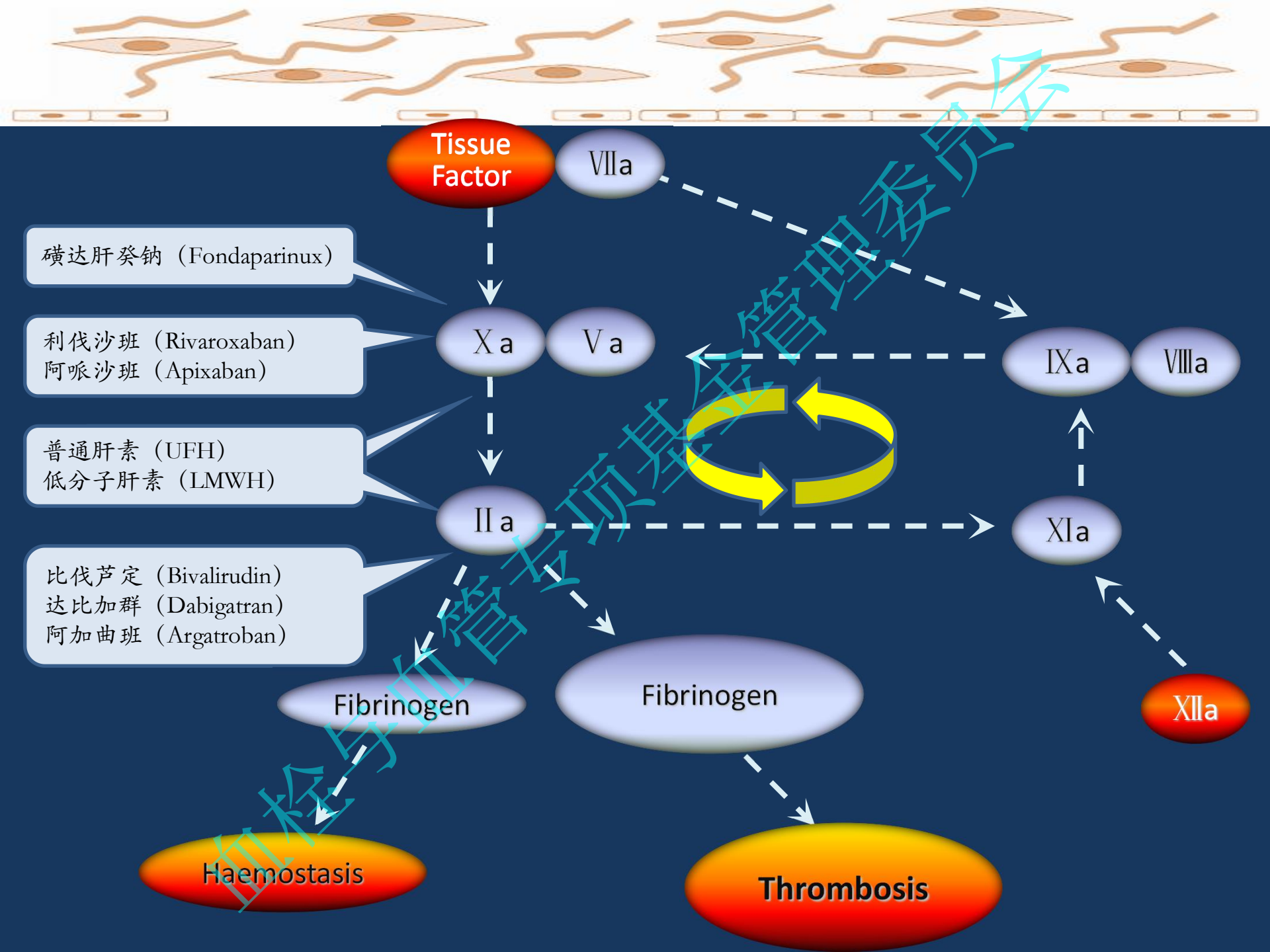
新型口服抗凝药物：如何监测

天津医科大学总医院 门剑龙


Tissue Factor
VIIa
磺达肝癸钠（Fondaparinux）
利伐沙班（Rivaroxaban）
阿哌沙班（Apixaban）
普通肝素（UFH）
低分子肝素（LMWH）
比伐芦定（Bivalirudin）
达比加群（Dabigatran）
阿加曲班（Argatroban）
Xa
Va
IIa
IXa
VIIIa
XIa
XIIa
Fibrinogen
Fibrinogen
Haemostasis
Thrombosis
血栓与血管专项基金管理委员会

中文名称	达比加群	利伐沙班	阿哌沙班	依度沙班
英文名称	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
药物类型	前体药物	直接起效	直接起效	直接起效
生物利用度	6.5%	10mg：80%-100% 20mg：66%	50%	62%
达峰时间	1.5-2 h	2-4 h	3-4 h	1-2 h
半衰期	12-14 h	5-9 h，老人11-13 h	8-15 h	9-10 h
血浆蛋白质结合	35%	92%-95%	87%	40%-89%
肾脏清除	80%	33%	25%	35%-39%
药物相互干扰	P-gp增强剂	P-gp增强剂	P-gp增强剂	P-gp增强剂
		P-gp抑制剂	P-gp抑制剂	P-gp抑制剂
	P-gp抑制剂	CYP3A4增强剂	CYP3A4增强剂	CYP3A4增强剂
		CYP3A4抑制剂	CYP3A4抑制剂	CYP3A4抑制剂
食物干扰	导致吸收延迟	无	无数据	无

[1] Sam Schulman. New oral anticoagulant agents – general features and outcomes in subsets of patients. 2014
[2] Bayer Inc. Product Monograph:PrXarelto. http://omr.bayer.ca/omr/online/xareto-pm-en.pdf.Accessed October 12,2015.

利伐沙班与药物和食物相互作用少

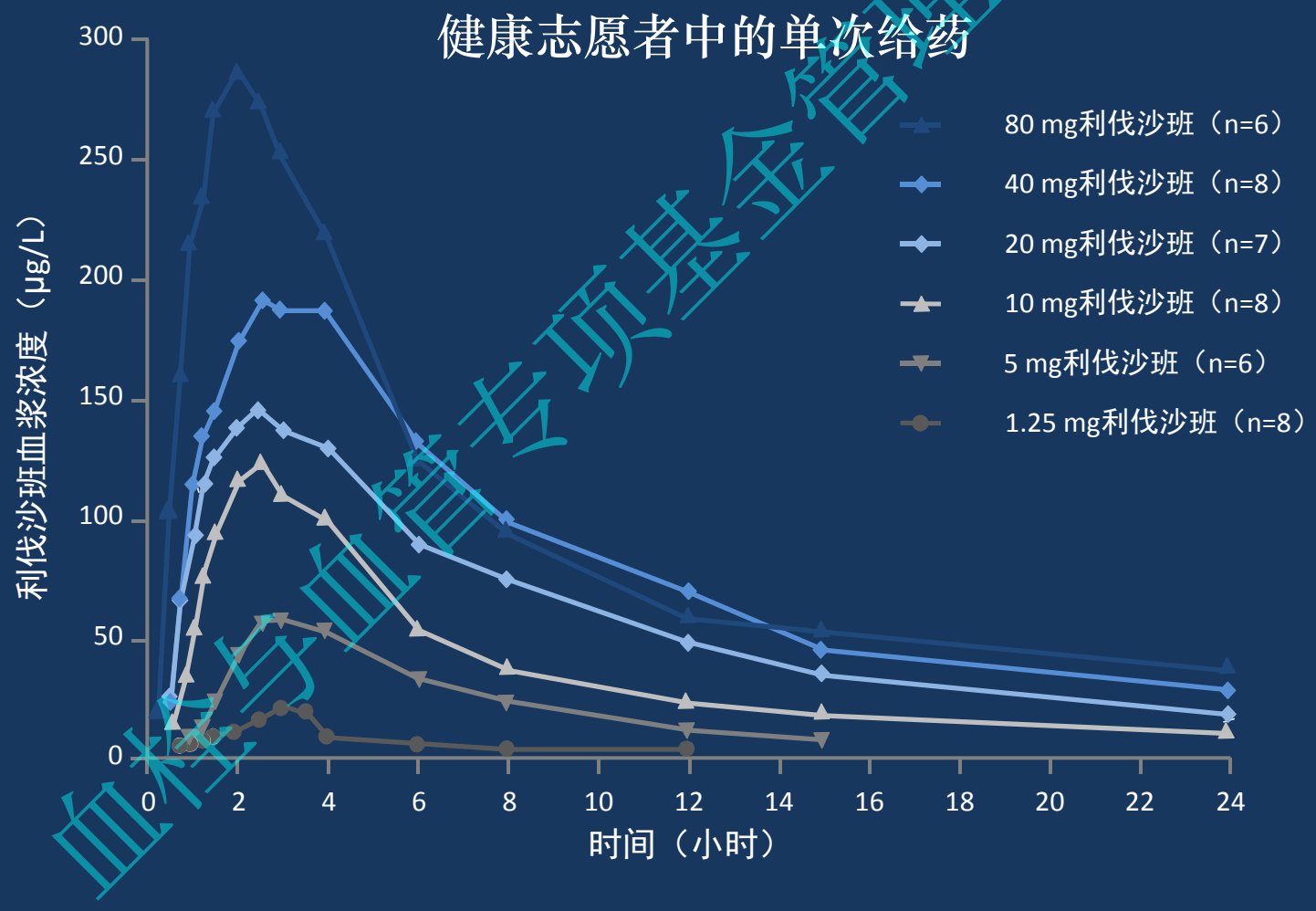
药　物		CYP3A4	P-gp	临床影响
抗真菌药 抗HIV药	如：吡咯抗真菌药 HIV蛋白酶抑制剂	强效抑制剂	强效抑制剂	全身用药升高利伐沙班的血药浓度，不推荐合用
抗癫痫药	如：利福平、苯妥英、 卡马西平、苯巴比妥	强效诱导剂		降低利伐沙班的血药浓度，除非对血栓形成的体征和症状进行密切观察，否则避免合用
抗心律失常药	如：胺碘酮		强效抑制剂	对利伐沙班无显著影响，可合用
抗生素	如：克拉霉素	强效抑制剂	中度抑制剂	对利伐沙班无显著影响，可合用
抗生素	如：红霉素	中度抑制剂	中度抑制剂	对利伐沙班无显著影响，可合用
抗真菌药	如：氟康唑	中度抑制剂		对利伐沙班无显著影响，可合用
抗失眠药	如：米达唑仑	底物		对利伐沙班无显著影响，可合用
抗心衰药物	如：地高辛		底物	对利伐沙班无显著影响，可合用
降脂药	如：阿托伐他汀	底物	底物	对利伐沙班无显著影响，可合用

CYP3A4：细胞色素酶3A4；P-gp：P糖蛋白

利伐沙班药物说明书

利伐沙班药代动力学可预测

（利伐沙班血药浓度呈剂量依赖性）



Kubitza D et al. Clin Pharmacol Ther 2005;78:412–21

轻度肝肾功能损害对PK/PD无显著影响

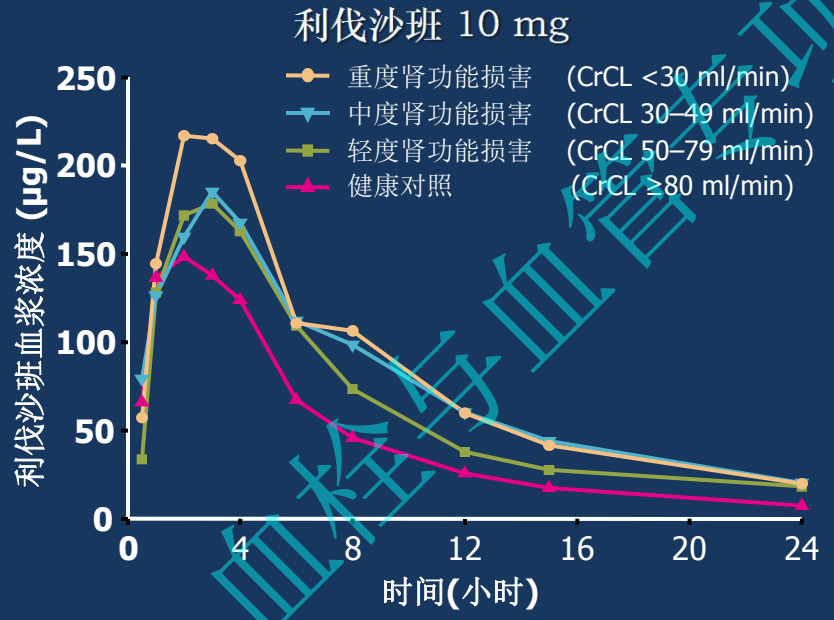
轻度肾功能损害，肝功能损害(Child Pugh A级)的肝硬化：无需调整剂量。

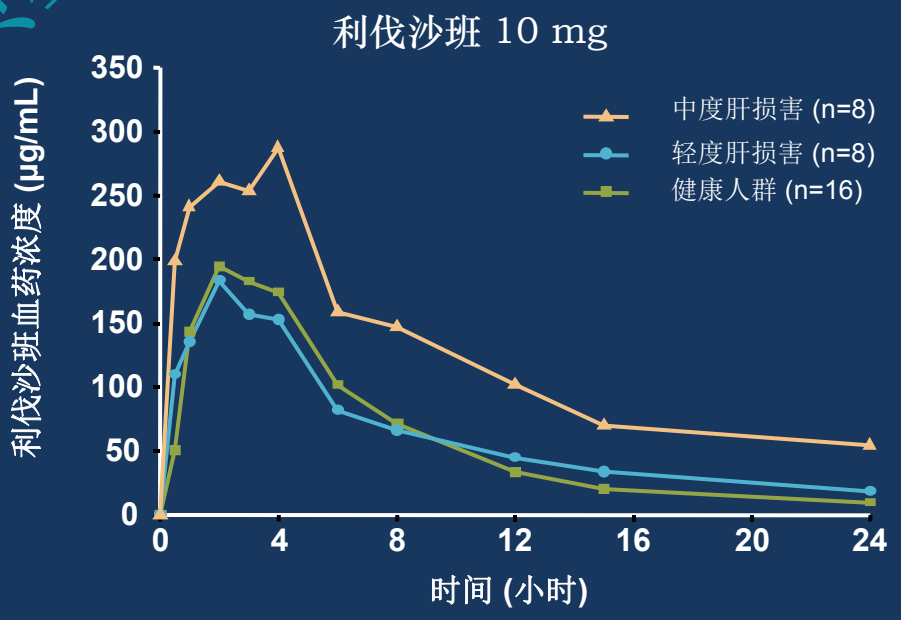
重度肾损害(CrCL:15~29mL/min)：慎用。

CrCL<15mL/min：建议不使用。

中度肝损害(Child Pugh B级)肝硬化：不伴有凝血异常（止凝血平衡），慎用。

伴有凝血异常（止凝血失衡）、临床相关出血风险的肝病：禁用。

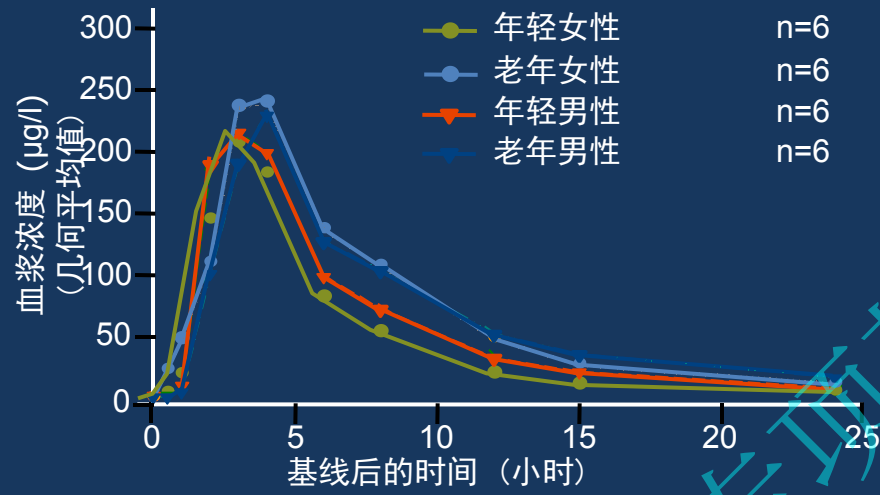


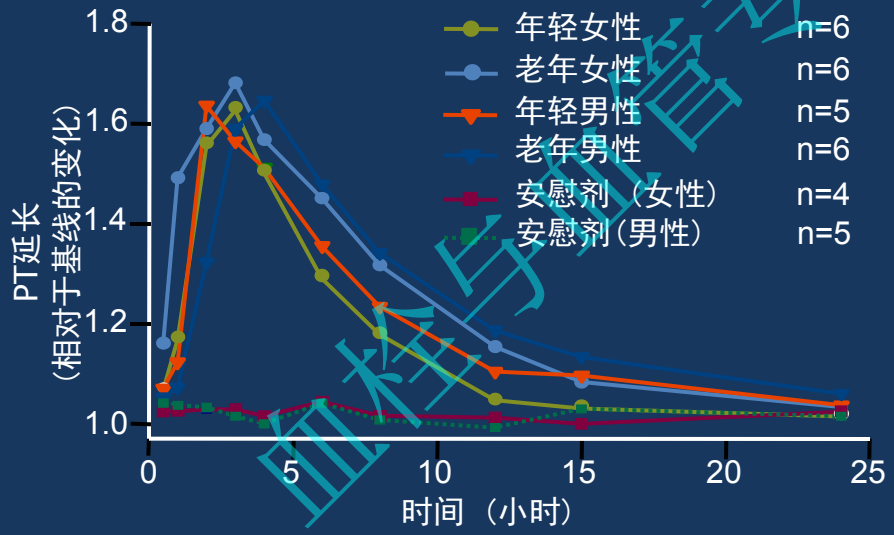


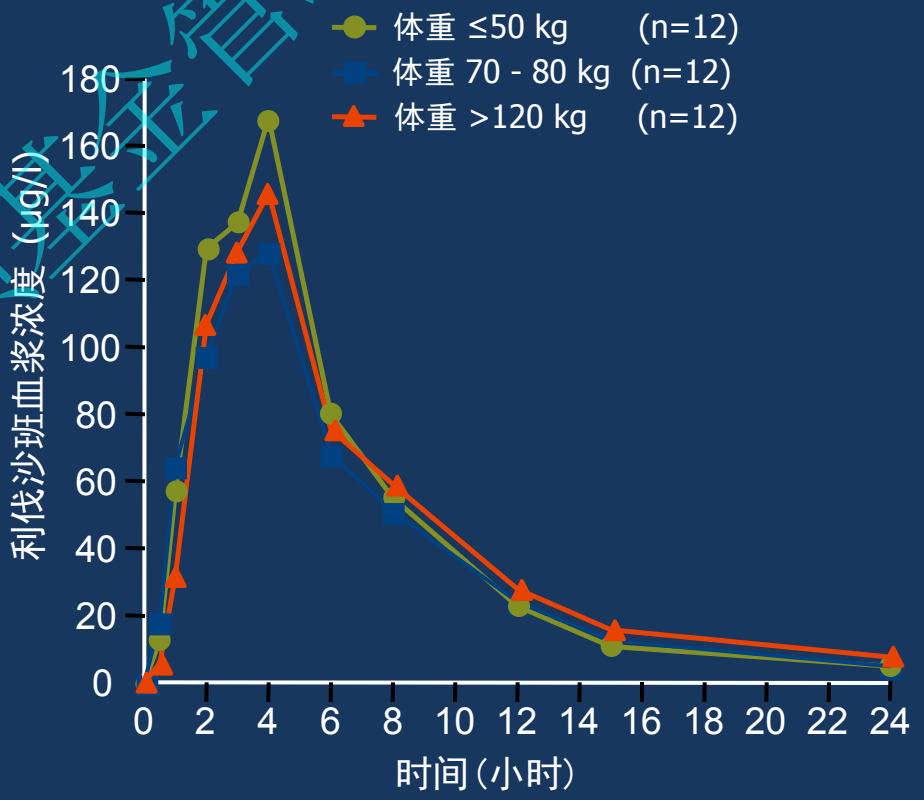
Halabi A et al. Blood 2006;108(11):Abstract 913; Kubitza et al. Br J Clin Pharmacol. 2010; 70 (5):703-712. Halabi A et al. J Thromb Haemost 2007;5(Suppl. 2):P-M-635.

年龄、性别、体重对利伐沙班PK/PD无显著影响

健康人群中使用利伐沙班10 mg







Data from Kubitza D, et al. *J Clin Pharmacol.* 2007;47:218-226.

中国人群的药理学特性与全球结果一致

	利伐沙班10mg单剂量	
	中国受试者(n=8)	白种人受试者(n=8)
BMI (kg/m^{-2})	20.9	24.9
时间内药时曲线下面积($\mu g\ h^{-1}I^{-1}$)	1022	1020
峰浓度($\mu g\ I^{-1}$)	143.2	141
达峰时间(h)	2.25	2.00
半衰期(h)	7.57	9.07
表观清除率($l\ h^{-1}$)	9.78	9.8
表观分布容积($l\ kg^{-1}$)	1.84	1.49
较基线Xa因子活性抑制最大程度(%)	40	33
较基线凝血酶原时间延长倍数	1.4	1.3
较基线活化部分凝血活酶时间延长倍数	1.3	1.3

Zhao x,et al.Br J Clin Pharmacol. 2009 Jul;68(1):77-88

利伐沙班无需“常规”凝血监测

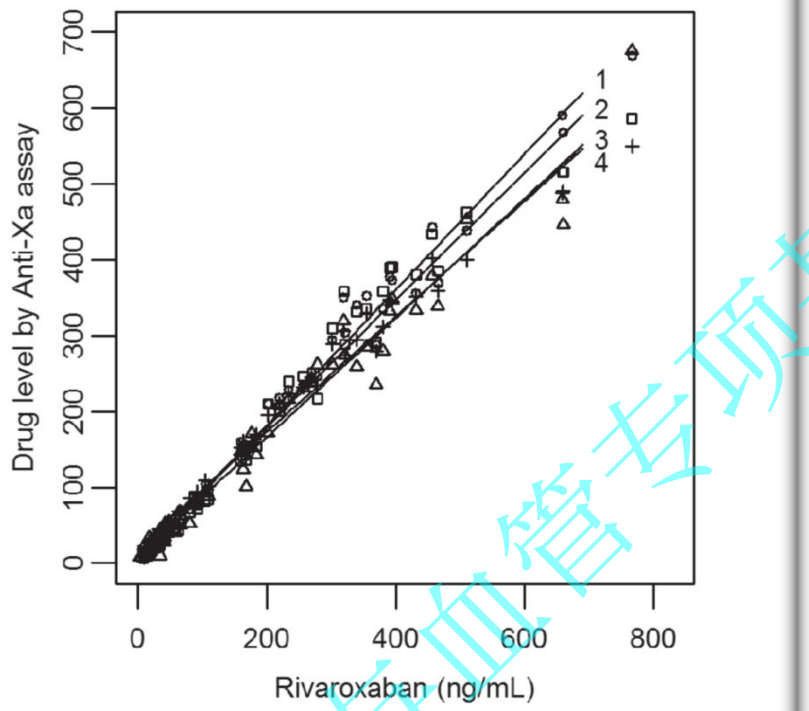
- 利伐沙班吸收迅速，药代动力学可预测
- 利伐沙班剂量依赖性延长凝血时间，药效学可预测
- 年龄、性别、体重对利伐沙班PK/PD无显著影响
- 轻度肝肾功能损害对PK/PD无显著影响
- 中国人群的药理学特性与全球结果一致
- III期研究证实利伐沙班疗效和安全性

需监测利伐沙班的特殊情况

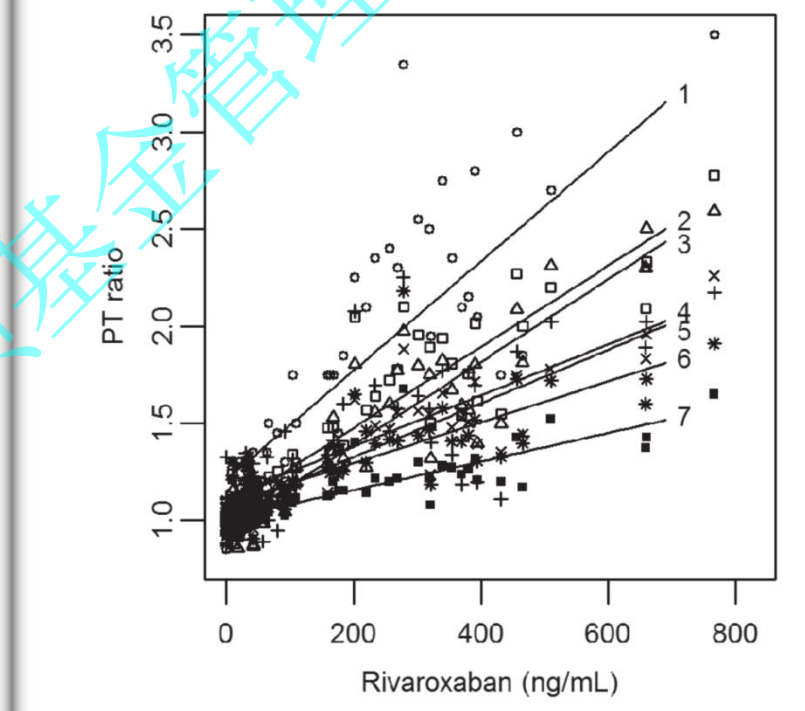
- 发生可能致命的大出血的病人
- 接受硬膜外间隙阻滞麻醉的病人
- 可能需要接受溶栓治疗的急性卒中病人
- 同时使用影响利伐沙班代谢药物的病人
- 胃肠道吸收营养不良的病人
- 体重过低或超重的病人
- 发生急性肾损害的病人
- 急诊外科手术病人
- 使用药物过量的人
- 治疗失败的病人

可监测利伐沙班的试验

抗F Xa活性（anti-Xa）



凝血酶原时间（PT）



Suzanne J. Francart; Emily M. Hawes1; Allison M. Deal, et al.Performance of coagulation tests in patients on therapeutic doses of rivaroxaban A cross-sectional pharmacodynamic study based on peak and trough plasma levels. 2014

可监测利伐沙班的试验

Prothrombin Time: We found 35 studies[24,40,45-48,51,52,56,58-63,66-68.70,73,75-77,79,80-87,90-92] evaluating the effect of rivaroxaban on PT (e-Table 2). Overall, rivaroxaban prolonged the PT in a concentration-dependent manner, but the correlation was generally weak[24,45,46,61-63,66.80,86,89] and became weaker with increasing concentrations (> 50-100 ng/mL).[63] Significant reagent-dependent differences in assay sensitivity were noted in multiple studies.[40,48,60-63,66,76,90]

利伐沙班可剂量依赖性地延长PT，但总体相关性较弱，低血药浓度时，PT敏感性差。

APTT: Seventeen studies[24,40,48,58,59,61,62,66,68,73,76,79,80,85,86,89,91] assessed the effect of rivaroxaban on APTT. A poor to moderate concentration-dependent prolongation of the APTT was noted.[48,61,62,68,73,76,80,81,85,89] APTT assay sensitivity was reagent dependent.[40,48,62,76,80,91] Variability within assays[40,80] and between laboratories (coefficient of variation, 14.3%-15.5%)[45,48,56] also reported.

Anti-Factor Xa Activity: Thirty studies[40,48,51,52,55-59,61-67,70-74,76,80,82,83,84,86,88,89,91] assessed the effect of rivaroxaban on anti-Xa activity (e-Table 2). Rivaroxaban-calibrated chromogenic anti-Xa activity assays showed linear, concentration-dependent correlations (r^2 = 0.95-1.00) over a wide range of rivaroxaban concentrations (0-755 ng/mL). The linear association between rivaroxaban and anti-Xa activity was marginally lower when assays were calibrated with unfractionated heparin (r^2 = 0.90-0.99) or low-molecular-weight heparin (r^2 = 0.92-0.98). Some assays showed variability at low and/or high concentrations[48,71,88] and reduced accuracy at upper and lower limits of quantitation.[63,71]

- 经校准的抗Xa因子活性试验（anti-Xa），与利伐沙班血药浓度有最佳的相关性。
- 血药浓度极低或极高时， anti-Xa则与利伐沙班血药浓度的相关性较弱。

Bethany T Samuelson… et al.Laboratory Assessment of the Anticoagulant Activity of Direct Oral Anticoagulants A Systematic Review.Chest, 2017，15(1)

anti-Xa监测利伐沙班和阿哌沙班

- anti-Xa试验对浓度>30 μg/L的利伐沙班可以准确定量。
- 经利伐沙班血浆校准后的anti-Xa试验，能准确反映治疗范围利伐沙班药物浓度变化，相关性强，敏感度优于PT。
- 阿哌沙班校准品校准后的anti-Xa试验，血药浓度检测范围和敏感度显著优于PT。

主试剂–定标–质控 组合				
主试剂	STA®-Liquid Anti-Xa Cat. Nr. 00311 (4 ml) / Cat. Nr. 00322 (8 ml)			
药物名称	普通肝素&低分子肝素	磺达肝素	利伐沙班	阿哌沙班
定标类型	普通肝素/低分子肝素专用定标 混合定标	专用定标	专用定标	专用定标
定标血浆	STA®-Multi-Hep Calibrator Cat. Nr. 00348	STA®-Fondaparinux Calibrator Cat. Nr. 00354	STA®-Rivaroxaban Calibrator Cat. Nr. 00704	STA®-Apixaban Calibrator Cat. Nr. 01075
质控品	STA®-Quality HNF/UFH Cat. Nr. 00381 STA®-Quality HBPM/LMWH Cat. Nr. 00686	STA®-Fondaparinux Control Cat. Nr. 00355	STA®-Rivaroxaban Control Cat. Nr. 00706	STA®-Apixaban Control Cat. Nr. 01074

STA-Liquid anti-Xa试剂说明书

PT监测利伐沙班

- 120μg/L和290μg/L的利伐沙班，可将PT延长至基线值的1.4和1.9倍。
- 120 μg/L的利伐沙班，即可使各类型PT检测系统的测定结果延长。
- 用PT（秒）监测利伐沙班。

——不同PT试剂对利伐沙班敏感性差异大。

（低敏感的PT试剂无法反映治疗剂量的利伐沙班。）

——可利用利伐沙班校准血浆建立PT检测。

——INR对高浓度利伐沙班的敏感性强，放大数据变异性。

Suzanne J. Francart et al. Performance of coagulation tests in patients on therapeutic doses of rivaroxaban A cross-sectional pharmacodynamic study based on peak and trough plasma levels. 2014, Throm Haemo.

Reagent	N	Instrument	N	120R	290R
Innovin	54	Sysmex CA-1500/7000	33	1.15 (1.3 %)	1.33 (2.0 %)
		Sysmex CS2100i	10	1.15 (1.2 %)	1.36 (1.4 %)
		Sysmex CA-540/560	6	1.15 (0.9 %)	1.33 (1.4 %)
Neoplastin CI Plus	55	STA Compact	29	1.36 (2.4 %)	1.86 (3.5 %)
		STA-R Evolution	22	1.37 (2.2 %)	1.88 (2.8 %)
Neoplastin R	20	STA-R Evolution	10	1.57 (2.0 %)	2.36 (2.3 %)
					2.27
R					
					(1.8 %)
				(1.1 %)	1.93 (1.0 %)
Thromborel S	13	Sysmex CA-1500/7000	6	1.16 (1.4 %)	1.41[1] (3.2 %)
		BCS, BCS XP	4	1.13 (1.4 %)	1.32[1] (2.8 %)

[1]p=0.04.

国产常规凝血设备
也逐步成为主流
标准和经验需积累

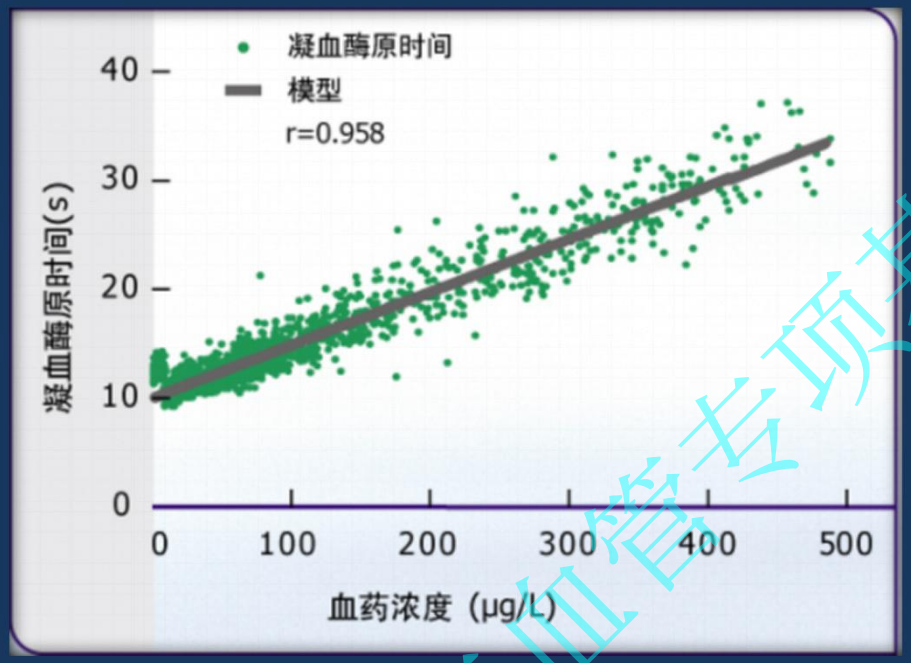
Reagent	N	PT ratio 120R	PT INR 120R	PT ratio 290R	PT INR 290R
Innovin	53	1.15 (1.5 %)	1.32 (2.8 %)	1.34 (2.8 %)	1.55 (4.8 %)
Neoplastin CI Plus	55	1.37 (2.3 %)	1.64 (4.5 %)	1.88 (3.3 %)	2.52 (5.3 %)
Neoplastin R	20	1.56 (3.5 %)	1.67 (4.5 %)	2.35 (4.2 %)	2.52 (2.5 %)
RecombiPlasTin 2G	45	1.37 (1.2 %)	1.43 (4.9 %)	1.95 (1.4 %)	2.00 (4.8 %)
Thromborel S	13	1.14 (1.6 %)	1.35 (3.3 %)	1.36 (3.5 %)	1.61 (3.7 %)
Global result	**189**	**1.35 (12.3 %)**	**1.45 (14.6 %)**	**1.87 (23.3 %)**	**2.03 (32.0 %)**

无论血药浓度高低
INR
都会放大抗凝效应

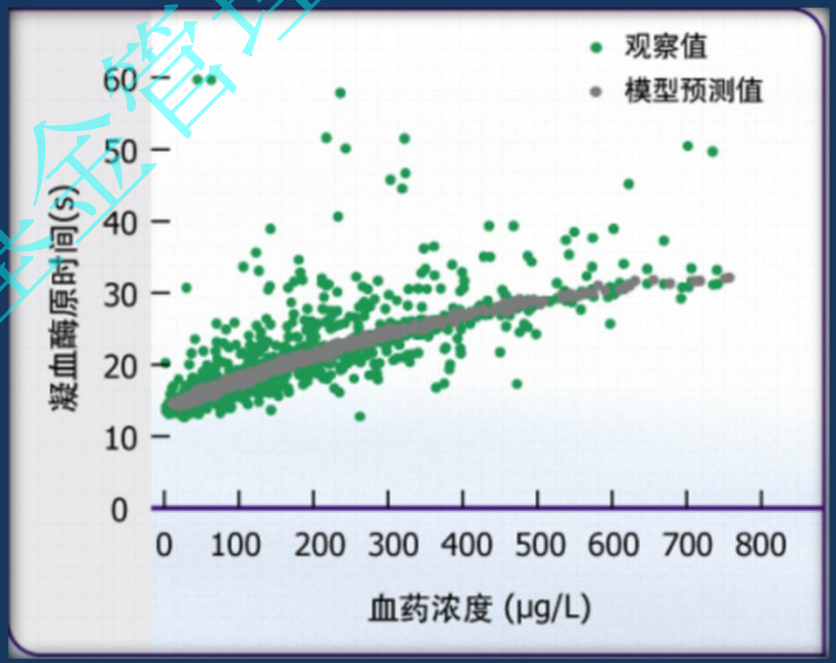
Marjan Van Blerk; Els Bailleul; Bernard Chatelain; Anne Demulder, et al. Influence of dabigatran and rivaroxaban on routine coagulation assays A nationwide Belgian survey. Thrombosis and Haemostasis 113.1/2015

利伐沙班对PT的影响呈剂量依赖性

健康受试者[1]



骨科大手术患者[2]



在健康人群和骨科大手术患者中，利伐沙班血药浓度与PT的关系是一致的。

1.Kubitza D,et al.Eur J Clin Pharmacol.2005;61:873-880. 2.Mueck W,et al.Clin Pharmacokinet.2008;47:203-216.

需要制定利伐沙班监测的规则

- 确认利伐沙班“末次给药时间”和“采样时间”。
- 临床医生需权衡手术的紧急性和出血风险。
- 根据手术类型决定手术时间（末次给药后24~48小时）。
- 发生出血事件：

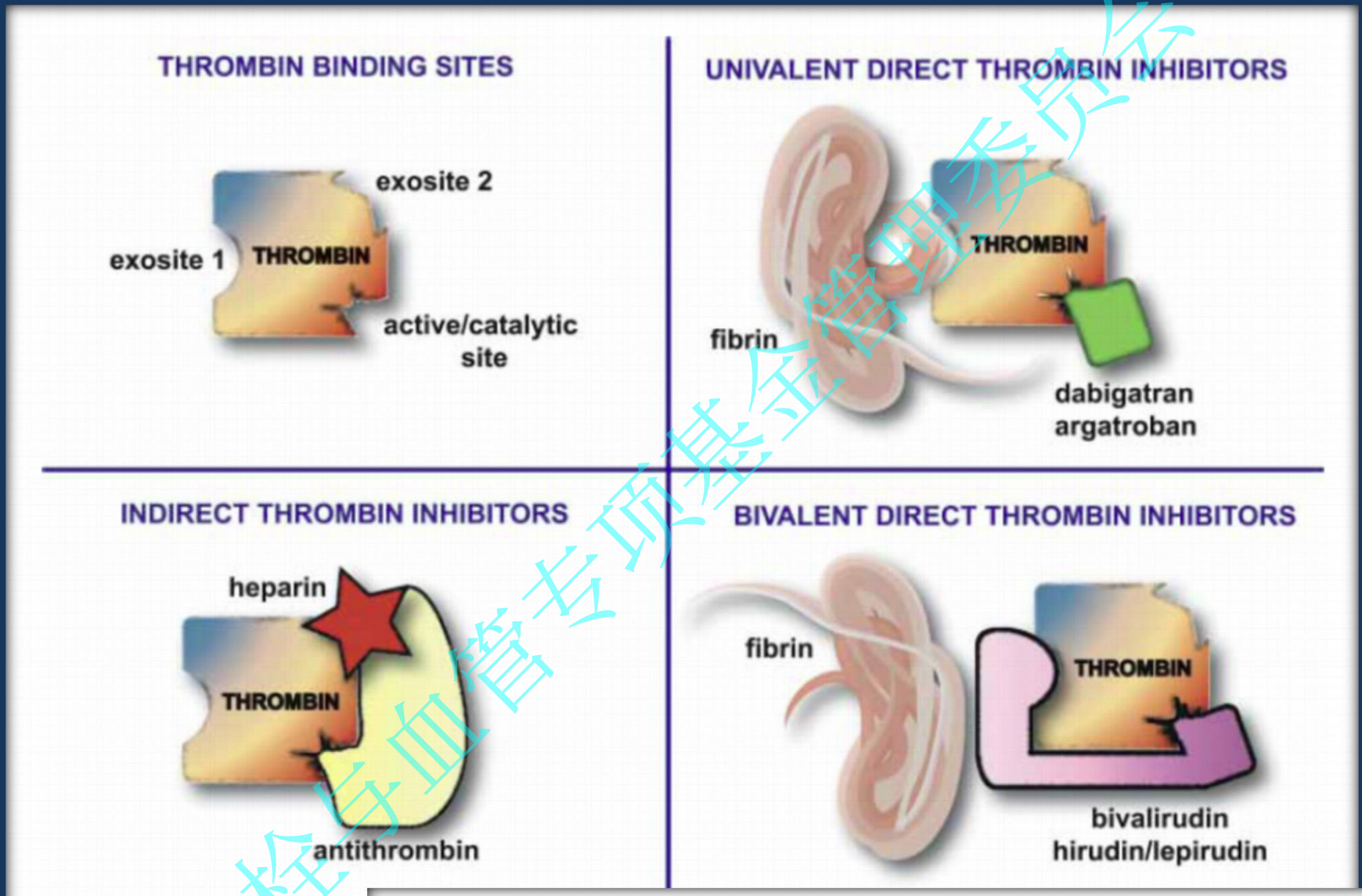
（1）评估利伐沙班抗凝活性。

（2）评估患者基础状态，包括肝肾功能和合并用药。

Ann Med. 2013 Sep;45(5-6):423-429

anti-Xa的“直观”与PT的“表观”

- anti-Xa检测：评估利伐沙班的“抗凝活性”。
  - —“直观”反映利伐沙班对F Xa的抑制程度。
  - —通过数据推导，获得相应的利伐沙班“血药浓度”。
  - —反映病生理环境对利伐沙班“药代”和“药效”的影响。
  - —结果正常时，说明“不存在”利伐沙班的抗凝活性。
- PT检测：评估利伐沙班的“抗凝效果”。
  - —反映利伐沙班对“表观”凝血途径的抑制程度。
  - —不能通过数据推导获得利伐沙班的“血药浓度”。
  - —反映“即时的”或“潜在的”出血风险。
  - —结果正常时，不能说明利伐沙班的抗凝活性。



Thrombin as a multi-functional enzyme

Focus on *in vitro* and *in vivo* effects

Jolanta M. Siller-Matula[1]; Michael Schwameis[2]; Andrew Blann[3]; Christine Mannhalter[4]; Bernd Jilma[2]

[1]Department of Cardiology, Medical University of Vienna, Austria; [2]Department of Clinical Pharmacology, Medical University of Vienna, Austria; [3]Haemostasis Thrombosis and Vascular Biology Unit, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [4]Department of Laboratory Medicine, Medical University of Vienna, Austria

监测达比加群酯的主要试验

Characteristic	PT/INR	aPTT	ECT	TT	dTT (Hemoclot)
Sensitivity to presence of drug	Low	Moderate	High	Very high	High
Correlation with drug levels	Moderate	Moderate	Strong	Moderate	Strong
Relationship to drug levels	Linear	Log-linear	Linear	Log-linear	Linear
Clinical utility	Limited	Normal aPTT suggests minimal drug levels	Potentially suitable for monitoring	Normal TT excludes presence of drug	Potentially suitable for monitoring

aPTT, activated partial thromboplastin time; dTT, dilute thrombin time; ECT, ecarin clotting time; PT/INR, prothrombin time/international normalised ratio; TT, thrombin time.

John W. Eikelboom; Jeffrey I. Weitz.Dabigatran monitoring made simple? 2013

监测达比加群酯的主要试验

Activated Partial Thromboplastin Time: Twenty-two eligible studies[14-18,21-24,26-30,32,33,35,36,39,40,45,48] reported simultaneous measurement of activated partial thromboplastin time (APTT) and dabigatran levels. Although the APTT was often prolonged, degree of prolongation correlated poorly with concentration, especially at higher APTT values. Furthermore, responsiveness varied across reagents, and several studies[14,16,36] reported that selected APTT assays can yield normal results in the presence of trough-like dabigatran concentrations.

APTT：中度敏感性

Dilute TT: Seventeen eligible studies[14-18,21-23,25,29,31,34-37,42,44] reported simultaneous measurement of dilute TT and dabigatran levels. The majority of studies used the Hemoclot thrombin inhibitor assay (Hyphen BioMed). Dilute TT results showed a strong, linear correlation with dabigatran concentrations in the 'on therapy' range. The correlation, though still present, was weaker at low (< 50 ng/mL) and high (> 500 ng/mL) dabigatran concentrations.[14,21,31,37]

dTT：敏感性高

Ecarin-based Assays: Fourteen studies[14,19,21-23,25,27-29,32,35,36,39,42] reported an association between ecarin-based assays, including ecarin clotting time (ECT) and/or ecarin clotting assay, and dabigatran levels. Ecarin is a metalloproteinase that cleaves prothrombin to an active intermediate called *meizothrombin*, which is inhibited by dabigatran much as thrombin is, a property that can be exploited for measurement of dabigatran in ecarin-based assays. Assays demonstrated high sensitivity for the presence of and strong correlation with the concentration of dabigatran below, within, and above 'on therapy' ranges, although this decreased somewhat at extremes (< 40 ng/mL or > 940 ng/mL).[22,29]

ECT：敏感性高

Thrombin Time: Eleven eligible studies[15-18,21,23,28,29,38,42,48] reported simultaneous measurements of thrombin time (TT) and dabigatran levels. TT, in general, was overly sensitive, with results often exceeding the upper limit of the assay at or even below the 'on therapy' range.[15,17,18,21] A normal TT effectively excluded the presence of dabigatran across all studies.

TT：敏感性极高

Bethany T Samuelson… et al.Laboratory Assessment of the Anticoagulant Activity of Direct Oral Anticoagulants A Systematic Review.Chest, 2017，15(1)

凝血酶时间（TT）

- TT对血液中的达比加群酯有高度敏感性，低水平或治疗水平的达比加群酯即可使TT过度延长。
- 血浆浓度为60 ng/ml时，TT延长超过300秒。
- TT的敏感性过高，使TT与血浆中达比加群酯水平的相关性不佳，以至于无法对血药浓度进行定量分析，因此仅可用于除外达比加群酯的存在。

衍生出来：稀释的凝血酶时间（dTT）

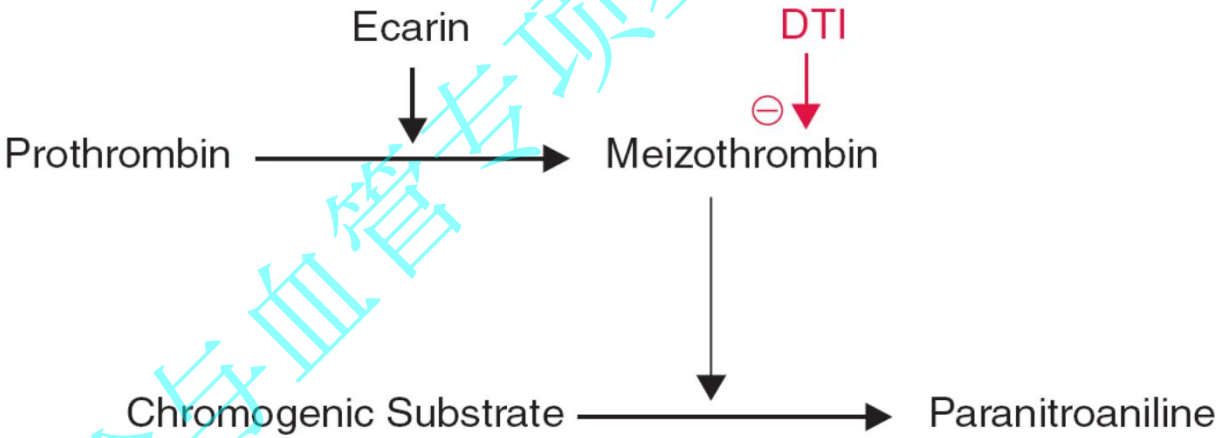
血药浓度-治疗范围：dTT有很好的“线性” 相关性

达比加群酯：<50ng/ml和>500ng/ml：“线性”相关性变差。

ECA监测达比加群酯抗凝活性

将达比加群酯抗IIa活性转换为相应血药浓度

The STA® - ECA II assay is based on the cleavage of prothrombin by ecarin, a snake venom metalloprotease from *Echis carinatus*. The generated activation products (mainly meizothrombin) enzymatically cleave a chromogenic substrate resulting in paranitroaniline release. This cleavage is inhibited in a concentration-dependent manner by direct thrombin inhibitors (DTI), when present in the plasma sample.



The quantity of paranitroaniline released measured at 405 nm is inversely proportional to the amount of direct thrombin inhibitors, such as dabigatran, present in the plasma.

APTT可以监测达比加群酯

- APTT对达比加群酯血药浓度变化敏感，呈剂量依赖性。
- APTT-R达到2.0前，可反映达比加群酯血药浓度变化。
- 110 mg bid，APTT-R达到2.0，有效且安全。
- 150 mg bid（血药浓度>200μg/L），APTT变化趋缓或停滞，APTT-R ≥ 2.0 提示达比加群血药浓度≥治疗水平。
- 不同APTT检测系统对达比加群酯的敏感性也存在差异。

[1] Greg Hapgood et al. The effect of dabigatran on the activated partial thromboplastin time and thrombin time as determined by the Hemoclot thrombin inhibitor assay in patient plasma samples.2013, Throm Haemo.
[2] Joanne van Ryn et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity.2010, Throm Haemo.

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谢谢