陽大附醫
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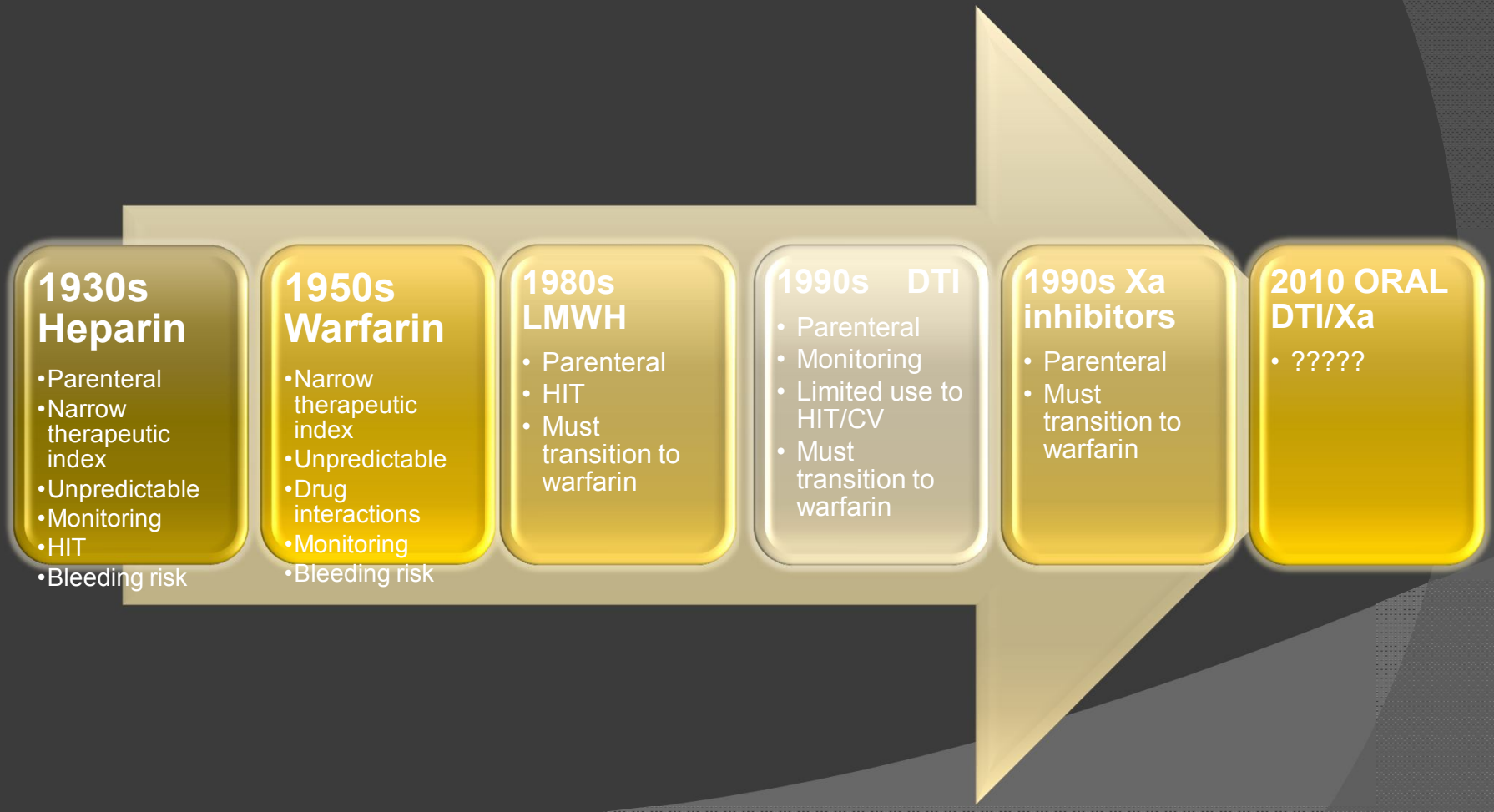
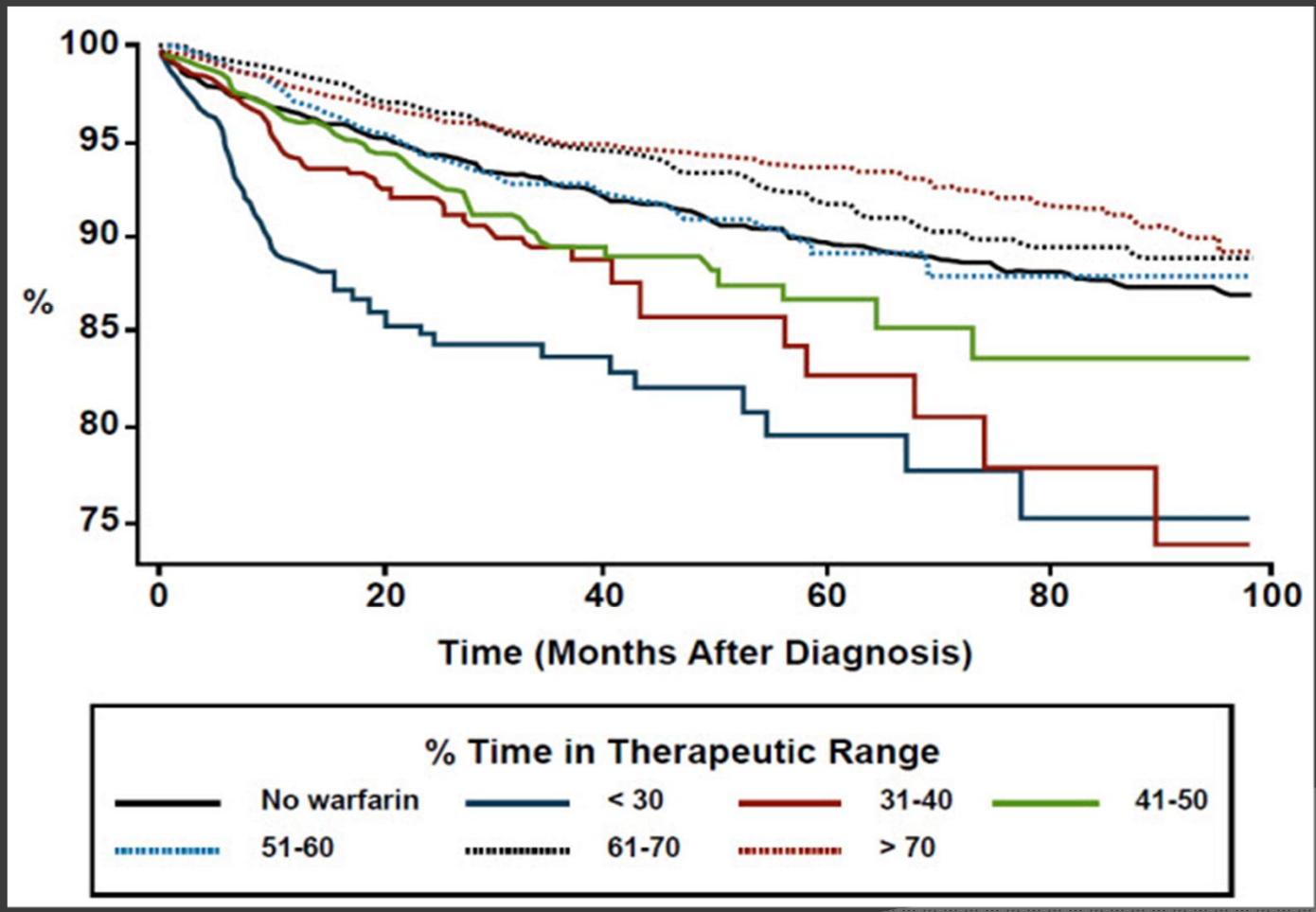
口服抗凝血藥物之進展

Evolution of Anticoagulation

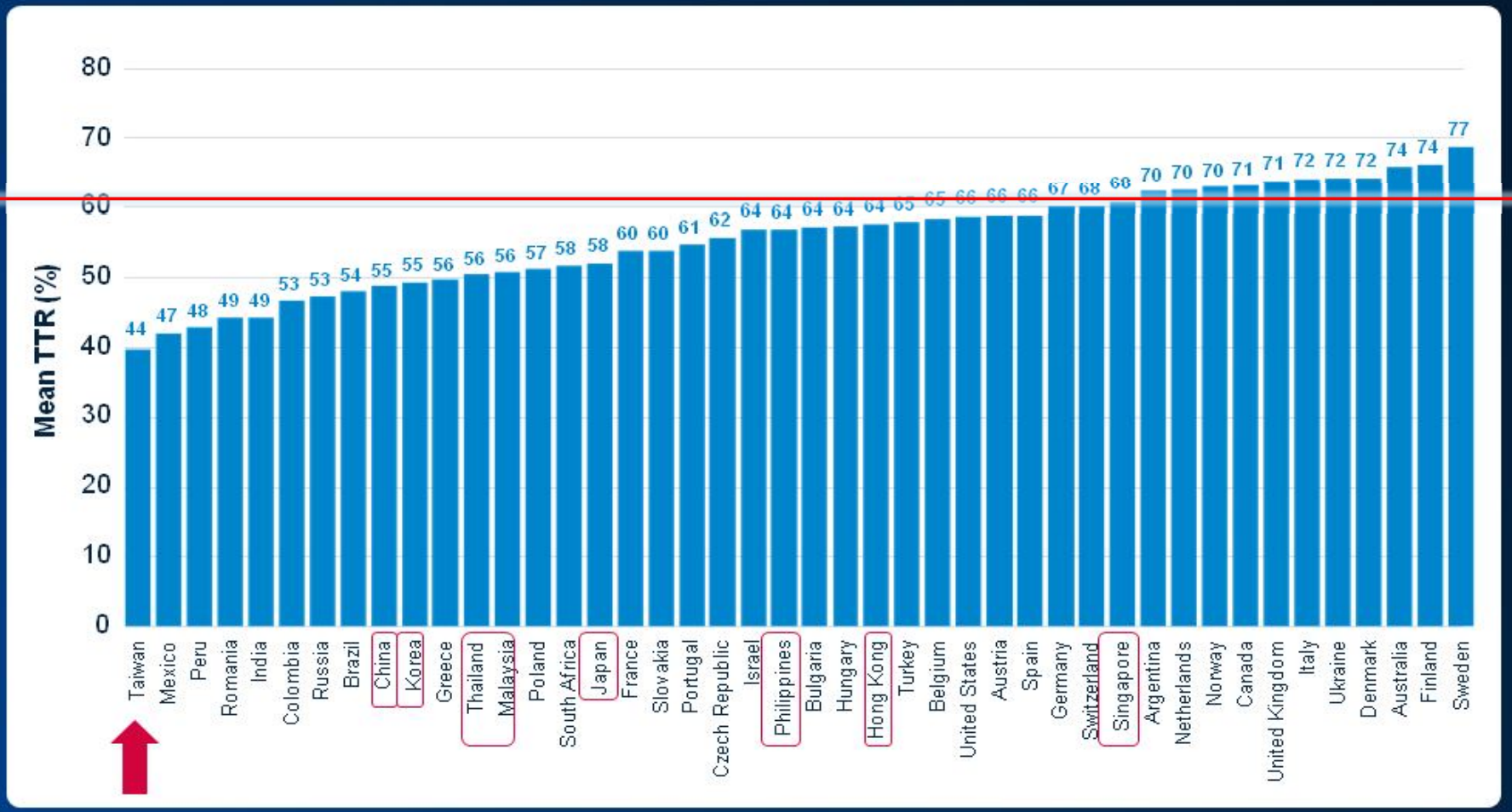


Time in therapeutic Range and stroke risk



Gallagher AM, et al. *Thromb Haemost*. 2011;106:968-977

TTR in Af under VKA treatment



TTR = time in therapeutic range.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Wallentin L, et al. *Lancet* 2010;376:975-983.

Warfarin 治療的上的限制極多而導致50%以上的病患無法使用妥善的治療

Unpredictable response

Narrow therapeutic window, difficult adjust

Slow onset/ offset of action

VKA therapy has several limitations that make it difficult to use in practice

Numerous food–drug interactions

Numerous drug–drug interactions

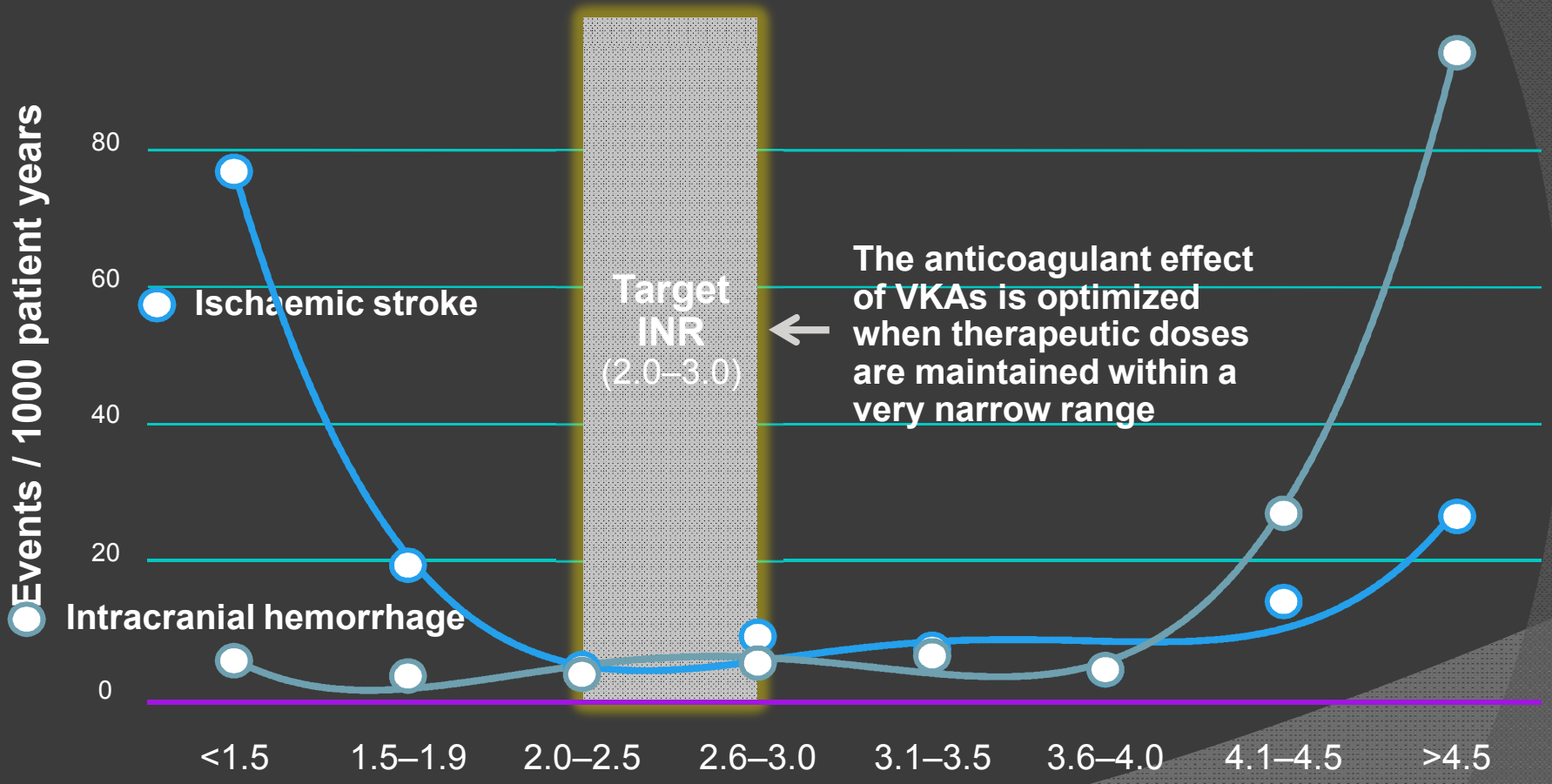
Warfarin resistance

Routine coagulation monitoring → Frequent dose adjustments

INR = International normalized ratio; VKA = vitamin K antagonist.

Ansell J, et al. *Chest* 2008;133;160S-198S. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008;22:129-137. Nutescu EA, et al. *Cardiol Clin* 2008;26:169-187.

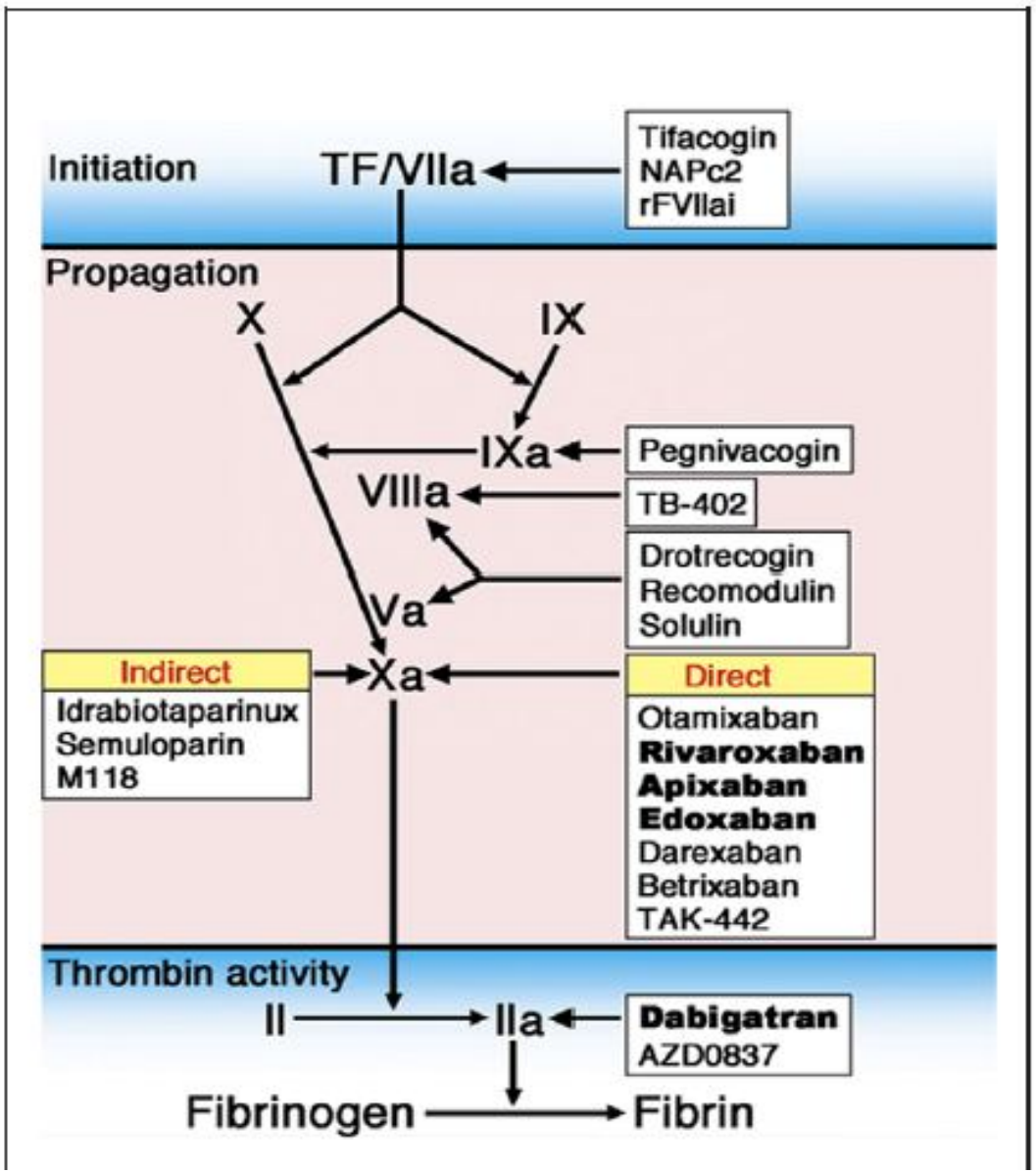
NARROW THERAPEUTIC RANGE WITH VKAs



INR = International normalized ratio; VKA = vitamin K antagonist.

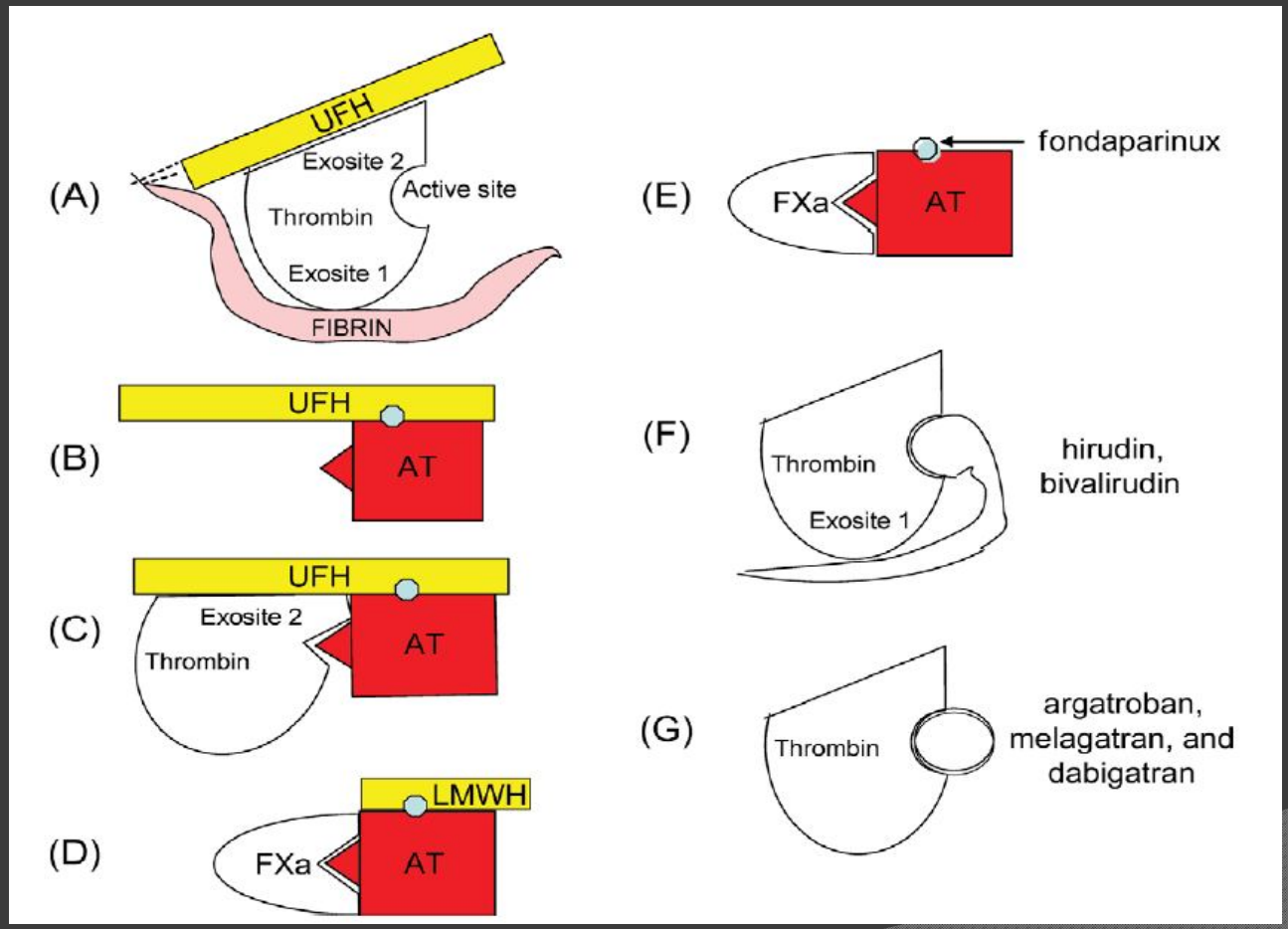
Hylek EM, et al. *N Eng J Med* 2003;349:1019-1026.

Targets of Novel anticoagulants



Anticoagulants in heart disease: current status and perspectives. Eur Heart J 2007;28:880–913.

Mechanism of Action of Novel Anticoagulants



Anticoagulants in heart disease: current status and perspectives. Eur Heart J 2007;28:880–913.

Table 2 A comparison of relevant pharmacological properties of the different thrombin inhibitors in current clinical use

	UFH	LMWH	Pentasaccharides	DTIs
Presence of cofactor required	+++	+++	+++	−
Renal clearance of clinical relevance	±	++	+	++
Non-specific protein binding	+++	+	+	−
Bioavailability by s.c. or oral administration	+(for s.c. UFH)	++	+++	+(for oral DTIs)
Predictability of pharmacological effect	−	++	++	++
Inhibition of thrombin generation	++	++	++	+
Inhibition of thrombin activity	+++	+	−	+++
Inhibition of bound-thrombin	−	−	−	+++
Rebound of thrombin generation after discontinuation	+++	++	−	++
Platelet activation	+++	+	−	−
Immune thrombocytopenia	+++	+	−	−
Decreased bone density	+++	+	−	−

Properties are semiquantitatively graded as −: absent; ±: barely present; +: present-to a low degree; ++: present-to an intermediate degree; +++: present-to a high degree.

Anticoagulants in heart disease: current status and perspectives. Eur Heart J 2007;28:880–913.

The ideal anticoagulant

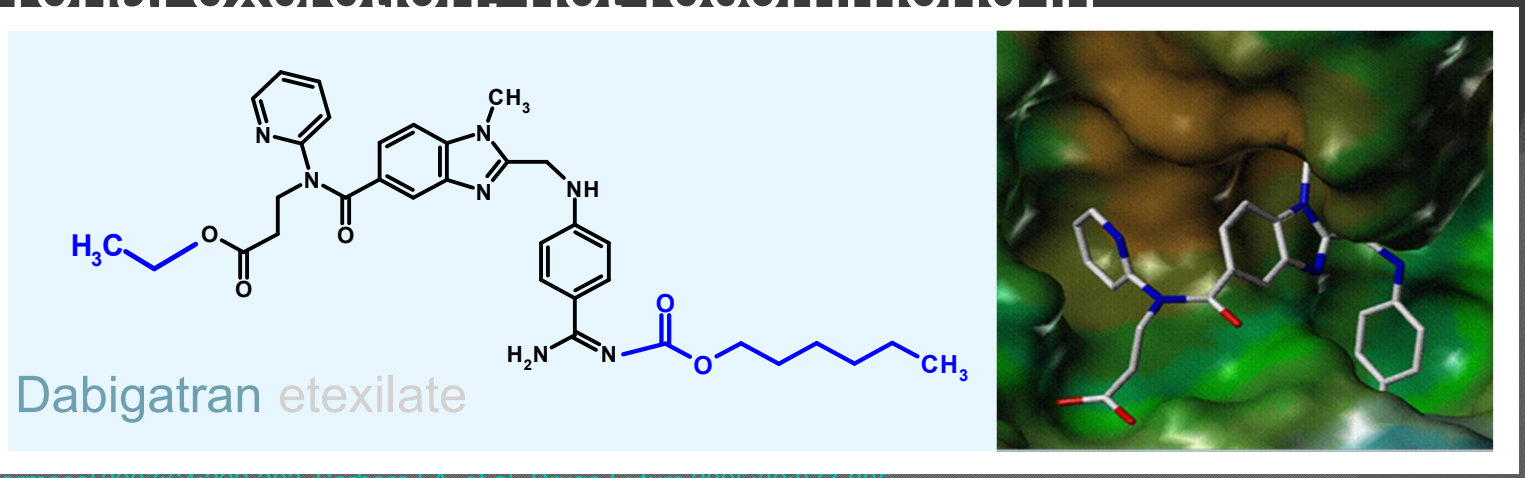
- Oral
- Once daily dosing
- Quick onset, and offset
- Limited monitoring (available)
- No need for monitor
- Limited or no drug , food interactions
- Fixed dose
- Available and effective antidote
- Wide therapeutic index
- Low cost

Novel anticoagulant

- Direct FIIa inhibitor
  - Pradaxa (Dabigtran etexilate)
- Direct FXa inhibitor
  - Xarelto(Rivaroxaban)
  - Eliquis (Apixaban)
  - Lixiana(Edoxaban)

Pradaxa (Dabigatran etexilate)

- Oral prodrug, converted to dabigatran, a potent but reversible DTI
- Inhibits both clot-bound and free thrombin
- Half-life of 12–17 hours
- Peak plasma levels of dabigatran achieved within 2 hours
- ~80% renal excretion, not recommend in CrCL



Dabigatran etexilate is not a

Stangier J, et al. *Br J Clin Pharmacol* 2007;64:292-303. Sorbera LA, et al. *Drugs Future* 2005;30:877-885.
Blech S, et al. *Drug Metab Dispos* 2008;36:386-399.

藥物交互作用

- 與quinidine/ketoconazole藥物之交互作用會增加dabigatran的暴露量，增加出血風險

- P-醣蛋白（P-gp）抑制劑如verapamil(110 mg BID)、amiodarone與clarithromycin的劑量無須進行調整
- 不可與potent P-gp inducer (Rifampin, St. John’s wort, carbamazepine,and phenytoin)並用, 會降低dabigatran暴露量,
- 不建議和Dronedarone 並用

使用Pradaxa的病人需進行緊急手術時該如何處置?

手術前階段

腎功能不足的病患可能需要較長的時間清除dabigatran。在任何醫療程序之前，皆應事先考量此點。

(表2) 進行侵入性或手術程序之前的中斷治療原則:

腎功能 (CrCL ml/min)	半衰期 估計值(小時)	於進行非急需之手術前 停用dabigatran	
		高出血風險或 重大手術	標準風險
≥80	~13	2天之前	24小時之前
≥50 - <80	~15	2-3天之前	1-2天之前
≥30 - <50	~18	4天之前	2-3天之前 (>48 小時)

若須接受緊急介入性醫療，即應暫時中斷PRADAXA® 治療。手術/介入性醫療應儘可能延至使用最後一劑PRADAXA® 之後至少12小時進行。若手術無法延後，出血風險可能增高，因此應權衡此出血風險與介入性醫療的迫切性。

接受PRADAXA® 治療者發生緊急狀況時的出血處置

抗凝血活性的評估

接受PRADAXA®的病患發生緊急狀況時，最好能夠為其評估抗凝血作用狀態。血漿的PRADAXA® 濃度與抗凝血作用高低之間存在密切相關性。PRADAXA®的半衰期為12–14小時；在此期間之後，80% 的PRADAXA®會經腎臟清除。請注意，PRADAXA®在腎功能不全病患的半衰期會延長。[1,2]

- **血液檢體採集時間點**：抗凝血反應高低視血液檢體採集與最後一劑用藥的相隔時間長短而定。[2]
- **抗凝血活性高低**：最靈敏的檢測法為凝血酶時間（Thrombin Time，簡稱TT）檢測。凝血酶時間量值正常表示此時PRADAXA®並無臨床上相關之抗凝血作用。活化部分凝血活酶時間（activated partial thromboplastin time，簡稱aPTT）與ecarin凝血時間（ecarin clotting time，簡稱ECT）量值正常亦表示此時PRADAXA®的並無藥理學上相關之抗凝血作用。[2]
- **不建議進行某些檢測**：凝血酶原時間（prothrombin time）（國際標準凝血時間比[INR]）的靈敏度不足以評估PRADAXA®的抗凝血活性。請注意：現場即時INR測定（point-of-care）裝置曾發生INR值假性升高的情形（假性升高2–4倍）。[2,3]

接受Pradaxa治療者發生出血的處置

*(fresh frozen plasma, prothrombin complex concentrates

與接受維他命K拮抗劑治療者採相同的措施，但不包括給予維他命K。血液透析為清除血漿中之PRADAXA®的另一種選擇。[1,2]

- 停止服用PRADAXA®。
- 尋找出血來源。
- 在啟動以下標準治療之前維持適當的排尿：
  - 手術止血。
  - 輸血（例如，新鮮全血或新鮮冷凍血漿）。
  - 給予凝血因子濃縮液（請注意：雖然有一些實驗證據支持這類藥物的效用，但臨床證據仍極有限）。
    - 凝血酶原複合體濃縮液（prothrombin complex concentrates，簡稱PCC）（例如，未活化型或活化型）
    - 基因重組活化型VIIa凝血因子（rFVIIa）
    - 發生血小板減少、或使用長效型抗血小板藥物（例如，乙醯水楊酸或clopidogrel）時，可考慮使用血小板濃縮液。
  - 藉由透析、持續血液灌注、或緊急活性碳過濾（請注意：目前尚無臨床經驗支持活性碳過濾方法）來移除PRADAXA®。

抗凝血作用檢測的連續測量可供指引PRADAXA®的相對清除狀況。請務必注意，儘管已使用凝血酶原複合體濃縮液，aPTT與ECT之類的凝血作用檢測值可能仍舊偏高。[5]