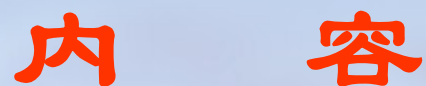


# 肺血栓栓塞症的抗凝治疗策略

## Strategy of anticoagulant therapy for Pulmonary thromboembolism

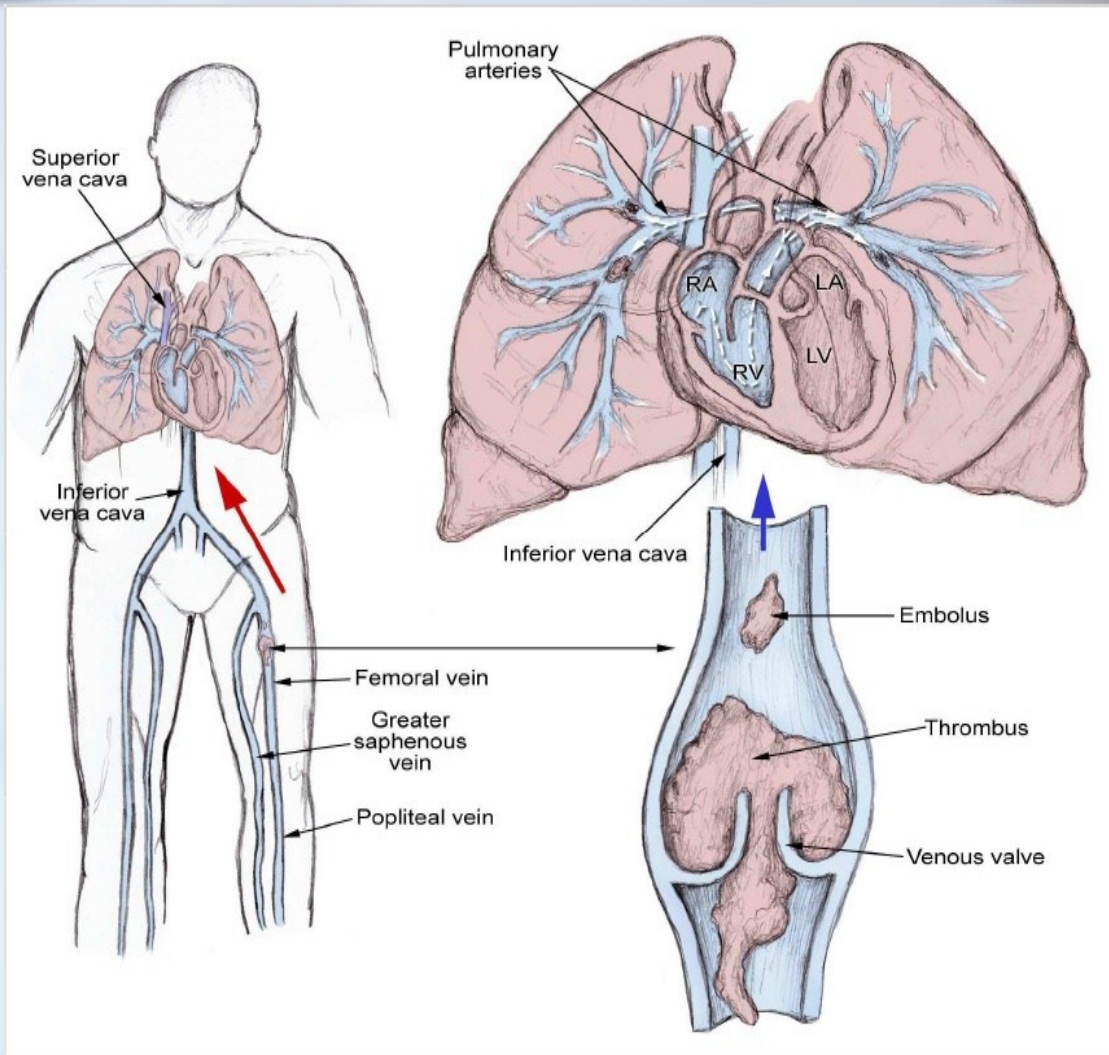
北京医院呼吸与危重症医学科  
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- 肺栓塞流行病学（发病率）
- 肺栓塞分类：传统分类      现在分类
- 治疗：                      分类治疗：
- 抗凝治疗：              溶栓后治疗
- 起始抗凝治疗                      when?
- 长期抗凝治疗                      how long?
- 抗凝监测                      how monitor?
- 抗凝时间                      how long?
- 抗凝药物（新型）                      what? new drugs?
- 副作用                      side effect?
- 特殊情况下的处理                      special management?
- 家庭管理：                      family management?
- 停药指证                      indication of stop use drug?



# Concept





# Epidemiology of PTE

- Pulmonary embolism (PE) is a common problem, though its exact incidence **is difficult to assess** due to its non-specific clinical presentation and frequently suboptimal diagnostic management affecting the quality of reporting.
- Data collected **3 decades ago** in the USA suggested a prevalence of PE of **0.4% among hospitalised patients**,
- while the overall annual incidence was estimated at **600 000** cases.
- Clinical and postmortem data collected in the Malmo area, a region of Sweden with a particularly high autopsy rate, suggested an incidence of PE of approximately **20/10 000 inhabitants/year**.1

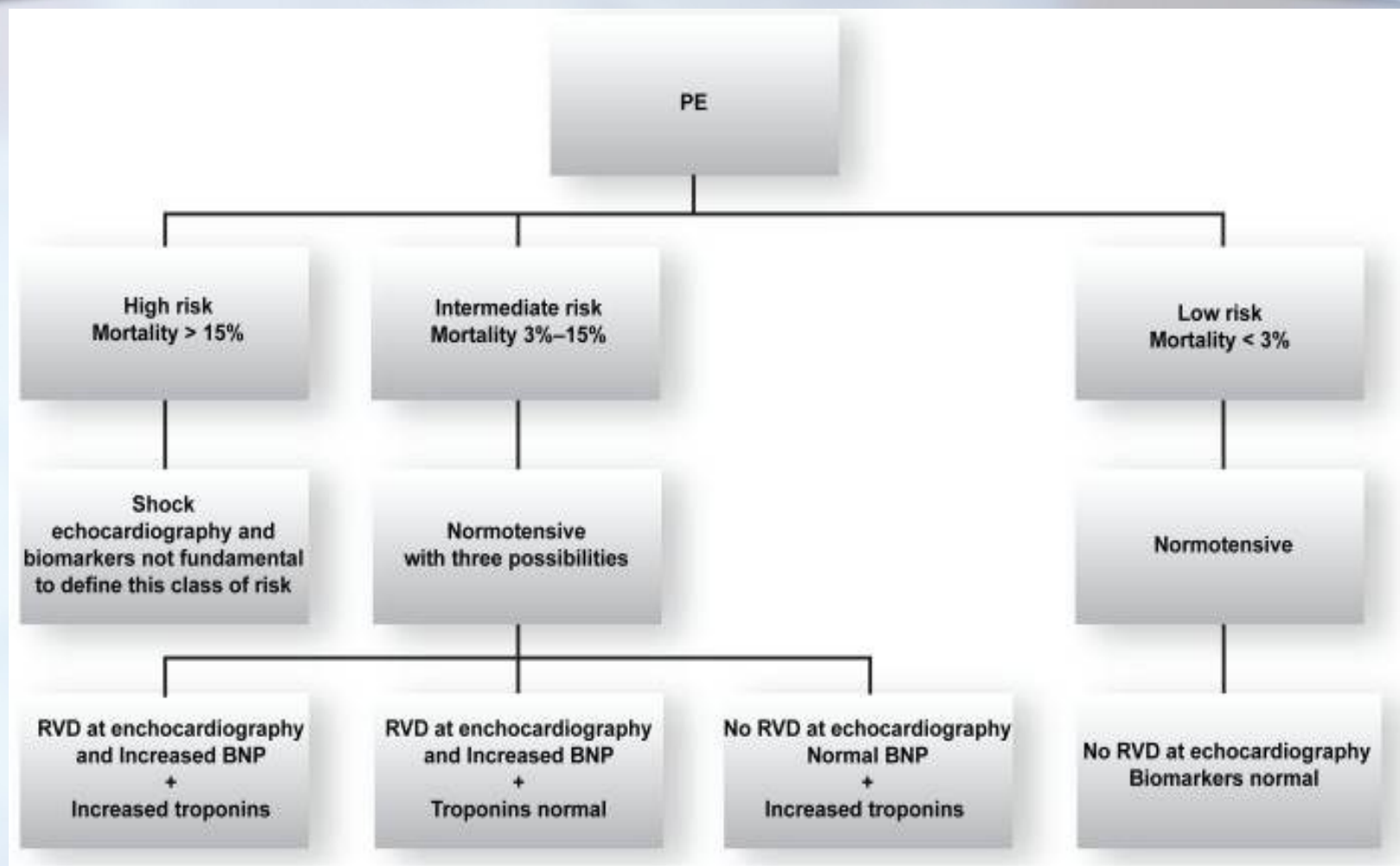


# Old and new clinical classification of PE

- Old ATS 1999, ESC 2000, BTS 2003, ACEP 2003, ACCP 2004, ACCP 2008
- MASSIVE (cardiac arrest, shock, hypotension)
- SUB-MASSIVE (normotensive PE with RHD )
- NON MASSIVE (normotensive PE without RHD)
- New ESC 2008
- HIGH RISK (cardiac arrest, shock, hypotension)
- NON HIGH RISK
  - INTERMEDIATE RISK (normotensive PE with RHD and/or high BNP and/or high troponins)
  - LOW RISK (normotensive PE without RHD and low BNP and low troponins)

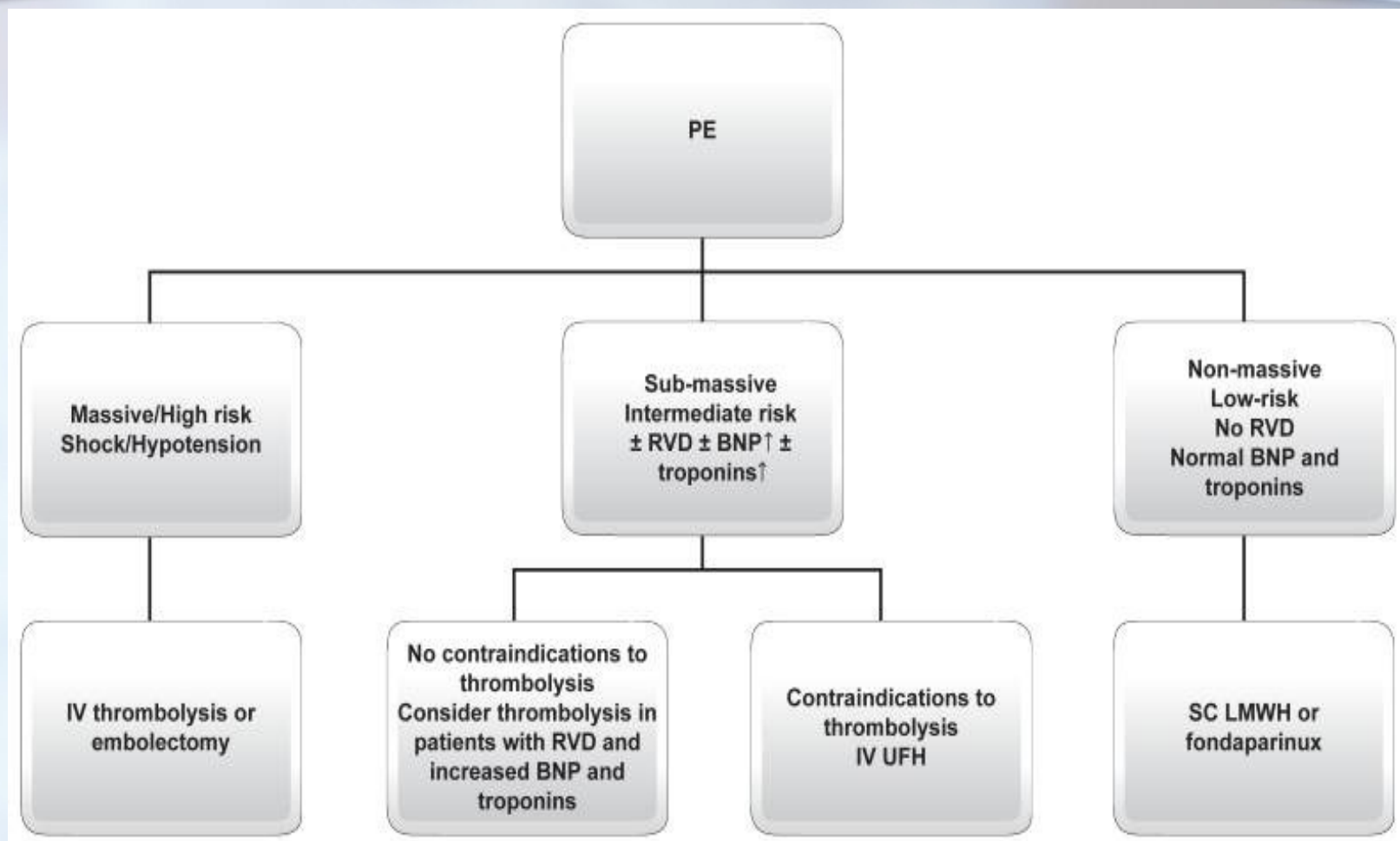


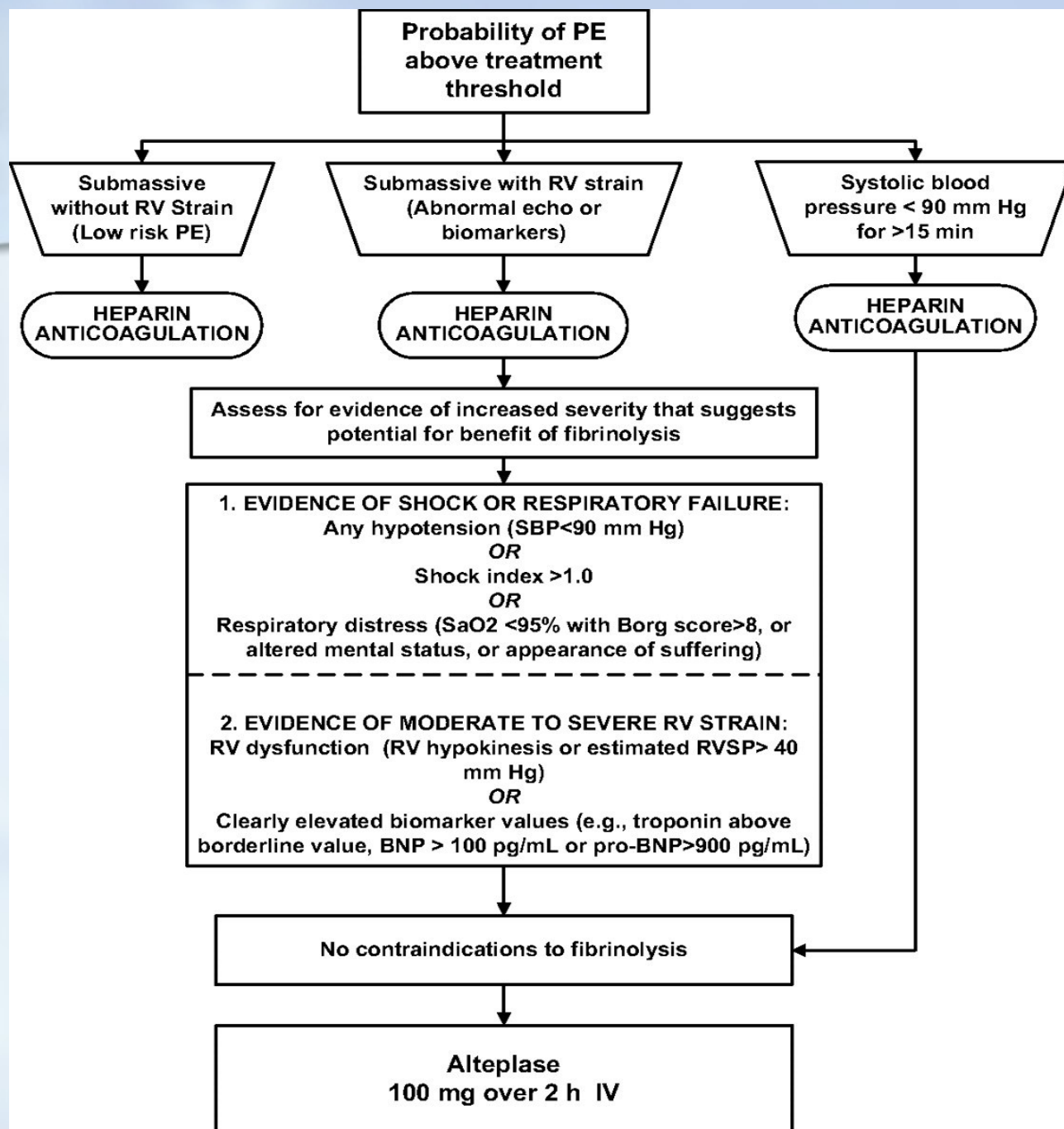
# Mortality and Classification





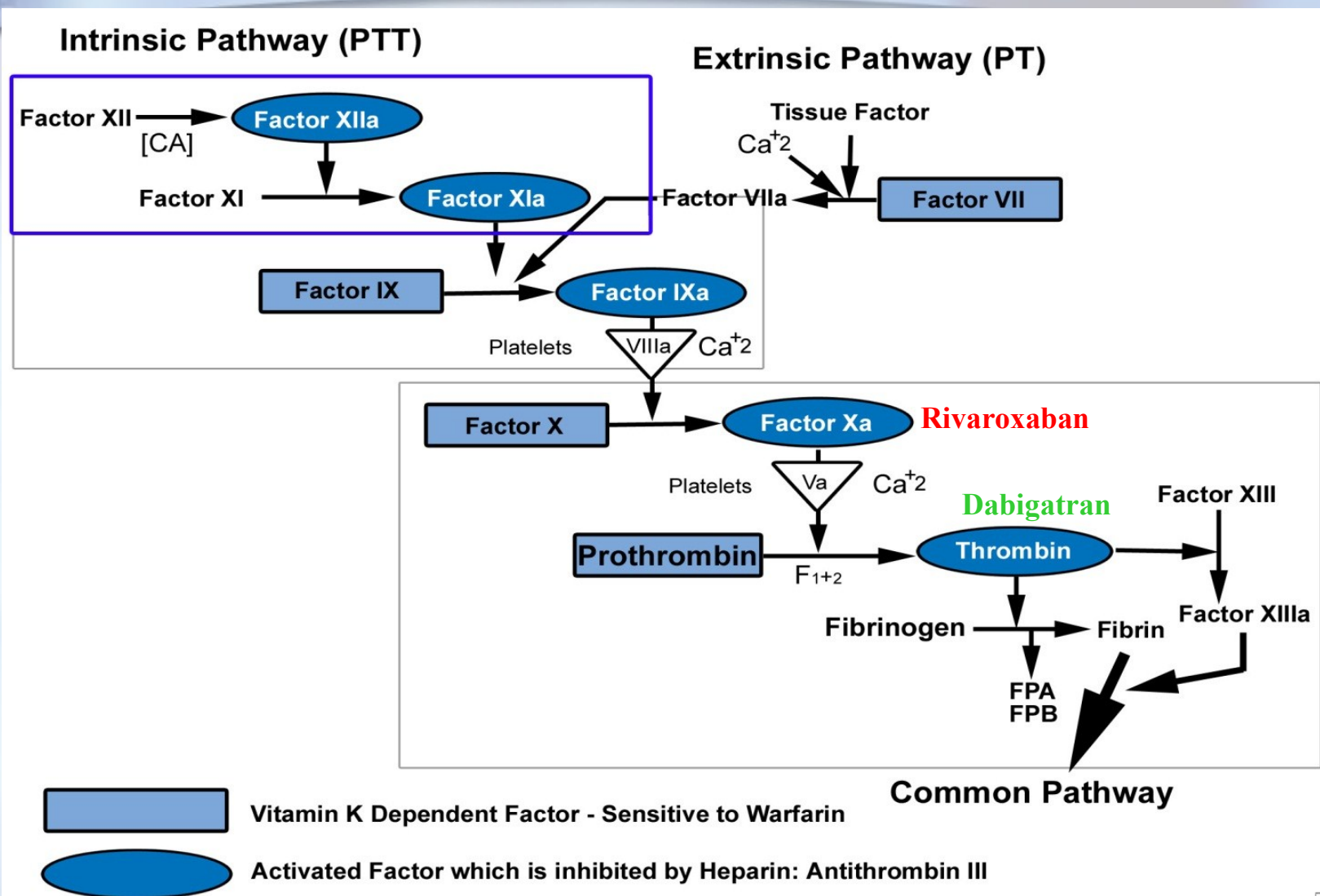
# Indication of Anticoagulation







# Mechanism of Anticoagulant in Intrinsic and Extrinsic Pathway



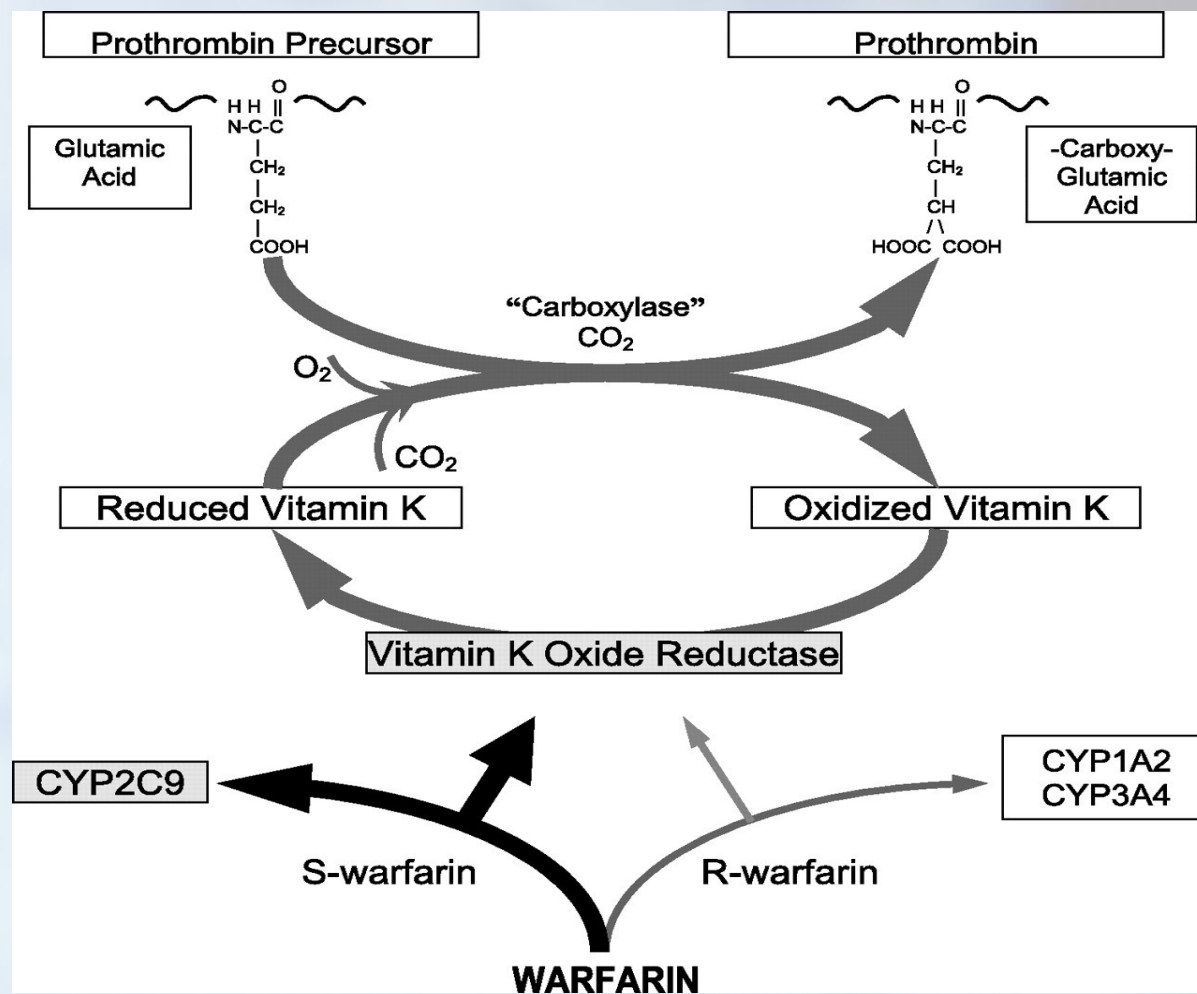


# Anticoagulation drugs

- Anticoagulate with LMWH,
  - IV/Sub-Q UFH,
  - or fondaparinux (IA)
  - Enoxaparin (依诺肝素)
  - Dalteparin (达肝素钠)
  - Tinzaparin (亭扎肝素)
- Vitamin K antagonists (VKAs): **Warfarin**
- Direct Thrombin Inhibitors: **Dabigatran Etexilate**
- Direct Factor Xa Inhibitors: **Rivaroxaban**



# warfarin





# Direct Thrombin Inhibitors: Dabigatran Etexilate

- Dabigatran is a selective, reversible, **direct thrombin inhibitor** given as dabigatran etexilate, an orally absorbable prodrug, since dabigatran itself is a strongly polar molecule that is not absorbed from the gut.
- Phase 3 clinical studies reported to date have evaluated the use of dabigatran etexilate **for the prevention of VTE after elective total knee or hip arthroplasty**, for **therapy of VTE**, and to prevent stroke or systemic embolism in nonvalvular AF.
- The drug is **approved** in many countries for the prevention of VTE in patients undergoing total hip or knee replacement surgery and in the United States and Canada for the prevention of stroke or systemic embolism in nonvalvular AF



# Direct Factor Xa Inhibitors: Rivaroxaban

- Rivaroxaban is a direct factor Xa inhibitor
- and is currently approved in many countries, including the United States,
- for the prevention of VTE in patients undergoing total hip or knee replacement surgery.
- The drug is undergoing an extensive clinical development program in other clinical settings,
- Including the treatment of VTE and the prevention of acute ischemic stroke in patients with AF.



- Anticoagulation is the mainstay of treatment for PE. Because of the risks of hypoxemia and hemodynamic instability associated with PE, close monitoring and supportive therapy are necessary. Therefore, outpatient treatment of PE is not advised.
- Unfractionated heparin most commonly is used to treat patients with PE, although LMW heparin also is safe and effective.
- Only enoxaparin and tinzaparin have received formal FDA approval for use in the treatment of PE.



# Thrombolysis

- Thrombolysis clearly is indicated in patients with massive PE and associated hemodynamic instability.
- However, the role of thrombolysis in patients with submassive PE remains controversial.
- In the largest study to date,<sup>19</sup> improved survival was observed in patients treated **with alteplase plus heparin compared with heparin alone**. Using death and major complications as the end point, the number needed to treat was 7.3. One fewer death was observed for every 82 patients treated with the combination therapy.<sup>10</sup>
- In patients with PE, the usual dose of alteplase (Activase) is **50 mg** given by intravenous infusion over a period of two hours.
- Streptokinase (Streptase) is given in a 250,000-IU loading dose, followed by 100,000 IU per hour for 24 hours.
- Delivery of thrombolytics directly into the thrombus by catheter has been described **but has not been shown** to be superior to peripheral infusion.



- The vitamin K antagonists (VKAs): **warfarin**
- Anticoagulation with warfarin should follow heparin therapy.
- The same regimens are used for DVT and PE



## Weight-Based Heparin Therapy with Adjustments Based on the APTT

- **Initial dosage**  
Bolus of 80 units per kg, then 18 units per kg per hour by infusion
- **APTT < 35 seconds (<1.2 times control)**  
Bolus of 80 units per kg, then 4 units per kg per hour by infusion
- **APTT = 35 to 45 seconds (1.2 to 1.5 times control)**  
Bolus of 40 units per kg, then 2 units per kg per hour by infusion
- **APTT = 46 to 70 seconds (1.5 to 2.3 times control)**  
No change
- **APTT = 71 to 90 seconds (2.3 to 3.0 times control)**  
Decrease infusion rate by 2 units per kg per hour.
- **APTT > 90 seconds (>3.0 times control)**  
Hold infusion for 1 hour, then decrease infusion rate by 3 units per kg per hour.



## Initiation of Warfarin Therapy at 5 mg per Day

<i>Day</i>	<i>INR</i>	<i>Warfarin dosage (mg per day)</i>
1		5
2		5
3	< 1.5	10
	1.5 to 1.9	5
	2.0 to 2.9	2.5
	> 3.0	0
4	< 1.5	10
	1.5 to 1.9	7.5
	2.0 to 2.9	5
	> 3.0	0
5	< 2.0	10
	2.0 to 2.9	5
	> 3.0	0
6	< 1.5	10
	1.5 to 1.9	7.5
	2.0 to 2.9	5
	> 3.0	0



## Initiation of Warfarin Therapy at 10 mg per Day\*

<i>Warfarin dosage (mg per day)</i>				<i>Warfarin dosage (mg per day)</i>			
<i>Day 3 INR</i>	<i>Day 3</i>	<i>Day 4</i>		<i>Day 5 INR</i>	<i>Day 5</i>	<i>Day 6</i>	<i>Day 7</i>
<1.3	15	15		<2.0	15	15	15
1.3 to 1.4	10	10		2.0 to 3.0	7.5	5	7.5
				3.1 to 3.5		0	5
				> 3.5	0	0	2.5
1.5 to 1.6	10	5		<2.0	7.5	7.5	7.5
1.7 to 1.9	5	5		2.0 to 3.0	5	5	5
				3.1 to 3.5	2.5	2.5	2.5
				> 3.5	0	2.5	2.5
2.0 to 2.2	2.5	2.5		<2.0	5	5	5
2.3 to 3.0	0	2.5		2.0 to 3.0	2.5	5	2.5
				3.1 to 3.5	0	2.5	0
				> 3.5	0	0	2.5
>3.0	0	0		<2.0	2.5	2.5	2.5
				2.0 to 3.0	2.5	0	2.5
				3.1 to 4.0	00	2.5	2.50
				> 4.0	0	00	02.5



## SPECIAL SITUATIONS

- Warfarin therapy is contraindicated during pregnancy. Therefore, long-term treatment with LMW heparin is used when PE occurs in a pregnant woman.



# Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines ,2012

- Acute PE, Recommend **initial treatment** with parenteral anticoagulation (**LMWH, fondaparinux, IV UFH, or SC UFH**) over no such initial treatment (Grade 1B).
- 1 **High clinical suspicion of acute PE**, Suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).
- 2. **Intermediate clinical suspicion of acute PE**, Suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed **for more than 4 h** (Grade 2C).
- 3. **Low clinical suspicion of acute PE**, Suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected **within 24 h** (Grade 2C).
- 5.3. Acute PE, Recommend **early initiation of VKA** (eg, same day as parenteral therapy is started) **over** delayed initiation, and continuation of parenteral anticoagulation for a minimum of **5 days** and **until** the INR is **2.0 or above** for **at least 24 h** (Grade 1B).



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- 5.4.1. **Acute PE, Suggest LMWH or fondaparinux over IV UFH** (Grade 2C for LMWH; Grade 2B for fondaparinux) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux).
- *Remarks:* Local considerations such as cost, availability, and familiarity of use dictate the choice between **fondaparinux and LMWH**.
- LMWH and fondaparinux are retained in **patients with renal impairment**, whereas this is not a concern with UFH.
- In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered or planned, initial treatment with **IV UFH is preferred to use of SC therapies**.
- 5.4.2. **Acute PE treated with LMWH, Suggest once- over twice-daily administration** (Grade 2C).



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- 5.5. low-risk PE and whose home circumstances are adequate, Suggest **early discharge over standard discharge** (after first 5 days of treatment) (Grade 2B).
- 5.6.1.1 Acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered **thrombolytic therapy** over no such therapy (Grade 2C).
- 5.6.1.2. Acute PE not associated with hypotension, Recommend **against** systemically administered thrombolytic therapy (Grade 1C).
- 5.6.1.3. Acute PE not associated with hypotension and with a low bleeding risk whose initial clinical presentation, or clinical course **after starting anticoagulant therapy**, suggests **a high risk of developing hypotension**, Suggest administration of thrombolytic therapy (Grade 2C)
- 5.6.2.1. Acute PE, when a thrombolytic agent is used, Suggest **short infusion times (a 2-h infusion) over prolonged infusion times (a 24-h infusion)** (Grade 2C).
- 5.6.2.2. Acute PE when a **thrombolytic agent** is used, Suggest administration through **a peripheral vein over a pulmonary artery catheter** (Grade 2C).



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- 5.7. Acute PE associated with hypotension and who have (i) **contraindications to thrombolysis**, (ii) **failed thrombolysis**, or (iii) **shock** that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, **Suggest catheter-assisted thrombus removal over no such intervention** (Grade 2C).
- 5.8. Acute PE associated with hypotension, Suggest **surgical pulmonary embolectomy over no such intervention** if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C).
- 5.9.1. Acute PE who are treated with anticoagulants, Recommend **against** the use of an IVC filter (Grade 1B).
- 5.9.2. Acute PE and **contraindication to anticoagulation**, Recommend the **use of an IVC filter** (Grade 1B).
- 5.9.3. Acute PE and an IVC filter inserted as an alternative to anticoagulation, Suggest **a conventional course of anticoagulant therapy** if their risk of bleeding resolves (Grade 2B).



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- 6.1. In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy (Grade 1B regardless of bleeding risk).
- 6.2. In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B).
- 6.3. In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy.
- 6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).



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- 6.3.2. First VTE that is an unprovoked PE and who have a high bleeding risk, Recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).
- 6.3.3. Second unprovoked VTE, Recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), suggest extended anticoagulant therapy in those with a moderate bleeding risk .
- 6.3.4 Second unprovoked VTE have a high bleeding risk, we suggest 3 months of therapy over extended therapy (Grade 2B).
- 6.4. In patients with PE and active cancer, if a low or moderate bleeding risk, Recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), and if a high bleeding risk, Suggest extended anticoagulant therapy (Grade 2B).
- 6.5. PE treated with VKA, Recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0–5.0) range for all treatment durations (Grade 1B).
- 6.6. PE and no cancer, Suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For PE and no cancer who are not treated with VKA therapy, Suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).



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- 6.7. PE and cancer, Suggest LMWH over VKA therapy (Grade 2B). PE and cancer who are not treated with LMWH, Suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2C).
- 6.8. PE who receive extended therapy, Suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C).
- 6.9. In patients who are incidentally found to have asymptomatic PE, Suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B).
- 7.1.1. In patients with chronic thromboembolic pulmonary hypertension (CTPH), Recommend extended anticoagulation over stopping therapy (Grade 1B).
- 7.1.2. In selected patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team, Suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C).



Thank for your attention!