# Perioperative Management of Antithrombotic Drugs

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Translated the American Pharmacists Association (APhA) Medication Therapy Management Services (MTMs) textbook into Chinese and led the drafting of China's first standard for Medication Therapy Management (MTM) Pharmacy Clinic Services.

# Perioperative risk of bleeding and thrombosis

## Bleeding related risk

- The incidence of major bleeding in patients receiving vit K antagonist therapy ranges from 1~ 3%.
- The gastrointestinal bleeding rate during antithrombotic therapy for AMI with PCI is 16.6%
- Approximately 25% of intracranial hemorrhage cases are associated with oral anticoagulant therapy.

## Thrombosis related risk

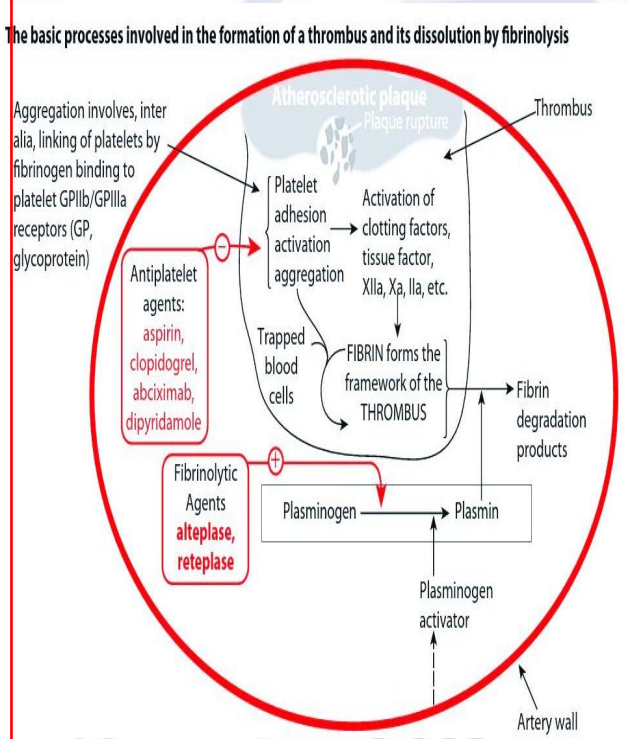
- Stroke and other thromboembolic events are the leading causes of death and disability in atrial fibrillation.
- The annual stroke incidence after mechanical valve replacement with anticoagulation is 5-10%.
- If antithrombotic drugs are stopped within 1 month after venous thrombosis, the monthly recurrence rate can be as high as 40%.

# CONTENT

# Common Antithrombotic Drugs

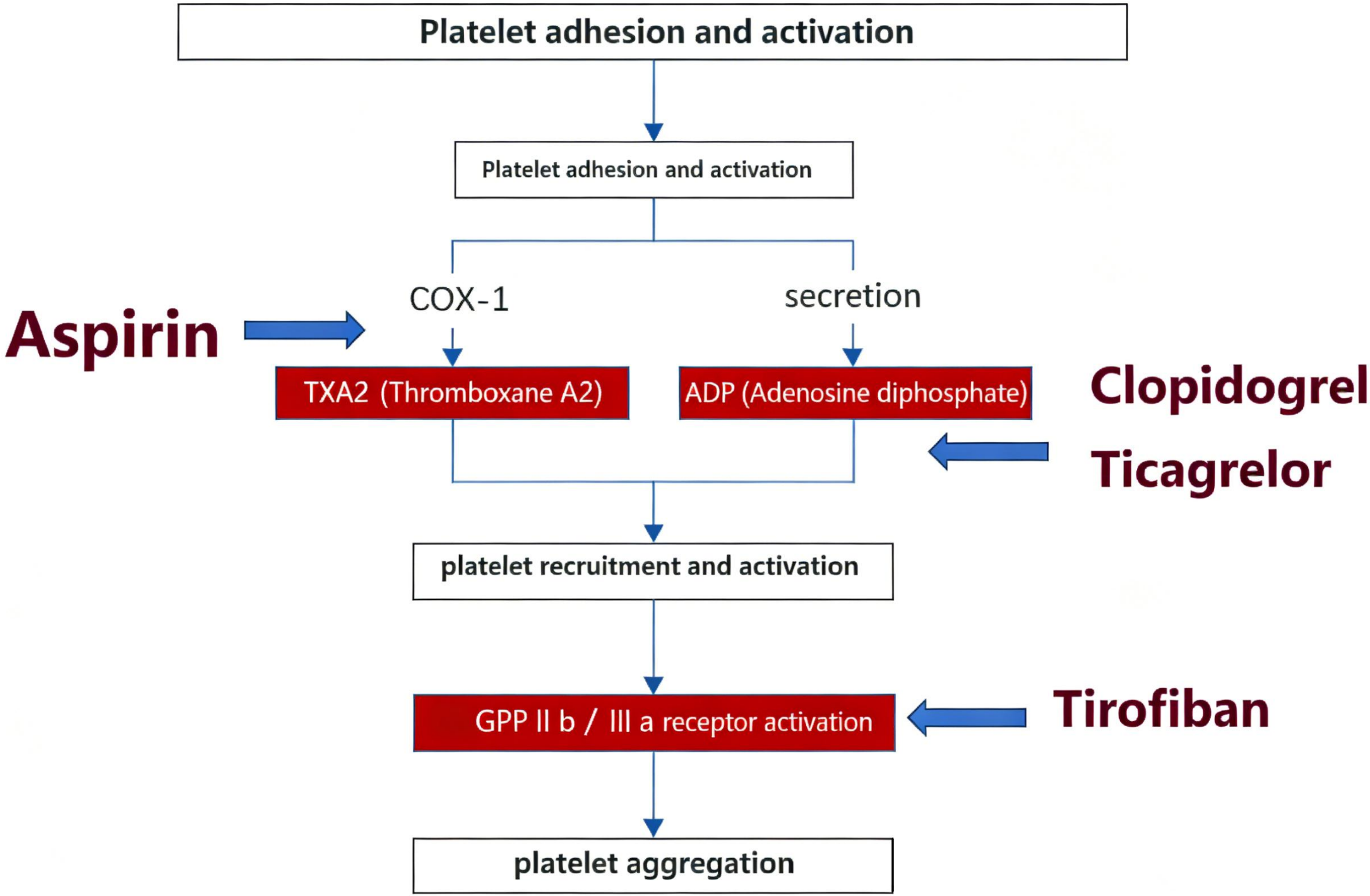
## Antiplatelet Drugs

- Thromboxane A2 inhibitors
- ADP P2Y12 receptor antagonists
- GPIIb/IIIa receptor inhibitors




## Anticoagulant Drugs

- Vitamin K antagonists
- Indirect thrombin inhibitors
- Direct thrombin inhibitors
- Factor Xa inhibitors


Platelet adhesion and activation
Platelet adhesion and activation
COX-1
secretion
Aspirin
TXA2 (Thromboxane A2)
ADP (Adenosine diphosphate)
Clopidogrel
Ticagrelor
platelet recruitment and activation
GPP II b / III a receptor activation
Tirofiban
platelet aggregation

# Antiplatelet Drugs

| Characteristics | Aspirin | ADP P2Y12 Receptor Antagonists | | | GPIIb/IIIa Receptor Inhibitors |
|---|---|---|---|---|---|
| | | Clopidogrel | Prasugrel | Ticagrelor | Tirofiban |
| MOA | Irreversible inhibition of cox1&2 | Irreversible $P_2Y_{12}$ inhibitor | Irreversible $P_2Y_{12}$ inhibitor | Reversible, noncompetitive $P_2Y_{12}$ inhibitor | GPIIb/IIIa eceptor inhibitors |
| Peak Effect | N/A | 6-8 hours | 2-4 hours | 2 hours | 30 mins |
| Half-life | 3~6 hours | ~6 hours | ~7 hours | 7~9 hours | 1.5~ 2 hours |

# Common Antithrombotic Drugs

## Antiplatelet drugs

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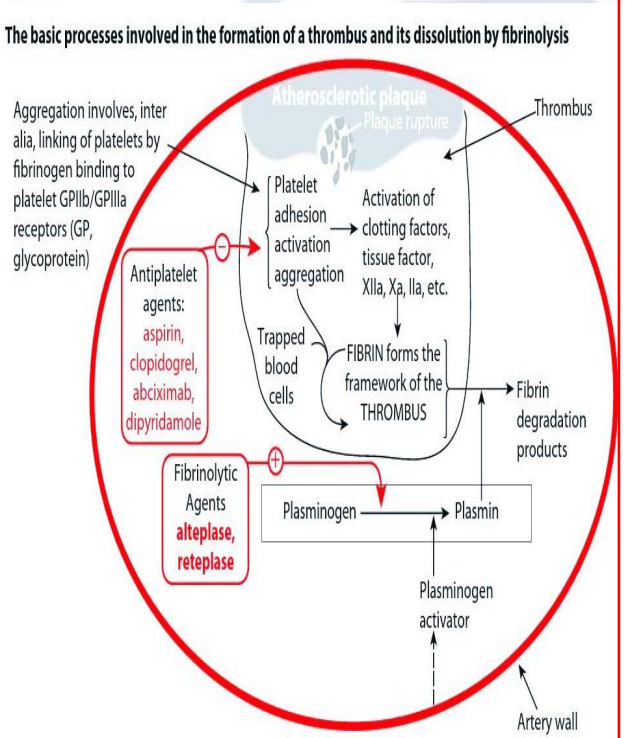
- ADP P2Y12 receptor antagonists
- GPIIb/IIIa receptor inhibitors




## anticoagulant drugs

- Vitamin K antagonists
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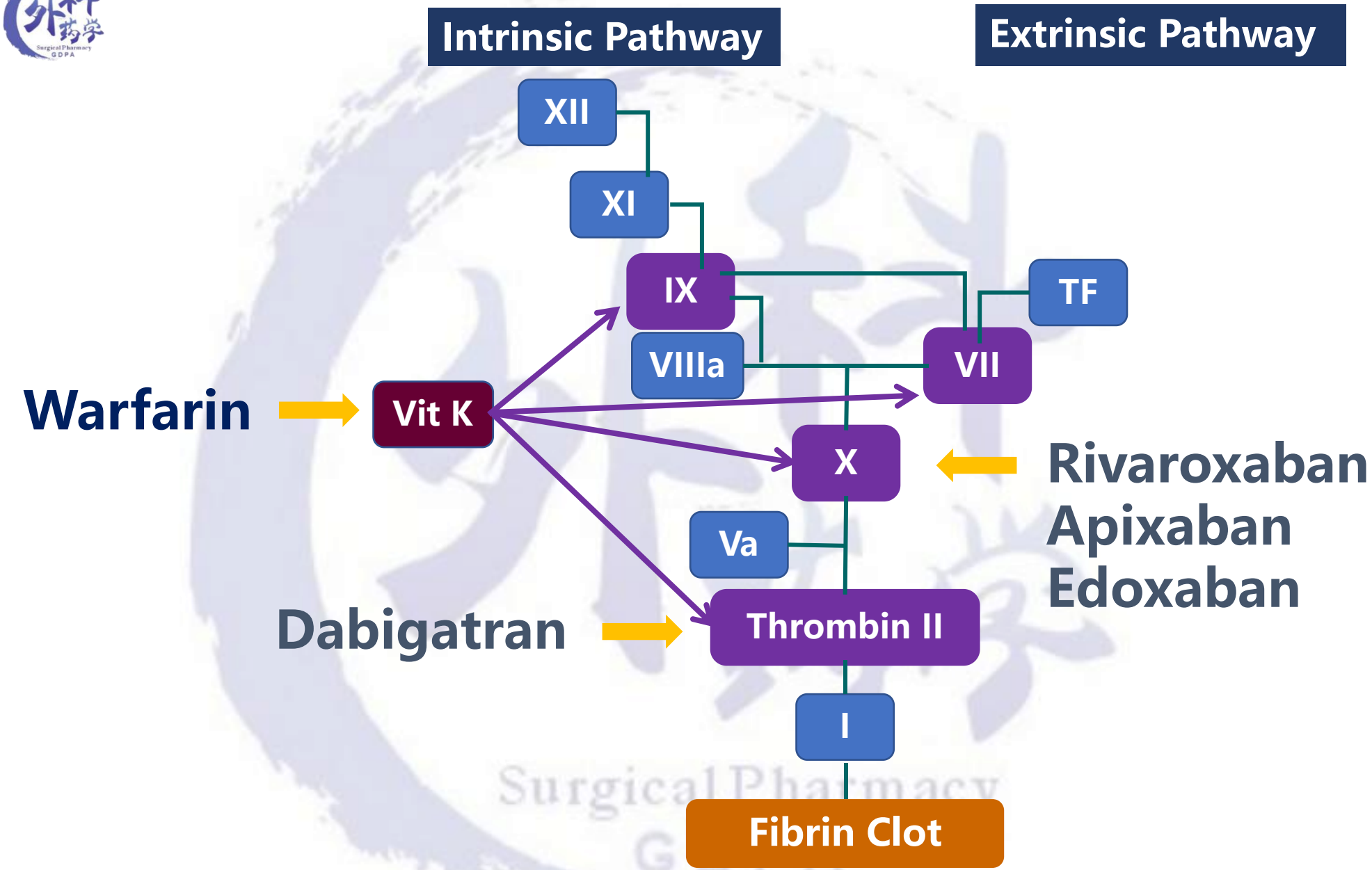

Intrinsic Pathway
Extrinsic Pathway
XII
XI
IX
VIIIa
TF
VII
Warfarin
Vit K
X
Rivaroxaban
Apixaban
Edoxaban
Va
Dabigatran
Thrombin II
I
Fibrin Clot

# Anticoagulant drugs

## Warfarin

| Characteristics | Warfarin |
| --- | --- |
| MOA | Vitamin Kantagonist |
| Peak Effect | 5 days |
| Half-life | 40 hours |
| Reversal agents | Vitamin K or prothrombin complex concentrate (PCC) |

- Target factors: II, VII, IX, X
- Anticoagulant efficacy can be monitored by INR (generally target 2.0-3.0)
- Onset of action in 2-3 days, reaching steady state in about one week
- Numerous drug/food interactions
- Rapid reversal: PCC+IV vitamin k

# Anticoagulant drugs

## DOACs

| Characterristics | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| MOA | Factor lla inhibitor | Factor Xa inhibitor | Factor Xa inhibitor | Factor Xa inhibitor |
| Peak Effect | 2-3 hours | 2-4 hours | 1-3 hours | 1-2 hours |
| Half-life | 12-17 hours | 5-9 hours | 9-14 hours | 9-11 hours |
| Reversal agents | Idarucizumab | Andexanet alfa or PCC | Andexanet alfa or PCC | Andexanet alfa or PCC |

# Anticoagulant drugs

## Heparin

| Characteristics | Low Molecular Weight Heparin | Unfractionated Heparin | Fondaparinux |
|---|---|---|---|
| MOA | Indirect factor Xa/lla inhibitor via AT | Indirect factor Xa/lla inhibitor via AT | Selective factor Xa inhibitor via AT |
| Peak Effect | 20-30 minutes | Instantaneous | 2-3 hours |
| Half-life | 3-5 hours | 45-60 minutes | 17-21 hours |
| Reversal agents | Protamine (70%) | Protamine(100%) | No approved agent |

# Main Detection indicators of Antithrombotic Drugs

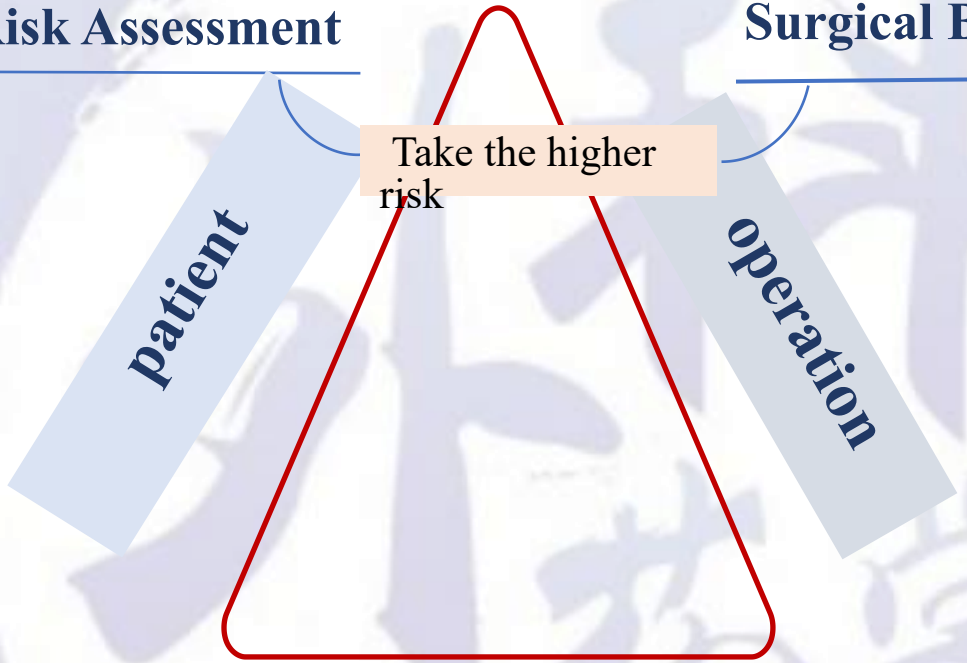
| Antithrombotic Agent | Main Detection Index |
|---|---|
| Antiplatelet Drugs | TEG-AA(Aspirin)<br>TEG-ADP(Clopidogrel)<br>LTA-AA(Aspirin)<br>LTA-ADP(Clopidogrel) |
| warfarin | PT/INR |
| Heparin | APTT<br>Anti-Xa color development method |
| LMWH | Anti-Xa color development method |
| Factor Xa inhibitor | golden standard：LC-MS/MS<br>quantitative test：Anti-Xa color development method<br>qualitative test：PT |
| Oral direct thrombin inhibitors | golden standar：LC-MS/MS法：<br>uantitative test： ECA法；<br>qualitative test：TT |
| Intravenous direct thrombin inhibitors | APTT |

# CONTENT

# Bleeding & Thrombosis Risk Assessment

**Individual Bleeding Risk Assessment**

**Surgical Bleeding Risk Assessment**




**Thrombosis risk**

**Thromboembolism risk assessment**

# Bleeding Associated with Antithrombotic Agents

## Bleeding scoring system

**ATRIA**

**HEMORR2HAGES**

**ORBIT**

**HAS-BLED**

**ABH**

| | ATRIA[11] | HEMORR2HAGES[12] | ORBIT[13] | HAS-BLED[14] | ABH[17] |
|---|---|---|---|---|---|
| Prior bleeding | 1 | 2 | 2 | 1 | 2 |
| Older age | | 1 | 1 | | |
| Age>75 | 2 | | | 1 | |
| Age>65 | | | | 1 | 1 |
| Age 65-75 | | | | | 2 |
| Age<65 | | | | | 0 |
| Renal disease | 3 | 1 | 1 | 1 | |
| Hypertension | 1 | 1 | | 1 | |
| Anemia | 3 | 1 | 2 | | |
| Non-bleeding-related hospitalization in the last 12 months | | | | | 1 |
| Alcohol | | 1 | | 1 | |
| Liver disease | | 1 | | 1 | |
| Stroke | | 1 | | 1 | |
| Platelet abnomality | | 1 | | | |
| Antiplatelet agents | | | 1 | | |
| Aspirin | | | | 1 | |
| INR | | | | 1 | |
| Malignancy | | 1 | | | |
| Genetic factor | | 1 | | | |
| Excessive fall risk | | 1 | | | |
| *Maximum score* | *10* | *12* | *7* | *9* | *5* |
| *High-risk cut-off* | *5* | *4* | *4* | *5* | *4* |



Elgamal H, et al. Best Pract Res Clin Anaesthesiol. 2020;34:141-152. doi: 10.1016/j.bpa.2020.06.002.

# Surgical Bleeding Risk Assessment

| High bleedng nsk procoduros(30-day risk of major boed >2%) | Low/moderate bleeding nisk proceduros(30-dayk of major bleed 0%-2%) | Minimal bleeding risk procedures(30-day isk of major bieod-0%) |
|---|---|---|
| Any major operaton<br>procedure duration >45min) Major surgery with exlensive tissue injury<br>Major orthopedic surgery<br>Urological or gastrointestina sungory<br>Roconstructive plastic surgory<br>Kdney biopsy<br>Colonic polyp resection<br>PEGplacement<br>ERCP<br>Surgery in highiy vascular organs<br>Cardiec,intracranial,o spinal surgery<br>Neuranal anesthesa | AthrosC0py<br>Cutaneous/ymph node biopsios Foovhand surgery<br>Coronary angiography<br>GIT endoscopy +1-biopsy<br>Abdominal hystereclormy<br>Laparoscopic cholocystocomy Abdominal hemia repair<br>Homorhoidal suroery<br>Bronchoscopy+/-biopsy Epidural injocfions | Minor dermatologic procedures<br>Ophthalmological procedures Minor dental procedures<br>Pacemaker or cardoverter defbilator device implantation |

## Risk Stratification Based on Surgical Type

- High bleeding risk: >2%
- Low to moderate risk: 0–2%
- Minimal risk: ~0%

# Surgical bleeding risk assessment

| Bleeding risk | Type of surgery |
|---|---|
| Very Low Risk | Tooth extraction<br>Skin biopsy or excision of skin tumors<br>Cataract surgery |
| Low Risk | Laparoscopic cholecystectomy<br>Laparoscopic hernia repair<br>Non-cataract ophthalmic surgery<br>Coronary angiography<br>Gastrointestinal endoscopy (with or without biopsy)<br>Bone marrow or lymph node biopsy<br>Pericardial, pleural, abdominal, or joint cavity puncture |
| Moderate -High Risk | Other abdominal/thoracic/orthopedic/vascular surgeries<br>Colon polypectomy<br>Prostate or cervical biopsy |
| High Risk | Craniotomy or spinal surgery<br>Major vascular surgery<br>Pneumonectomy<br>Major orthopedic surgery (e.g., hip replacement)<br>Oral and maxillofacial surgery<br>Small bowel anastomosis<br>Kidney biopsy / Multi-site colon biopsy<br>Large colon polypectomy<br>Permanent pacemaker/implantable cardioverter-defibrillator (ICD) placement<br>Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy<br>Major urological surgery (e.g., prostatectomy, bladder tumor resection)<br>Major hepatic surgery (e.g., hepatectomy, liver transplantation, portosystemic shunt or devascularization)<br>Major abdominal surgery (e.g., pancreaticoduodenectomy, biliary tract tumor resection) |

- **When the patient's bleeding risk level and the surgical bleeding risk level differ, the higher risk level should be applied.**

# Embolism Risk Assessment--Stroke

| Clinical Area | Guidelines |
|---|---|
| Non valvular AF | Stratify risk using the CHA2DS2-VASe score |
| Prosthetie heart valve | Stratify risk according to valve type,location,and individual thromboembolie risk factors(AF,history of thromboembolism). |
| VTE | Stratify based on time elapsed since VTEdiagnosis and individual risk factors(cancer,thrombophilia) Elective operation should be deferred for3months after VTE diagnosis. |
| CAD | Elective operation should be deferred for214d for ballon angioplasty,30 days for bare metal stent placement,and iyear for drug-eluting stent placement |
| Stroke | Elective operation should be deferred for 29 months after an ischemic stroke |
| Peripheral arterial disease | Symptomatie patients should be managed in dose consultation with a vascular specialist or vascular surgeon. |

**Indication**

↓

**Stroke risk**

| Condition | $CHA_2DS_2$-VASc score | Points |
|---|---|---|
| C | Congestive heart failure(or left ventricular systolic dysfunction) | 1 |
| H | Hypertension | 1 |
| A2 | Age≥75years | 2 |
| D | Diabetes mellitus | 1 |
| S2 | Prior stroke or TIA or thromboembolism | 2 |
| V | Vascular disease | 1 |
| A | Age 65-74years | 1 |
| Se | Sex category(iLe. female sex) | 1 |

**Stroke prediction in patients with atrial fibrillation**

↓

**Normal sinus rhythm? Other blood clots?**

**0 points:** No anticoagulation needed or only aspirin

**1 point:** Preferred oral anticoagulant or aspirin

**≥2 points:** Oral anticoagulant"

https://doi.org/10.1016/j.bpa.2020.06.002

# Embolism Risk Assessment--VTE

| Provoked | | | Unprovoked |
|---|---|---|---|
| Transient | | Permanent | |
| Major: within the last 3 months | Minor: within the last two months | | |
| Surgery with general anesthesia for > 30 min. *or* Confined to bed in hospital for at least 3 days *or* Caesarean section | Surgery with general anesthesia for < 30 min. or Admission to hospital for < 3 days with an acute illness *or* Pregnancy or puerperium *or* Estrogen therapy *or* Confined to bed out of hospital for at least 3 days with an acute illness *or* Leg injury with reduced mobility for at least 3 days dd | Active cancer with ongoing treatment or Inflammatory bowel diseases | Not exposed to any of these risk factors |
| >10-fold increased risk of recurrent VTE | 3-10-fold increased risk of recurrent VTE | 2-fold increased risk of recurrent VTE | |

The risk of VTE in high-risk years is >10%

The risk of VTE in moderate risk years is 5-10%

The risk of VTE in low-risk years is <5%

Additional risk factors(cancer)need.to be considered as well

Elgamal H, et al. Best Pract Res Clin Anaesthesiol. 2020;34:141-152. doi: 10.1016/j.bpa.2020.06.002.

# CONTENT

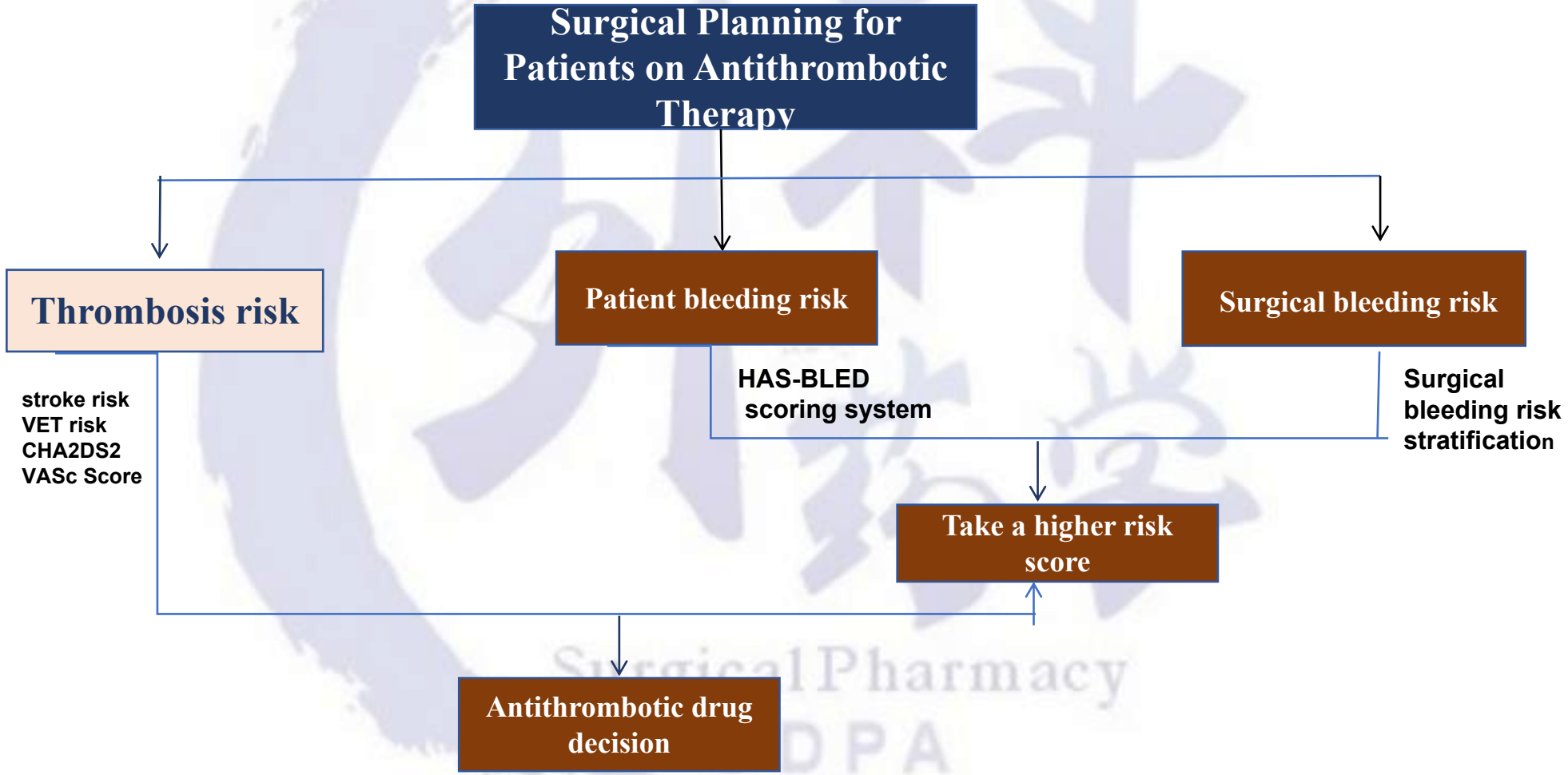
# Withdrawal and bridging strategies of antithrombotic drugs

| Drug | Preoperative Discontinuation | Postoperative Resumption |
|---|---|---|
| Vitamin K Antagonists (e.g., Warfarin) | Discontinue 5 days pre-op (target INR ≤1.5) | 24-72 hours post-op (after hemostasis, often with heparin bridging) |
| Aspirin | Low-bleeding-risk surgery: Continue;<br>High-bleeding-risk surgery: Discontinue 7 days pre-op | 24 hours post-op (if no active bleeding) |
| Clopidogrel/Ticagrelor | Discontinue 5-7 days pre-op | 24 hours post-op (early reassessment for coronary stent patients) |
| NOACs (Rivaroxaban, Apixaban, Dabigatran) | Based on renal function:<br>- Low-bleeding-risk surgery: 24-48 hours pre-op;<br>- High-bleeding-risk surgery: 3-5 days pre-op (CrCl ≥30 ml/min) | 48-72 hours post-op (after confirmed hemostasis) |
| Unfractionated Heparin | IV infusion: Stop 4-6 hours pre-op;<br>Subcutaneous: Stop 12 hours pre-op | 6-12 hours post-op (depending on bleeding risk) |
| LMWH (e.g., Enoxaparin) | Prophylactic dose: Stop 12 hours pre-op;<br>Therapeutic dose: Stop 24 hours pre-op | 24-72 hours post-op (based on surgical bleeding risk) |

# Antithrombotic drug decision

| | | |
|---|---|---|
| Bleeding risk<br>Thromboembolic risk | → | Whether to discontinue medication before surgery |
| Drug half-life<br>Creatinine clearance rate | ⇒ | Timing of medication discontinuation before surgery |
| Drug onset time | → | Timing of postoperative resumption |

# Withdrawal and bridging strategies of antithrombotic drugs



# Bridging strategies for anticoagulant drugs

## ➢ Bridging drug selection

LMWH

## ➢ Bridging contraindications

· Severe renal damage

· Immediate reversal indicated (UFH preferred)

## ➢Creatinine clearance correction dose

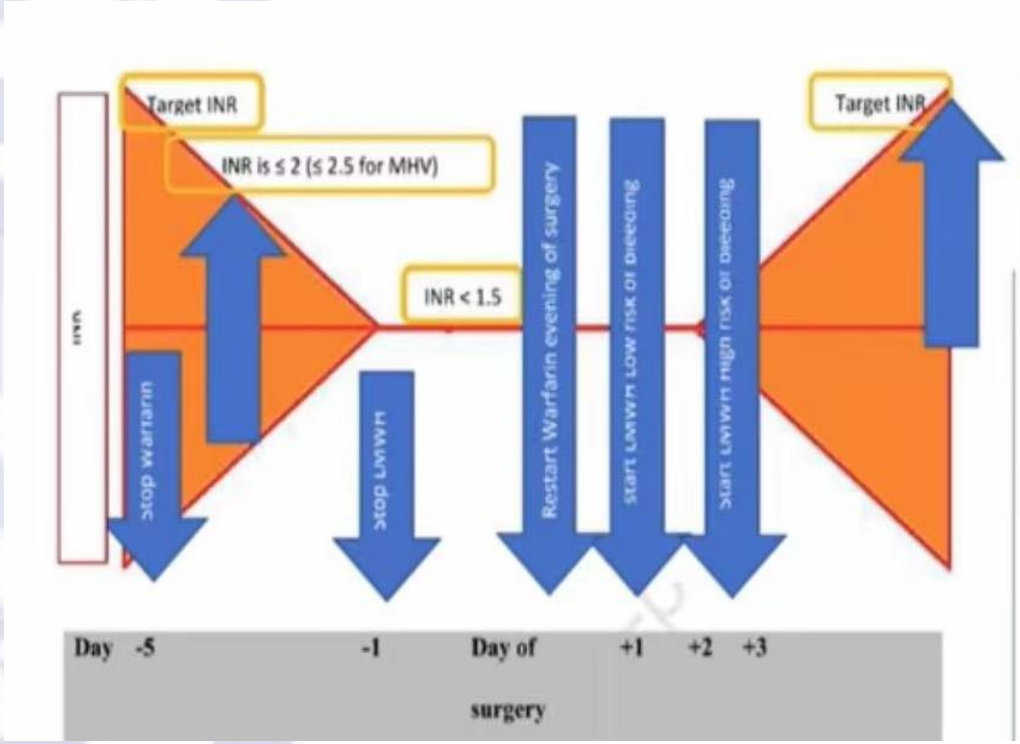
· Crd<30,1mg/kg qd

· Crd≥30,1mg/kg or 1.5mg/kg bid

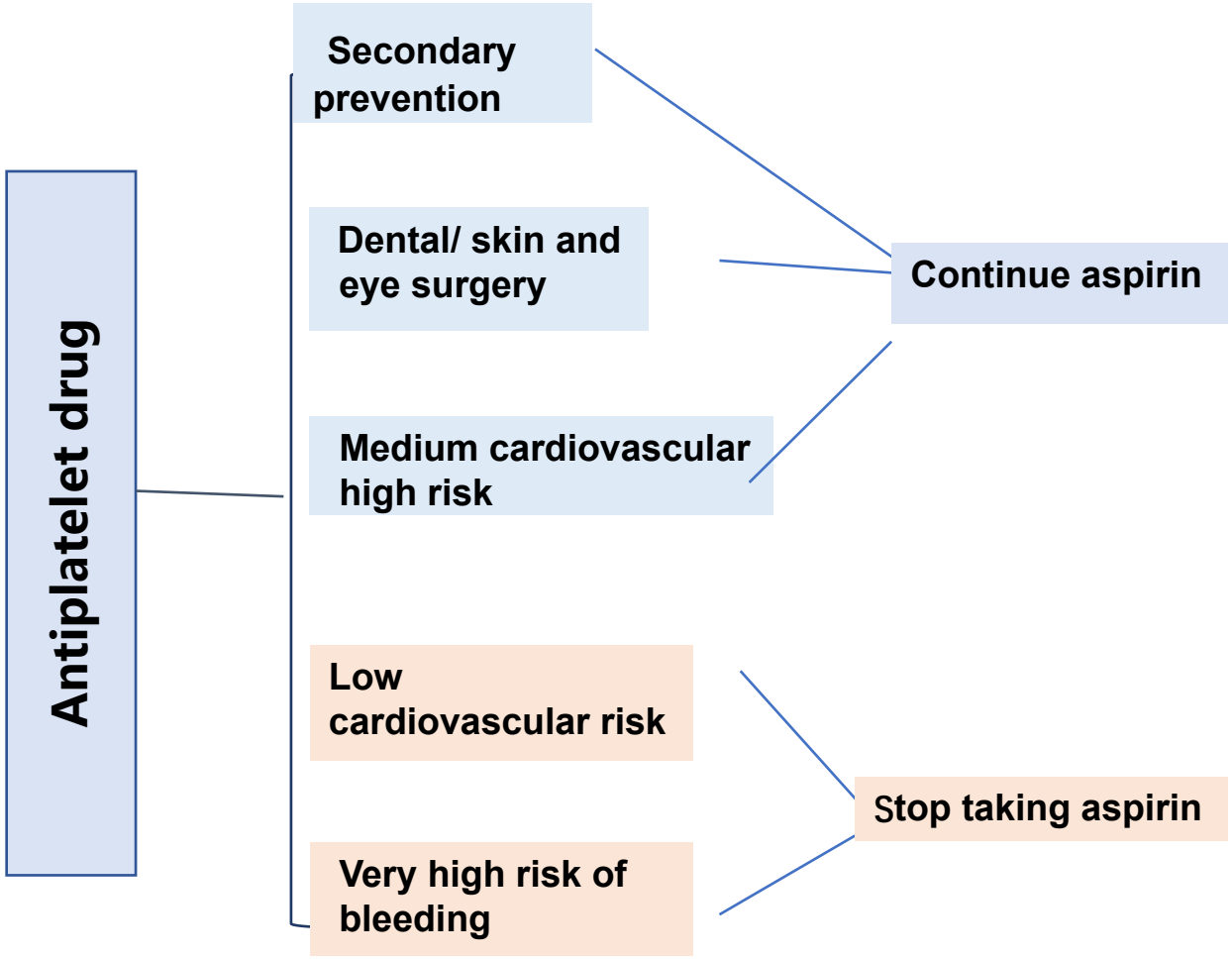
## ➢ Withdrawal and resume timing

· 5 days before surgery;Patients with moderate risk of bleeding 3d

· Time of onset of hemostasis Risk of sufficient bleeding (12-24h after surgery)



# Bridging strategy for antiplatelet agents




## Bridging drug selection

- Short-acting - No evidence to support
- Long-acting - Not recommended (UFH, LMWH, NSAIDs)
- ·Intravenous antiplatelet agents

**Post-PCI 1 month + time-sensitive surgery + high bleeding risk**

- Multidisciplinary consultation
- Bridging with intravenous antiplatelet agents
- Intensive care unit + close monitoring

## Postoperative recovery

- Clopidogrel 600mg loading dose recommended

# Urgent Surgical Management for Patients on Antithrombotics

Vitamin K(1-10mg>30min)
Prothrombin complex concentrate(PCC)(25-50U/kg)
Fresh frozen plasma (FFP)(10-15ml/kg)

UFH- Protamine(1mg vs 80-120U)
LMWH- Protamine (0.5-1mg vs 1mg)
LMWH-Aripazine Under study


Consider platelet transfusion (1 apheresis unit or 10 mg/kg) preoperatively in DAPT patients if platelet function testing is feasible

Clearance is usually 48-72 hours
The dabigatrate-specific antagonist: 5g Edacezumab, can be cleared by dialysis

# Urgent Surgical Management for Patients on Antithrombotics

Reversal of bleeding associated with antithrombotic drugs

- Use PCC + vitamin K for warfarin-induced bleeding.
- Protamine is preferred for hepan reversal.
- Use specific antidotes or hemodialysis for direct thrombin inhibitor bleeding.
- Use specific reversal agents or PCC for factor Xa inhibitor bleeding.
- Give fibrinogen + antifibrinolytics for thrombolytic-related bleeding.
- Reverse antiplatelet bleeding guided by platelet function tests.
- Urgent reversal is needed for surgery-requiring bleeding on antithrombotics.

Clarify present illness history/Past medical and medication history → Bleeding Severity Assessment → Discontinue antithrombotic agents Emergency reversal → Hemostasis Maintain hemodynamic stability

# Perioperative Management of Antithrombotic drug

## ■ Oral antiplatelet agents

If discontinuation is required, stop 5–10 days in advance.

## ■ Anticoagulants

Warfarin: Discontinue 5 days prior, until INR <1.5.
NOACs (DOACs): Generally stop 1–2 days before (earlier if renal impairment).

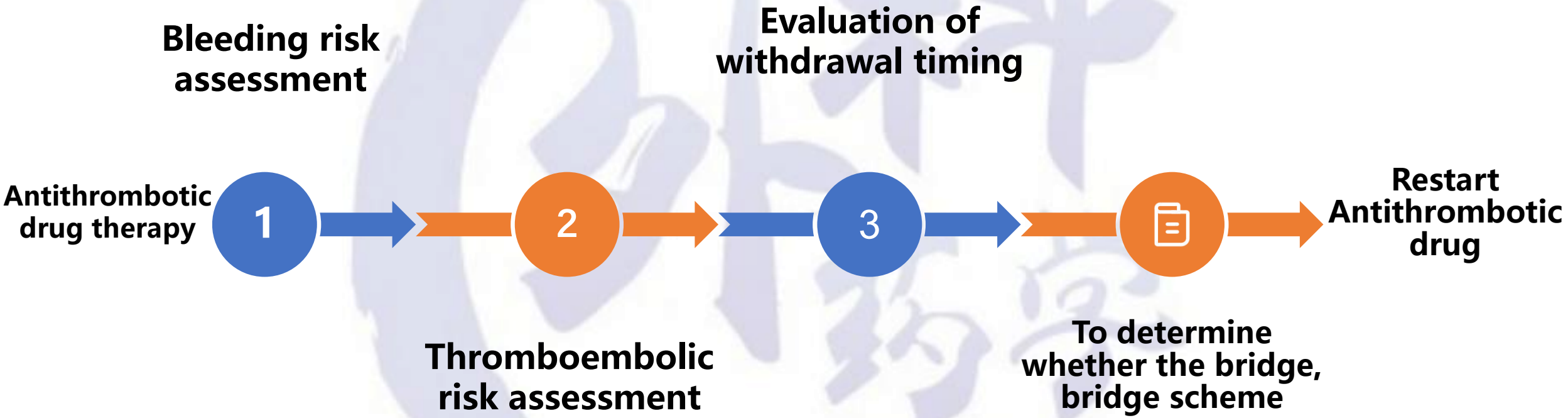
## ■ High thrombotic risk patients( Consider bridging therapy during discontinuation)

Warfarin → Low-molecular-weight heparin (LMWH)
Antiplatelet drugs → Tirofiban

**The management of antithrombotic drugs in perioperative patients should involve a careful balance of benefits and risks, with individualized drug administration.**

# CONTENT

# Perioperative Antithrombotic drug Management Process



# Perioperative pharmaceutical care of antithrombotic therapy

## 一、Bleeding Risk Assessment

- **Patient-specific factors:**

  General condition, age, body weight, hepatic/renal function, coagulation status, etc.

- **Primary disease status**

- **Comorbidities:** Uncontrolled hypertension, active bleeding, etc.

- **Surgical factors:** Procedure type, operative site, duration of surgery

- **Concurrent medications:** Antiplatelet agents, anticoagulants, hemostatics, hormonal drugs, etc.

# Perioperative pharmaceutical care of antithrombotic therapy

## 二、Thrombosis Risk Assessment

- **Patient-specific factors**: General condition, age, body weight, hepatic/renal function, coagulation status, smoking history, etc.
- **Primary disease status**: Based on indications for antithrombotic therapy and relevant risk stratification scores
- **Comorbidities:** Diabetes mellitus, coronary artery disease, stroke, peripheral vascular disease, hyperlipidemia, etc.
- **Hemostatic agents used during surgery**
- **Postoperative immobilization:** Bed rest, restricted turning, indwelling invasive catheters, and other factors contributing to VTE risk

# Perioperative pharmaceutical care of antithrombotic therapy

## 三、Indicators that require monitoring

- **Efficacy evaluation:** Symptoms related to thrombotic events， Diagnostic tests: ECG, color Doppler ultrasound, CTA, MRI
- **Safety evaluation:** Bleeding-related symptoms, allergic reactions, adverse drug reactions (ADRs)， Postoperative drainage volume, blood tests (hemoglobin, platelet count), coagulation parameters, hepatic/renal function tests
- **Assessment of medical order adherence and patient compliance**

# Perioperative pharmaceutical care of antithrombotic therapy

- Discontinue antithrombotic drug at the appropriate time before surgery

- Achieve effective hemostasis postoperatively

- Restart antithrombotic therapy at the optimal postoperative timing

# Thanks for your attention