Anticoagulants and their Monitoring

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Tehran, 5 th congress of IRSTH
10-12 Day, 1404

pediatric thrombosis is a phenomenon recognized worldwide

- Thrombotic events are increasingly recognized in the pediatric population.

- According to recent reports from the United States, the frequency of pediatric VT increased 300%, from 34 /10,000 admissions in 2001 to 106 /10,000 admissions in 2019.

Drug Class of Anticoagulants

A. Parenteral

Unfractionated heparin (UFH)

LMWH: (enoxaparin, dalteparin, …)

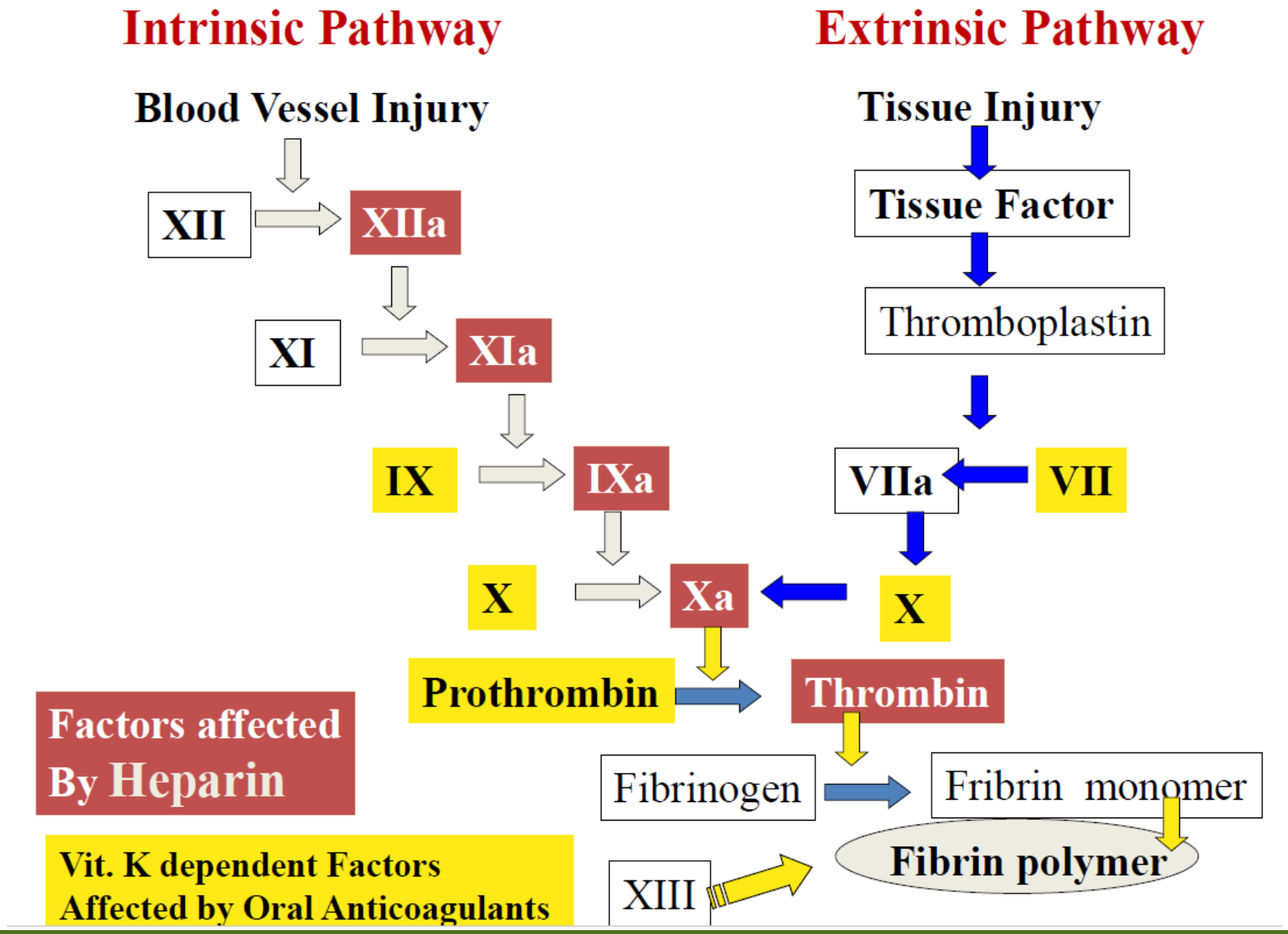
Fondaparinux: (synthetic LMWH, Indirect Xa inhibitor)

Bivalirudin (Direct thrombin inhibitor)

B. Oral

Vitamin K antagonist (warfarin)

DOACs (rivaroxaban, apixaban, edoxaban, dabigatran)


Intrinsic Pathway
Extrinsic Pathway
Blood Vessel Injury
Tissue Injury
XII
XIIa
Tissue Factor
Thromboplastin
XI
XIa
IX
IXa
VIIa
VII
X
Xa
X
Prothrombin
Thrombin
Factors affected
By Heparin
Fibrinogen
Fribrin monomer
Fibrin polymer
XIII
Vit. K dependent Factors
Affected by Oral Anticoagulants

Heparin

Native heparin is a polymer. Molecular weight of most commercial heparin preparations is in the range of 12 to 15 kDa. Heparin is a member of the glycosaminoglycan family. It was originally isolated from dog liver cells.

Heparin is a naturally occurring substance produced by mast cells found mainly in liver, lungs and intestinal mucosa. Commercial heparin is extracted from animal tissues, Porcine intestinal mucosa.

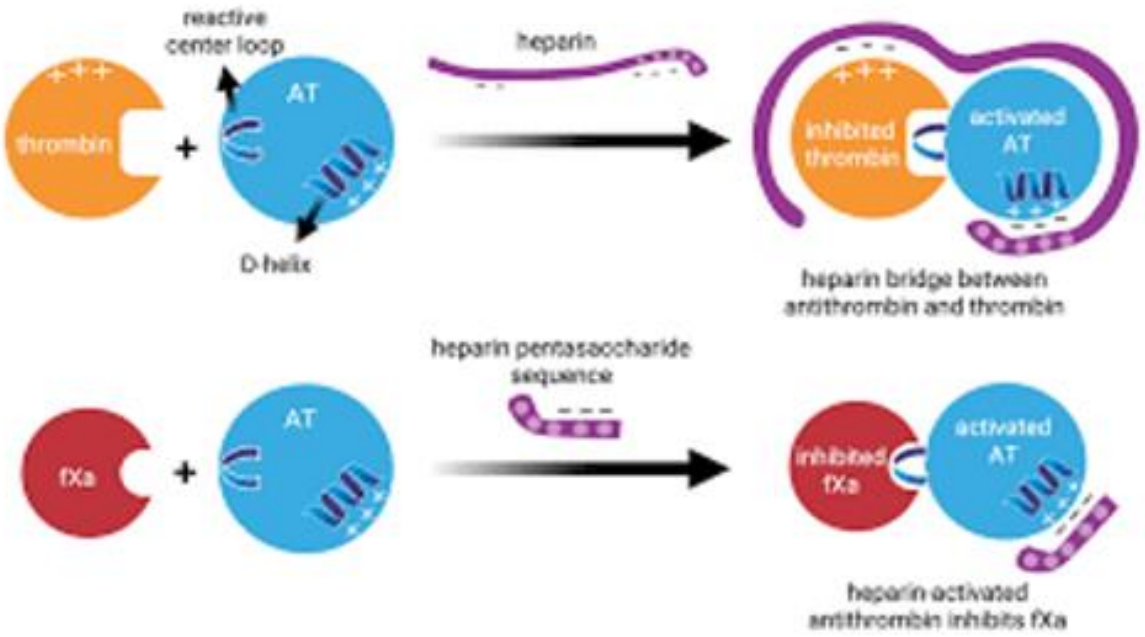
The mechanism of action of heparin is ATIII-dependent. It acts by accelerating the rate of the neutralization of certain activated coagulation factors by antithrombin, but other mechanisms may also be involved. The antithrombotic effect of heparin is well correlated to the inhibition of factor Xa.

Heparin

A polymer of varying chain size

- **Mechanism of action**
- binds to the enzyme inhibitor antithrombin III (AT), causing a conformational change that results in its activation
- The activated AT then inactivates thrombin, factor Xa and other proteases

1 unit of heparin is the amount of heparin that prevents clotting of 1 mL of citrated plasma for 1 hour under standardized laboratory conditions.



Main indications of thrombolytics in children

1. Acute arterial ischemic stroke (AIS): Age ≥2 years, Presentation within time window of 4.5 hours, Large-vessel occlusion, Severe, disabling neurological deficit, No ICH on imaging.

2. Life-threatening VTE:

- Massive pulmonary embolism with cardiac arrest or shock
- Extensive DVT: Limb-threatening ischemia
- Right atrial or intracardiac thrombosis, Prosthetic valve thrombosis.

3. Occluded central venous catheters (Alteplase: catheter-directed, not systemic)

DOACs

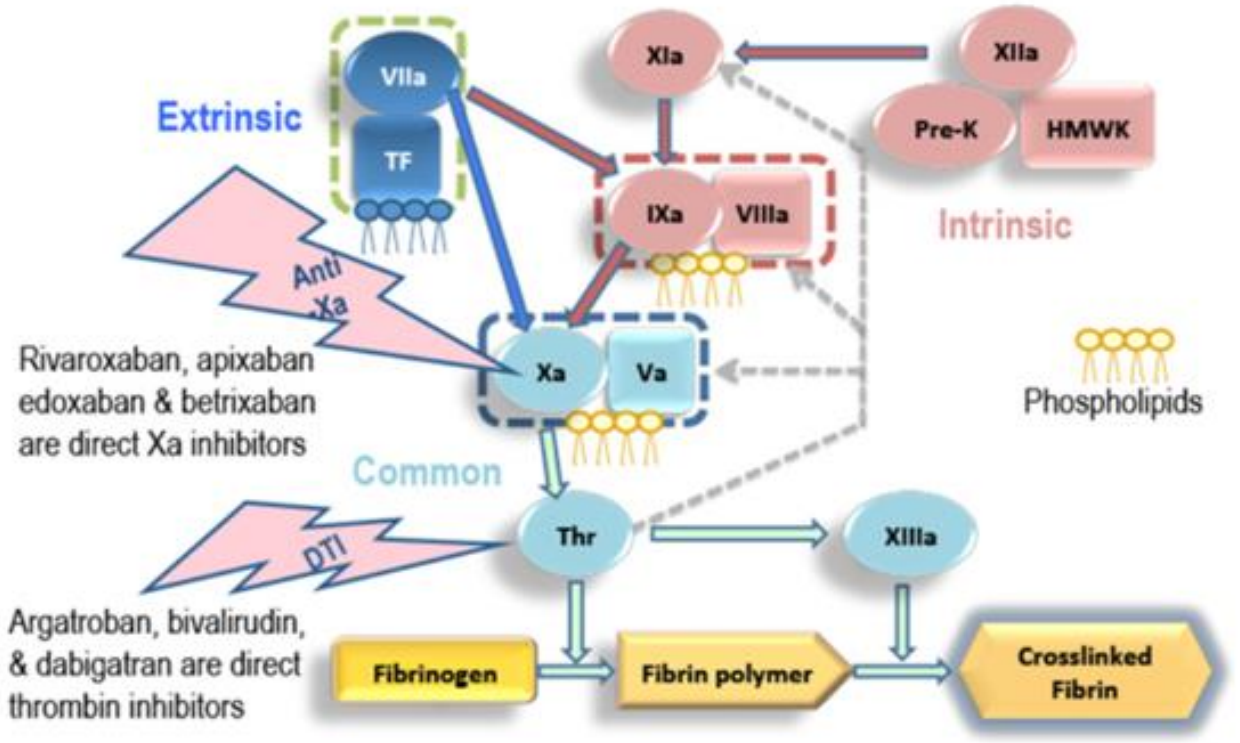
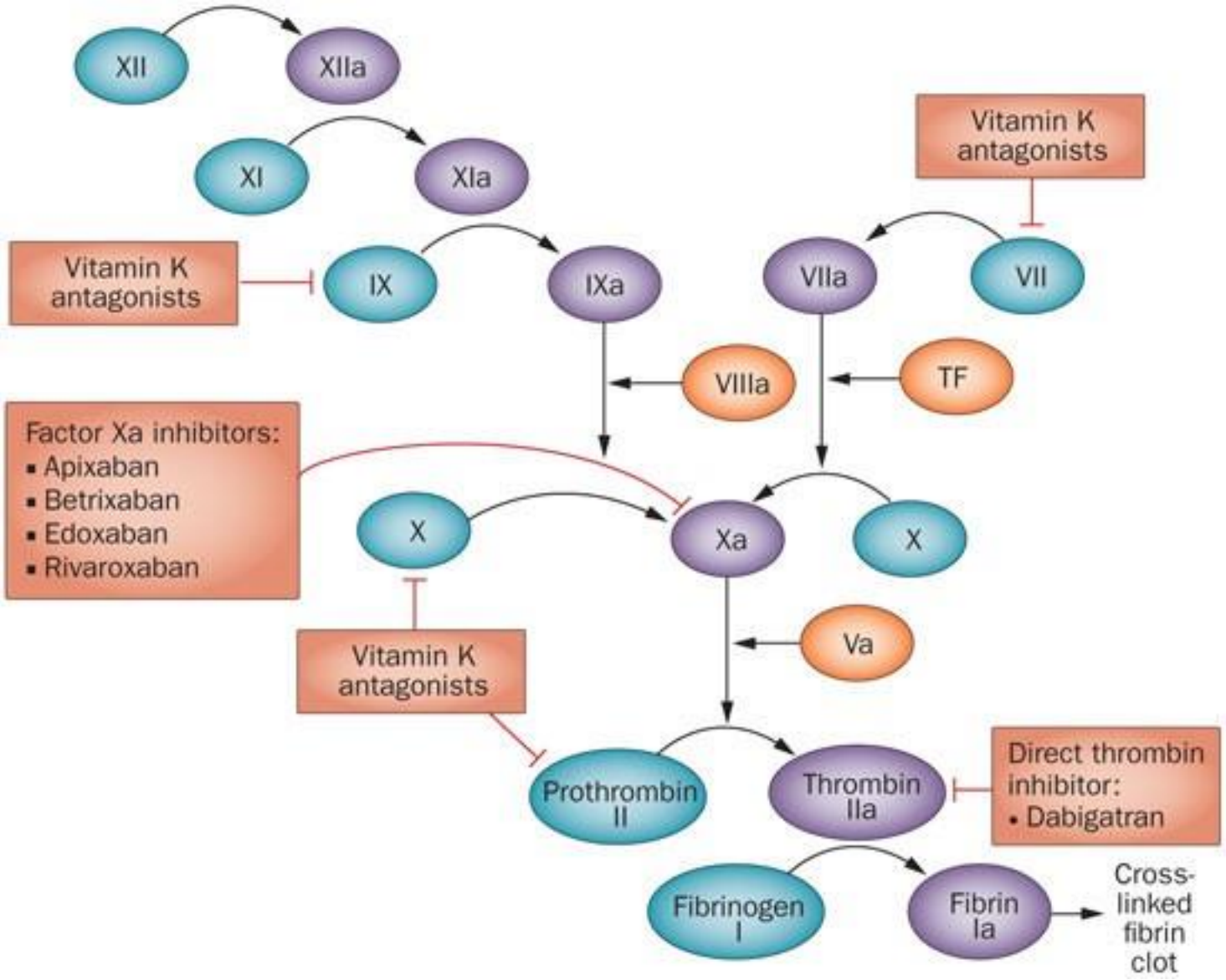


Figure courtesy of George A. Fritsma; The Fritsma Factor, Your Interactive Hemostasis Resource
TF, tissue factor; pre-K, pre-kallikrein; HMWK, high molecular weight kininogen; DTI, direct thrombin inhibitor, Thr, thrombin


XII
XIIa
XI
XIa
Vitamin K antagonists
IX
IXa
Vitamin K antagonists
VIIa
VII
VIIIa
TF
Factor Xa inhibitors:
▪ Apixaban
▪ Betrixaban
▪ Edoxaban
▪ Rivaroxaban
X
Xa
X
Vitamin K antagonists
Va
Prothrombin II
Thrombin IIa
Direct thrombin inhibitor:
• Dabigatran
Fibrinogen I
Fibrin Ia
Cross-linked fibrin clot

The first DOAC was approved by FDA in 2010 in adults.

The EINSTEIN Jr trial resulted in FDA approval of rivaroxaban for treatment of VTE, prevention of recurrent VTE in children from birth to <18 years and post-Fontan prophylaxis (after ≥5 days of initial parenteral anticoagulant).

DIVERSITY trial resulted in FDA approval for dabigatran for treatment of VTE and prevention of recurrent VTE in children 3 months through 17 years, and post Fontan primary prophylaxis in children with congenital heart disease.

More recently, EMA approved apixaban for the treatment of VTE and prevention of recurrent VTE in pediatric patients from 28 days to less than 18 years of age.

Emergence of DOACs

Timeline of Direct Oral Anticoagulants

Pre-2000s (Before DOACs)

- Warfarin (1940s–1990s)
- Heparin & LMWHs 1970s–1990s

Early 2000s Development

- Targeted Anticoagulants
- Focus on Oral Agents

2008–2011 First Approvals

- 2008 Dabigatran
- 2010 AF Stroke Prevention
- 2011 Rivaroxaban

2012–2014 Factor Xa Inhibitors

- Apixaban
- Edoxaban

2015–2020 Reversal Agents

- Idarucizumab
- Andexanet Alfa

2020s & Beyond

- Cancer & VTE
- Special Populations

PRE-2000s → EARLY 2000s → 2008–2011 → 2012–2014 → 2015–2020 → 2020s & BEYOND

From Warfarin to Modern Anticoagulation

DOACs have several potential advantages

- Oral administration
- Predictable effect
- Fewer drug-drug and drug-diet interactions
- Wide therapeutic window
- Lack of need for routine laboratory monitoring
- Do not interact with other coagulation factors resulting in predictable PK.

Anticoagulation Category	Medication Name(s)	Mechanism of Action	Route(s) of Administration
Vitamin K Antagonists	Warfarin, Acenocoumarol, Phenprocoumon	Inhibition of vitamin K epoxy reductase to decrease the synthesis of vitamin K-dependent coagulation factors	Oral
Heparin (Unfractionated)	Heparin	Inhibition of thrombin and several activated coagulation factors (including Xa) by binding to and enhancing the activity of antithrombin III	Intravenous or Subcutaneous paretneral injection
Heparin (Low Molecular Weight)	Enoxaparin, Dalteparin, Tinxaparin, Nadroparin	Binds to antithrombin III and inhibits thrombin to a much lesser extent than unfractionated heparin; primarily inhibits factor Xa	Subcutaneous parenteral injection
Factor Xa Inhibitors	Fondaparinux *, Rivaroxaban, Apixaban, Edoxaban, Betrixaban	Prevents the cleaving of prothrombin by factor Xa to form thrombin	Fondaparinux- Subcutaneous parenteral injection Rivaroxaban, apixban, edoxaban, betrixaban- Oral
Factor IIa Inhibitors (Direct Thrombin Inhibitors)	Dabigatran, Bivalirudin, Argatroban	Directly binds to and inhibit thrombin	Dabigatran- Oral Bivalirudin- Intravenous Argatroban- Intravenous or Subcutaneous parenteral injection

* Fondaparinux, while technically a synthetic low molecular weight heparin, is considered an indirect factor Xa inhibitor.

Biomedicines 2021, 9, 262.

TABLE 1. ADVANTAGES AND DISADVANTAGES OF VARIOUS ANTICOAGULANTS

	UFH	LMWH	VKA	DOAC
Mechanism of action	Binding anti-thrombin III	Binding anti-thrombin III	Inhibits vitamin K–dependent clotting factors II, VII, IX, and X	Direct thrombin or Xa inhibitor
Route and frequency of administration	Intravenous infusion	Subcutaneous injection of 1-2 daily doses	Oral with once-daily dose	Oral with 1-2 daily doses
Mean plasma half-life	Minutes to 1-2 hours	6-12 hours	40 hours	12-14 hours
Monitoring of efficacy	aPTT or Xa (0.3-0.7 U/mL), but poor measure in cirrhosis	None required	INR target range of 1.5 to 2.5*	None required
Role	Initiation of anticoagulation	Initiation or maintenance of anticoagulation	Maintenance of anticoagulation	Maintenance of anticoagulation
Use in pregnancy	Recommended at delivery given rapid reversibility	Recommended throughout pregnancy except at delivery	Contraindicated	Not studied in pregnancy and not recommended
Advantages	Unaffected by hepatic or renal function	Good safety profile in liver disease	Ease of administration	No need for monitoring
	Rapidly reversible effect	Better efficacy in malignancy	Cheap and widely available	Antidote available
	Antidote available	Antidote available	Antidote available	
Disadvantages	Heparin-induced thrombocytopenia	Cannot use with severe renal dysfunction	Drug-drug interaction	Cannot use with severe liver disease (CTP class B or C)
	Need for hospitalization	Subcutaneous route	Drug-food interaction	Expensive and limited experience
			Requires regular monitoring	Absorption may be affected from bowel edema in PHT
			Absorption may be affected from bowel edema in PHT	

Heparins has been a cornerstone for initiation of anticoagulant therapy for more than 60 years. Acutely, UFH and LMWH, are used to initiate anticoagulation.

Various properties including unpredictable PK, interpatient variability, and narrow therapeutic index necessitates close monitoring of UFH.

Two different strategies are commonly used to monitor therapeutic effects of UFH:

activated partial thromboplastin time (aPTT)

Anti factor-Xa (Anti-Xa) heparin assay

ELSEVIER

International Journal of Cardiology

Volume 419, 15 January 2025, 132680

Initial anticoagulation therapy with single direct oral anticoagulant in patients with intermediate-high risk acute pulmonary embolism: From the COMMAND VTE Registry-2

Ryo Shigeno [a], Kitae Kim [a], Yugo Yamashita [b], Takeshi Morimoto [c], Ryuki Chatani [d], Kazuhisa Kaneda [b], Yuji Nishimoto [e], Nobutaka Ikeda [f], Yohei Kobayashi [g], Satoshi Ikeda [h], Moriaki Inoko [i], Toru Takase [j], Shuhei Tsuji [k], Maki Oi [l], Takuma Takada [m], Kazunori Otsui [n], Sakamoto [o], Yoshito Ogihara [p], Takeshi Inoue [q], Shunsuke Usami [r]...Takeshi Kimura [aa]

Conclusions

In this registry, a certain number of patients with intermediate-high risk acute PE were treated with initial single DOAC therapy without parenteral anticoagulation, did not show worse outcomes compared with patients with initial parenteral anticoagulation therapy.

Article published online: 2025-02-19

The Use of DOACs in Pediatrics: Current Therapeutic and Prophylactic Indications, Cardiac Indications, and Real-World Evidence—A Review

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Hamostaseologie 2025;45:89–101.

Current standards to initiate DOACs in children

- **Diagnosis of VTE**
  - Limited experience of DOACs for arterial thrombotic events, stroke
- **Age**
  - Neonates>37 gestational weeks and >2.6 kg or >3rd weight percentile
  - More experience with children aged >2 years
- **Clinically stable patient & low bleeding risk**
  - No immediate procedures planned, no intracranial haemorrhage within 30 days, no severe thrombocytopenia, not post operative, no recent severe trauma
  - Re-evaluate continuously according to patient's evolving clinical presentation
- **No severe renal dysfunction**
  - GFR >30 mL/min/1,73 m² for apixaban
  - GFR >50 mL/min/1,73 m² for rivaroxaban
- **No severe hepatic dysfunction**
  - AST/ALT<3-5xULN, no coagulopathy based on liver dysfunction
- **Adequate oral intake**
  - Oral or nasogastric tube feeding for at least 48h
  - Naso-jejunal tube not optimal due to absorption site of DOACs (generally distal stomach and proximal duodenum)
- **Initial parenteral or subcutaneous anticoagulation for at least 5 days**
- **No relevant drug-drug interactions**
  - Strong inducers or inhibitors of CYP3A4 and/or P-glycoprotein (e.g. Azole antifungals, anticonvulsants, others)
- **Available drug formulations**
  - Able to swallow pills/ liquid/ pellets
- **Dosing regimens from published trials**
  - Age specific dosing regimens based on PK (increased clearance at younger ages)
  - Adapt dosing to body weight regularly
- **No triple positive antiphospholipid-syndrome (limited paediatric data)**
- **No mechanical heart valve (limited paediatric data)**

Fig. 2 Current standards to initiate DOACs in children—based on inclusion and exclusion criteria of clinical trials. DOAC, direct oral anticoagulant; VTE, venous thromboembolic events; GFR, glomerular filtration rate; AST, aspartate transaminase; ALT, alanine amino-transferase; PK, pharmacokinetics; ULN, upper limit of normal.

UNFRACTIONATED HEPARIN (IV)

Monitoring test Target:

aPTT: 1.5–2.5 × control (60–80 seconds)

Anti-Xa: 0.3–0.7 IU/mL

Start bolus + infusion: Loading 75 units/kg, IV over 10 minutes. Maintenance: 28 units/kg/h (< 1 year of age): 20 units/kg/h (> 1 year of age).

Check aPTT 6 hours after initiation and 6 hours after each dose change.

Adjust infusion per nomogram: 1.5–2.5 × control (60–80 seconds)

Once at therapeutic range → monitor daily

Additional monitoring

Platelets: every 2–3 days (days 5–15) to detect HIT

Stop if:

Platelet drop >50%

Major bleeding

UFH Titration Nomogram

aPTT times of normal	Bolus (units/kg)	Dose change (units/kg/h) (increase or decrease of bolus dose)	Intervals of testing aPTT (h)
<2	50	20% increase	4
2	–	10% increase	4
>2	–	No change	4
2½	–	No change	24
>2½[a]	–	10% decrease	4
>3[b]	–	20% decrease	4

[a] *Hold the dose 30 min.*

[b] *Hold the dose 1 h.*

Note: Heparin solution at concentrations of 80 units/mL for children 10 kg or less or 40 units/mL for children greater than 10 kg.

Heparin therapy

1. Initiate bolus of 80 units/kg (provider may choose not to order an initial bolus)
2. Start infusion at 18 units/kg/hr.
3. Titrate per table below:

PTT	Repeat bolus	Stop infusion	Dose change
< 40	60 unit/kg	-	Increase by 3 units/kg/hr
40-49.9	30 unit/kg	-	Increase by 2 units/kg/hr
50-59.9	-	-	Increase by 1 unit/kg/hr
60-80	-	-	No change
80.1-100	-	-	Decrease by 2 units/kg/hr
> 100	-	60 min Call House Officer to confirm dose change	Decrease by 3 units/kg/hr (if confirmed by House Officer)

Figure 1. Unfractionated heparin (UFH) titration nomogram for goal PTT 60-80. PTT indicates partial thromboplastin time.

When heparin is interrupted for more than 1 hour, reestablish the heparin infusion at the previous rate. After that, administer heparin in accordance with the aPTT results.

Prophylactic dosing of UFH is 10 units/kg/h has been commonly used.

When the platelet count is <100,000, discontinue heparin therapy and consider alternative therapy, because the risk of HIT is greater after 5 days of therapy.

Avoid aspirin or other antiplatelets and IM injections during heparin therapy.

The anti-Xa should be monitored after a therapeutic aPTT is achieved in order to ensure a level between 0.35 and 0.70 units/mL.

Heparins Monitoring

Both HEPARINS are safe for use in patients with severe liver disease/cirrhosis. However, aPTT prolongation at baseline in patients with cirrhosis may confound the monitoring.

In liver disease, **aPTT may be prolonged at baseline** and **AT may be low**, so **aPTT becomes unreliable** and UFH effect may be **unpredictable**.

In liver disease, UFH should be monitored with anti-Xa levels and not aPTT.

Due to its short half-life, UFH is also useful in situations such as hemodynamic instability and invasive procedures.

UFH is preferred for patients with severe renal dysfunction.

What happens when you give UFH in cirrhosis

a) Baseline aPTT already prolonged

- UFH further prolongs PTT and You **cannot interpret aPTT**
- Risk of **underdosing** if you reduce UFH because aPTT “looks high”.

b) Low antithrombin

- UFH effect is **blunted** (heparin resistance)
- aPTT may not rise appropriately **despite therapeutic dosing**

How to monitor UFH in liver disease

Test	Use in cirrhosis
aPTT	❌ Unreliable
Anti-Xa	✅ Best test

Target anti-Xa for UFH : **0.3–0.7 IU/mL** (institution-dependent)

📌Anti-Xa measures **actual heparin activity**, independent of:

Clearance of UFH

UFH is cleared mostly by the reticuloendothelial system (liver/spleen), not renal.

Renal impairment has minimal effect on UFH pharmacokinetics.

No dose adjustment is needed for renal impairment in most cases.

UFH is preferred in severe renal dysfunction because it is not renally accumulated and reversible with protamine.

Patient comorbidities may affect monitoring UFH. A patient with an active infection may have a large burden of inflammatory mediators that elevate the aPTT. In this case, the anti-Xa may be considered more reliable and indicative of the degree of anticoagulation.

Adjusting UFH, particularly in critically ill patients requires assessment of the clinical scenario and may warrant the use of multiple coagulation tests.

Why TEG in liver disease

- TEG is a whole-blood test that assesses global hemostasis in real time, showing how a clot forms, strengthens, and breaks down.
- PT/INR is often prolonged in liver disease but does not reflect true bleeding.
- TEG often shows balanced or even hypercoagulable states.
- Guides targeted blood product therapy
- Normal TEG despite high INR → do NOT transfuse prophylactically

Low-molecular-weight heparin: No routine monitoring is required

- LMWHs preferentially inhibit FXa over thrombin.
- Infants have accelerated clearance of LMWH compared to older children.
- The advantages of LMWH include reduced frequency for monitoring, reduced risk of HIT and lack of interference by other drugs or diet.

Adjusting LMWH dose

The dose of LMWH can be adjusted according to the antifactor Xa level achieved

Anti-FXa level (units/mL)[a]	Dose
<0.35	25% increase
<0.5	10% increase
0.5–1.0	No change
>1.0	20% decrease
>1.5	30% decrease
>2.0	Hold for 24 h

[a]Repeat anti-FXa level 4 h post next dose until 0.5–1.0 units/mL, then once weekly at 4 h postdose.

Lanzkowsky's Manual of Pediatric Hematology and Oncology

Monitoring of LMWH therapy

If the platelet count drops to < 100,000, HIT must be ruled out; it rarely occurs with LMWH therapy.

Post-treatment anti-FXa level should be determined after three doses, 4-6 hours after last SC administration; then, weekly monitoring.

The therapeutic anti-FXa level is 0.5-1.0 units/mL and prophylactic anti-FXa level is 0.1-0.3 units/mL.

Antidote for LMWH: Termination of LMWH is usually sufficient.

When an immediate effect is required, 1-mg protamine per 100 units (1 mg) of LMWH may be given. It is not as effective as when used for UFH.

Anti-Xa measures the functional activity of factor Xa inhibition in plasma

Drugs monitored by Anti-Xa

✓ **Heparins**

- **UFH**
- **LMWH**
- **Fondaparinux**

→ Anti-Xa measures **heparin–antithrombin mediated Xa inhibition**.

✓ **DOACs (factor Xa inhibitors)**

Anti-Xa can detect presence/effect **if calibrated specifically**, but:

- Not used for routine monitoring
- Different calibration needed than heparin assays

LMWH monitoring

- Routine monitoring not usually needed in normal renal function.
- Clearance of LMWH is primarily by kidneys. Renal impairment (CrCl <30 mL/min) → accumulation → increased bleeding risk.
- Measure anti-Xa levels 4 hours post-dose (peak).
- Target anti-Xa (for treatment dose) are typically:
  - 0.6–1.0 IU/mL for twice-daily dosing
  - 1.0–2.0 IU/mL for once-daily dosing
- Dose adjustments: Reduce dose or switch to UFH if severe renal impairment.

UFH vs LMWH in liver disease

	UFH	LMWH
Monitoring test	Anti-Xa	Usually none
AT dependence	High	Less
Reversibility	Protamine (complete)	Partial
Use in unstable/ICU	✓	⚠
Renal failure	Preferred	Avoid if severe

4Ts Score for Heparin-Induced Thrombocytopenia

Component	2 points	1 point	0 points
Thrombocytopenia	Platelet fall >50% AND nadir ≥20 $\times 10^9$/L	Platelet fall 30–50% OR nadir 10–19 $\times 10^9$/L	Platelet fall <30% OR nadir <10 $\times 10^9$/L
Timing of platelet fall	Clear onset day 5-10, OR ≤1 day if heparin exposure within last 30 days	Consistent with day 5-10 but unclear, OR ≤1 day if exposure within last 30-100 days	Platelet fall <4 days without recent exposure
Thrombosis or sequelae	New thrombosis, skin necrosis, or acute systemic reaction after IV heparin	Progressive/recurrent thrombosis OR suspected thrombosis	None
other causes of thrombocytopenia	No other cause evident	Possible other cause	Definite other cause

HIT is unlikely (score 0-3) , HIT is possible (score 4-5) , HIT is likely (score 6-8)
https://www.mdcalc.com/calc/1787/4ts-score-heparin-induced-thrombocytopenia

Heparin antidote

- If heparin needs to be discontinued, termination of the heparin infusion will be sufficient (because of the rapid clearance of heparin).
- If an immediate effect is required, protamine sulfate administration may be indicated. Following administration of IV protamine sulfate, neutralization occurs within 5 minutes. Repeat aPTT 15 min after administration of protamine sulfate.

Last dose of heparin	Protamine dose[a] (per 100-mg heparin)
<30 min	1 mg
30 min	0.5 mg
1 h	0.75 mg
>1 h	0.375 mg
>2 h	0.25 mg

Maintenance of Anticoagulation

Warfarin has been drug of choice for long-term anticoagulation.

The onset of effect of warfarin and the time to therapeutic effect are partially dependent on its PK properties and half-life of coagulation factors.

The average elimination half-life of warfarin, is approximately 30 hours. warfarin must be dosed daily for 4 to 5 days to reach steady state.

For dose adjustment of VKA, therapeutic level of INR should be maintained between 2-3.

Warfarin

A loading dose of 0.2 mg/kg as a single daily dose (maximum 10 mg) should be employed when the INR <1.3.

When INR>1.3, reduce the loading dose to 0.1 mg/kg.

For a patient having undergone a Fontan procedure or liver dysfunction, the daily dose should be reduced by 50%.

The subsequent dose is age dependent (infants having the highest 0.3 mg/kg and teenagers the lowest 0.1 mg/kg and based on the INR response.

Warfarin loading period is approximately 3-5 days for most patients before a stable maintenance phase is achieved.

The INR should be obtained 5-7 days after initiating a new dose.

To facilitate absorption the patient is instructed to take it on an empty stomach or 2 hours after a meal, without any other medications.

Warfarin Maintenance

- Warfarin should be started on day 1-2 of heparin therapy. Heparin should be continued for a minimum 5 days. When the target INR is 2 for 2 consecutive days and at least 5 days of heparin are completed, heparin can be discontinued.
- For extensive DVT with or without PE, warfarin should be started on day 5 of heparin therapy.
- Children with mechanical heart valves require an INR between 2.5-3.5.
- Once the patient has two INRs between 2-3 (or 2.5-3.5 for mechanical valves)/weekly, the INR determinations could be carried out every 2 weeks. If the INR remains stable, the INR could be determined once monthly.
- Children with a thrombotic event and a persistent, significant, predisposing factor (e.g., continued presence of a central venous catheter, persistence of an APLA) may be placed on low-dose warfarin (0.1 mg/kg) target INR: 1.5-2.0 following 3 months of treatment with full-dose warfarin until the predisposing factor is present.

Warfarin daily loading doses (approximately 3–5 days)

INR[a]	Warfarin loading doses
1.1–1.3	Repeat initial loading dose
1.4–1.9	50% of initial loading dose
2.0–3.0	50% of initial loading dose
3.1–3.5	25% of initial loading dose
>3.5	Hold until INR <3.5, then restart at 50% less than previous dose

Warfarin maintenance doses for long-term therapy

INR	Warfarin dose
1.1–1.4	Increase dose by 20%
1.5–1.9	Increase dose by 10%
2.0–3.0	No change
3.1–3.5	Decrease dose by 10%
>3.5	Hold until INR < 3.5, then restart at 20% less than previous dose

General principles of dose adjustment of Warfarin

Adjust	Adjust total weekly dose, not just a single day dose, because warfarin dose changes should be made by changing the sum of all doses taken over one week, rather than just increasing or decreasing a single day's dose.
Avoid	Avoid large or frequent changes, Recheck INR 3-7 days after a dose change.
Consider	Consider diet, drugs, illness, adherence before changing dose.

Warfarin maintenance doses for long-term therapy

INR	Warfarin dose
1.1–1.4	Increase dose by 20%
1.5–1.9	Increase dose by 10%
2.0–3.0	No change
3.1–3.5	Decrease dose by 10%
>3.5	Hold until INR < 3.5, then restart at 20% less than previous dose

Example: Current regimen:

5 mg every day

Total weekly dose = **35 mg**

INR is slightly low (e.g., 1.7) → increase by ~10%

New weekly dose:

35 mg + 10% = **38.5 mg/week**

How to prescribe it:

Instead of “just one extra pill,” you spread the increase across the week.

6 mg on 3 days

5 mg on 4 days
= **38 mg/week**

INR monitoring and Warfarin in Liver disease

- Baseline PT&INR is often elevated among patients with cirrhosis, making INR an unreliable test for monitoring VKA therapy in patients with cirrhosis.
- INR is not a predictor of bleeding or not reliable to monitor the efficacy of hemostasis in patients with cirrhosis.
- In Liver disease, thrombin generation tests or TEG may perform better indication for predicting bleeding risk than INR.
- In general, target INR for patients with cirrhosis is a goal INR of 1.0 higher than baseline, if the baseline INR is >1.5.

Half-life of warfarin , heparin and LMWH

Drug	Half-life	Duration of Action	Monitoring	Reversal
Warfarin	36–42 h	2–5 days (depends on clotting factor depletion)	INR	Vitamin K, PCC, FFP
Unfractionated Heparin (UFH)	1–2 h	Hours	aPTT	Protamine sulfate
LMWH (Enoxaparin)	4–6 h	~12–24 h	Usually none (anti-Xa if needed)	Protamine (partial)

Warfarin = "W" for Weeks (long effect) , **Heparin = "H" for Hours , LMWH = "Longer" heparin**

Warfarin Reversal

1- INR ≥10, no active bleeding:

Consider FFP or PCC

2- Active Bleeding (Any INR Elevation):

FEIBA: 50 units/kg OR Kcentra (4-factor PCC): 25–50 units/kg

Vitamin K: 0.5 mg IV, slow infusion over 20 minutes

Warfarin Perioperative Anticoagulation Management

INR Targets Prior to Procedures

1- Low-risk (for bleeding) procedures: INR should be reduced to ≤1.5 prior to procedure.

2- High-risk surgery (for bleeding) : Discontinue warfarin 72 hours prior surgery

Warfarin Perioperative management in surgical procedures with low risk of thrombosis (No Recent Thrombosis)

- Stop warfarin 72 hours before surgery
- No bridging anticoagulation
- Resume warfarin maintenance dose the day after surgery

Warfarin Perioperative management in surgical procedures with high risk of thrombosis (Bridging Required)

➢ Preoperative

- Stop warfarin 72 hours before surgery
- Start LMWH: 1 mg/kg SC every 12 hours and discontinue LMWH 24 hours prior to surgery
- If using UFH: stop 6 hours prior to surgery
- If INR >1.5 at 12 hours pre-op:

  Give Vitamin K1: 0.5 mg SC

  Recheck INR ~6 hours later

➢ Postoperative

- Resume **UFH**: **~8 hours post-op**
- Resume **LMWH**: **~12 hours post-op**, once surgical clearance obtained
- Balance bleeding vs thrombotic risk

➢ Warfarin Re-initiation

- Resume **oral warfarin on postoperative day 2** if no bleeding.
- Continue LMWH/UFH until **two consecutive INRs are therapeutic.**

Anticoagulant	Mechanism	Dose	Monitoring	Half-life (h)	Reversal agent
Fondaparinux	Indirect FXa inhibitor	0.1 mg/kg sc daily	Anti-Xa levels calibrated 0.5–1 IU/mL	17–21	rVIIa
Rivaroxaban	Direct FXa inhibitor	15 mg PO BID × 21 days → 20 mg PO daily (adult)	Anti-Xa levels calibrated	5–9	Four-factor PCC (Kcentra, Octaplex) 50 units/kg Andexanet alfa
Apixaban	Direct FXa inhibitor	10 mg PO BID × 7 days → 5 mg PO BID daily (adult)	Anti-Xa levels calibrated	12	Andexanet alfa

Maintenance of Anticoagulation with DOACs

- There is a safety concern in patients with cirrhosis due to increased drug levels in patients with severely reduced hepatic function and potential of drug-induced liver injury with these drugs.

- In general, DOACs are not recommended for use among patients with advanced cirrhosis.

- Compared with traditional anticoagulation with warfarin, use of DOAC is associated with similar or lower risk for bleeding in patients with cirrhosis.

Monitoring of DOACs

Test	Xa inhibitors	Dabigatran
PT/INR	Variable, unreliable	Usually normal
aPTT	Usually normal	Prolonged (qualitative)
Thrombin time (TT)	Normal	Very sensitive (↑)
ACT	Minimal effect	Prolonged
Anti-Xa (heparin-calibrated)	Unreliable	N/A

DOACs have **predictable pharmacokinetics.**

Routine monitoring is not needed.

DOACs half-life, clearance, and monitoring

Drug	Target	Half-life	Dosing	Renal Clearance	Monitoring	Reversal Agent
Dabigatran	Direct thrombin (IIa)	12–17 h	BID	~80%	None	Idarucizumab
Apixaban	Factor Xa	~12 h	BID	~25%	None	Andexanet alfa
Rivaroxaban	Factor Xa	5–9 h (young) 11–13 h (elderly)	QD	~33%	None	Andexanet alfa
Edoxaban	Factor Xa	10–14 h	QD	~50%	None	Andexanet alfa

Table 5. DOAC Laboratory Monitoring

Drug Name	Qualitative			Quantitative				Other	
	aPTT	TT	PT	Anti-FXa Levels	Plasma Drug Concentration	dTT	ECT	CBC	CMP
Dabigatran	x	x	x		x	x	x	x	x
Rivaroxaban			x	x	x			x	x
Apixaban			x	x	x			x	x
Edoxaban			x	x	x			x	x
Betrixaban				x	x			x	x

aPTT indicates activated partial thromboplastin time; CBC, complete blood count; CMP, comprehensive metabolic panel; dTT, dilute thrombin time; ECT, ecarin thrombin time; FXa, activated factor X; PT, prothrombin time; and TT, thrombin time.

Pediatric Rivaroxaban Dosing for VTE

- **Start rivaroxaban after ≥ 5 days of parenteral anticoagulation** (e.g., LMWH or UFH).
- **Weight-based dosing is essential**; children < 6 months may not be recommended unless specific criteria are met (≥10 days oral feeding, ≥ 2.6 kg body weight).
- Doses should be taken **always with food** to improve absorption.

Pediatric Rivaroxaban Dosing for VTE

Body weight (kg)	Dose per administration	Dosing frequency	Total daily dose
2.6–2.9	0.8 mg	Every 8 h	2.4 mg
3–3.9	0.9 mg	Every 8 h	2.7 mg
4–4.9	1.4 mg	Every 8 h	4.2 mg
5–6.9	1.6 mg	Every 8 h	4.8 mg
7–7.9	1.8 mg	Every 8 h	5.4 mg
8–8.9	2.4 mg	Every 8 h	7.2 mg
9–9.9	2.8 mg	Every 8 h	8.4 mg
10–11.9	3.0 mg	Every 8 h	9.0 mg
12–29.9	5 mg	Every 12 h	10 mg
30–49.9	15 mg	Once daily	15 mg
≥ 50	20 mg	Once daily	20 mg

Pediatric Apixaban Dosing for VTE (EU/EMA)

Start apixaban after ≥ 5 days of initial parenteral anticoagulation (e.g., LMWH or UFH)

💊 Children ≥ 35 kg

- Days 1–7: Apixaban 10 mg twice daily
- Day 8 and beyond: Apixaban 5 mg twice daily

💊 Children < 35 kg

Body weight (kg)	Days 1–7 (acute phase)	Day 8 and beyond (maintenance)
4–<5 kg	0.6 mg BID	0.3 mg BID
5–<6 kg	1 mg BID	0.5 mg BID
6–<9 kg	2 mg BID	1 mg BID
9–<12 kg	3 mg BID	1.5 mg BID
12–<18 kg	4 mg BID	2 mg BID
18–<25 kg	6 mg BID	3 mg BID
25–<35 kg	8 mg BID	4 mg BID
≥ 35 kg	10 mg BID	5 mg BID

Renal Clearance of DOACs

	% Renal Excretion	Renal Safety Implication
Apixaban	**~27% (lowest)**	**Best choice in CKD**
Rivaroxaban	~33%	Use caution in CKD
Edoxaban	~50%	More renal dependence
Dabigatran	**~80% (highest)**	**Avoid in renal dysfunction**

Renal dose adjustments of DOACS

DOAC	CKD preferred	Avoid when
Apixaban	✅ Yes	CrCl <15
Rivaroxaban	⚠️ Moderate	CrCl <30
Edoxaban	⚠️ Moderate	CrCl <15
Dabigatran	❌ No	CrCl <30

DOACs in Hepatic Impairment

DOACs depend on hepatic metabolism → liver disease is a major limitation

Child–Pugh class	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
A (mild)	✅ Use	✅ Use	✅ Use	✅ Use
B (moderate)	⚠️ Caution	❌ Avoid	⚠️ Caution	⚠️ Caution
C (severe)	❌ Contraindicated	❌ Contraindicated	❌ Contraindicated	❌ Contraindicated

Timing of DOAC cessation

Low bleeding-risk procedures (e.g. dental work, central line, LP)

Renal function	Apixaban /Rivaroxaban /Edoxaban	Dabigatran
Normal renal function	Stop 24 h before	Stop 24 h before
CrCl 30–49	Stop 24–36 h before	Stop 48 h before
CrCl <30	⚠ Specialist advice	❌ Avoid dabigatran

Timing of DOAC cessation in High bleeding-risk procedures (major surgery, neurosurgery, spinal/epidural)

Renal function	Apixaban / Rivaroxaban / Edoxaban	Dabigatran
Normal renal function	Stop 48 h before	Stop 48–72 h before
CrCl 30–49	Stop 72 h before	Stop 96 h before
CrCl <30	❌ Avoid DOACs	❌ Contraindicated

Betrixaban

- **Adults:** Betrixaban is FDA-approved in adults for VTE prophylaxis in high-risk medically ill hospitalized patients (initial dose 160 mg, then 80 mg once daily for 35–42 days).
for 35–42 days).

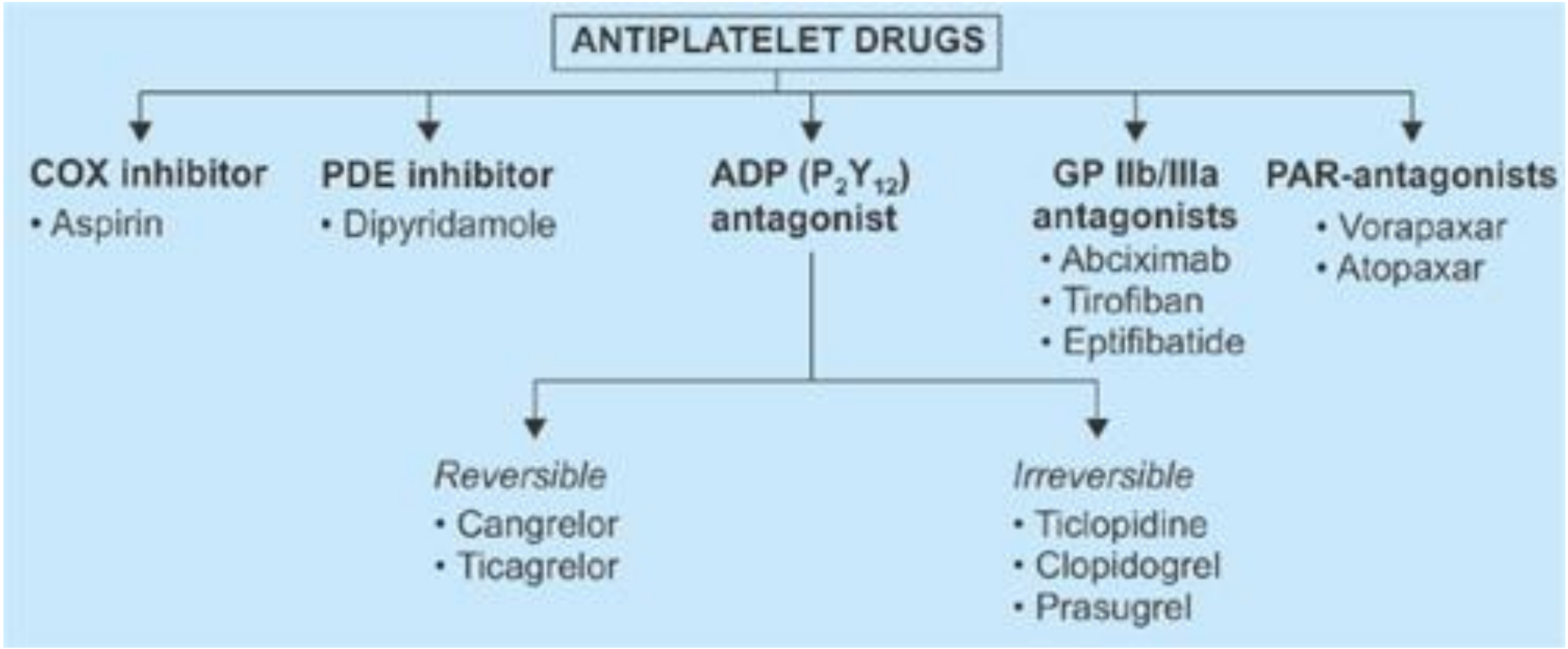
- **Pediatrics:** There is *no labeled pediatric indication* for betrixaban. Safety and efficacy in children have not been established, and it is *not approved for use in patients <18 years*.

Thromboprophylaxis

- Both dabigatran and rivaroxaban are FDA approved for secondary prophylaxis after initial therapy for VTE.

- Additionally, rivaroxaban is approved for primary prophylaxis in pediatric patients 2 years or older with congenital heart disease after the Fontan procedure and is dosed lower in this setting

J Am Heart Assoc. 2021;10(22):e021765. doi:10.1161/JAHA.120.021765


ANTIPLATELET DRUGS
COX inhibitor
• Aspirin
PDE inhibitor
• Dipyridamole
ADP (P_2Y_{12}) antagonist
GP IIb/IIIa antagonists
• Abciximab
• Tirofiban
• Eptifibatide
PAR-antagonists
• Vorapaxar
• Atopaxar
Reversible
• Cangrelor
• Ticagrelor
Irreversible
• Ticlopidine
• Clopidogrel
• Prasugrel

When to Interrupt and Restart DOAC Therapy During Elective Procedures

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Minor-bleeding-risk procedure					
Recommended to not stop in most minor surgical procedures					NA[†]
STOP: 12–24 h before procedure*					
RESTART: 6 h after intervention					
Low-bleed-risk procedure Stop 24–96 h before procedure					
CrCl ≥80 mL/min	STOP: ≥24	STOP: ≥24	STOP: ≥24	STOP: ≥24	STOP: ≥96
CrCl ≤50–79 mL/min	STOP: ≥36	STOP: ≥24	STOP: ≥24	STOP: ≥24	STOP: ≥96
CrCl ≤30–49 mL/min	STOP: ≥48	STOP: ≥24	STOP: ≥24	STOP: ≥24	Not indicated
CrCl ≤15–29 mL/min	Not indicated	STOP: ≥36	STOP: ≥36	STOP: ≥36	Not indicated
CrCl ≤15 mL/min	Consider measuring drug activity to determine absence of drug affect				Not indicated
RESTART	≥24 h after intervention				
High-bleed-risk procedure Stop 48–96 h before procedure					
CrCl ≥80 mL/min	STOP: ≥48	STOP: ≥48	STOP: ≥48	STOP: ≥48	STOP: ≥96
CrCl ≤50–79 mL/min	STOP: ≥72	STOP: ≥48	STOP: ≥48	STOP: ≥48	STOP: ≥96
CrCl ≤30–49 mL/min	STOP: ≥96	STOP: ≥48	STOP: ≥48	STOP: ≥48	Not indicated
CrCl ≤15–29 mL/min	Not indicated	STOP: ≥48	STOP: ≥48	STOP: ≥48	Not indicated
CrCl ≤15 mL/min	Consider measuring drug activity to determine absence of drug effect			Not indicated	
RESTART	≥48 to 72 h after intervention				

UFH vs DOACs vs LMWH in Liver Disease

Feature	UFH	LMWH	DOACs
Monitoring	Anti-Xa (preferred)	Usually none	None
Antithrombin dependence	High	Moderate	None
Reversibility	Full (protamine)	Partial	Drug-specific
Renal failure	Best choice	Avoid severe RF	Dose adjust / avoid
Hepatic metabolism	Minimal	Minimal	Significant
Use in decompensated cirrhosis	✅ ICU/unstable	⚠	❌ (Child-Pugh C)

Switching Between Anticoagulants

1. VKA to DOAC
2. DOAC to VKA
3. DOAC to DOAC
4. DOAC to parenteral anticoagulant
5. Parenteral anticoagulant to DOAC

Table 7. INR Considerations When Transitioning Between VKA and DOAC

VKA-to-DOAC Conversion	
INR ≤2	Start DOAC immediately
INR 2–2.5	Start DOAC immediately or preferably the next day
INR 2.5–3	Postpone DOAC Recheck INR in 1–3 d
INR ≥3	Postpone DOAC Recheck INR in 3–5 d
DOAC-to-VKA Conversion	
INR ≤2	Continue DOAC (half-dose for edoxaban) while INR remains ≤2 Recheck INR in 1–3 d (before DOAC intake)
INR >2	Stop DOAC Recheck INR 1 d after discontinuing DOAC

DOAC indicates direct oral anticoagulant; INR, International Normalized Ratio; and VKA, vitamin K antagonist.

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Algorithm for Switching Between Anticoagulants

From	To	Action
VKA	DOAC	Stop VKA and start DOAC once INR is <2 or lower INR limit of therapeutic range Measurement of INR before and after DOAC initiation is warranted as DOAC may falsely elevated INRs
Dabigatran	VKA	CrCl >50 mL/min: start VKA and stop dabigatran 3 d later CrCl 31 to 50 mL/min: start VKA and stop dabigatran 2 d later CrCl 15 to 30 mL/min: start VKA and stop dabigatran 1 d later
Rivaroxaban Apixaban	VKA	Start VKA and stop DOAC 3 d later OR for continuous anticoagulation: Stop DOAC and start LMWH and VKA at the time DOAC would have been due, then stop LMWH when INR is within therapeutic range
Edoxaban	VKA	Start VKA and stop DOAC 3 d later OR for continuous anticoagulation: Patients taking 60 mg: reduce edoxaban to 30 mg and start warfarin concomitantly. Stop edoxaban when INR >2 Patients taking 30 mg: reduce edoxaban to 15 mg and start warfarin concomitantly. Stop edoxaban when INR ≥2
Betrixaban	VKA	Start VKA and stop DOAC when INR > lower limit of therapeutic range
DOAC	DOAC	Stop current DOAC regimen and begin the new DOAC agent at the time next dose of DOAC is due
DOAC	Parental anticoagulant*	Stop DOAC and start parenteral anticoagulant at the same time that the next dose of DOAC would have been given
Parenteral anticoagulant*	DOAC	Intravenous: Start DOAC 0 to 2 h after stopping UFH Subcutaneous: Stop LMWH and start DOAC at the same time that the next dose of LMWH would have been given

Transitioning a patient from a Vitamin K Antagonist (warfarin) to a Direct Oral Anticoagulant

1- Stop the VKA: Discontinue warfarin. Measure INR before starting the DOAC.

2- Check the patient's INR: VKAs have a delayed offset. These cut-offs ensure the VKA effect is sufficiently reduced before starting the DOAC.

DOAC	Recommended INR for initiation
Dabigatran, Apixaban, Edoxaban	INR < 2.0
Rivaroxaban	INR < 3.0

3- Start the DOAC: Begin the DOAC **once the INR is below the recommended threshold**. Use **standard DOAC dosing** based on indication, renal function, and age.

Transitioning a patient from a warfarin to DOAC

4- Consider renal function

DOAC dosing may need adjustment for **renal impairment**.

For dabigatran, apixaban, and edoxaban, check creatinine clearance before starting.

5- Overlap is generally not needed

Unlike transitioning from heparin, **DOACs do not require overlap with VKA**.

Overlapping could increase bleeding risk.

6- Monitor for bleeding and efficacy of anticoagulation

Routine lab monitoring is not needed but check for signs of bleeding or recurrent thrombosis.

- Measure DOAC-specific levels in special situations:
  (e.g., severe renal impairment, extreme body weight, or urgent surgery).

Transitioning a patient from warfarin to DOAC

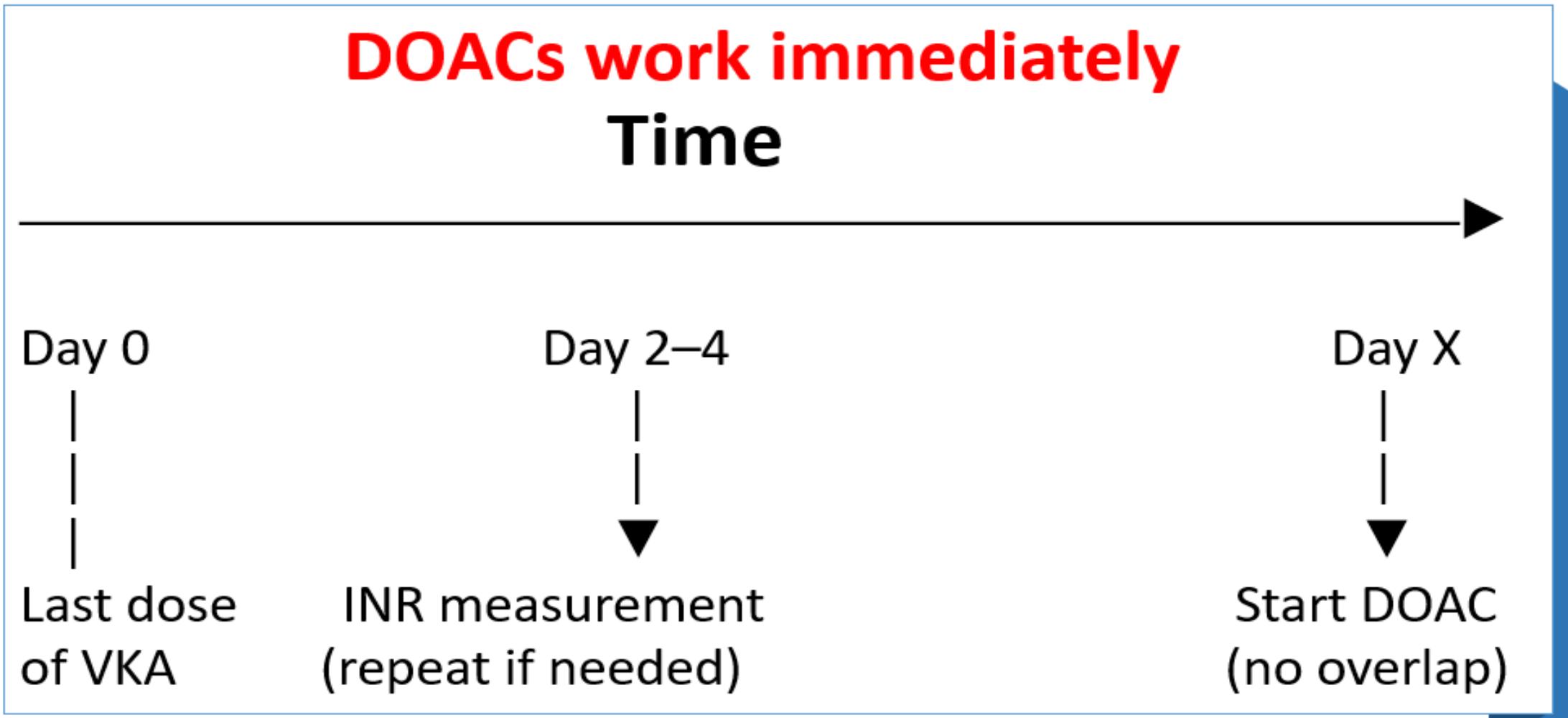
7- Special situations

- **High thrombotic risk patients**: sometimes bridging with LMWH may be considered.

- **Extremely high INR** (>3.0): delay starting DOAC start or use low-dose LMWH until INR falls below threshold.

- **Renal impairment**: may require DOAC dose adjustment or selection of agent with lower renal clearance.

DOACs work immediately



Transitioning a patient from a warfarin to DOAC
When Bridging is NOT Needed

Do NOT bridge in:

- Stable atrial fibrillation
- Remote VTE (>3–6 months ago)
- Routine switch from **VKA → DOAC**
- DOAC interruption for minor procedures

Bridging in low–moderate risk patients
increases bleeding risk without reducing thrombosis

Transitioning from a warfarin to DOAC
When Is Bridging Needed?

1. Very High Thrombotic Risk Patients

Bridging is considered when **interrupting VKA** would expose the patient to high risk of thrombosis.

Mechanical heart valves

- Mitral valve prosthesis
- Older-generation aortic valves

• Recent venous thromboembolism (VTE)

- VTE within **≤ 3 months**

• Severe thrombophilia

- Antiphospholipid syndrome (especially triple-positive)
- Protein C, protein S, or antithrombin deficiency with prior thrombosis

• Recent arterial thrombosis

- Stroke or systemic embolism within **≤ 3 months**

How to Bridge when the patient is on warfarin (If Indicated)
Preferred Agent: Low-molecular-weight heparin (LMWH)

- **Stop warfarin 5 days before interruption**
- **Start LMWH when INR < 2.0 with therapeutic dose:**
- **Enoxaparin 1 mg/kg SC every 12 h or 1.5 mg/kg SC once daily**

- **Before Procedure**

  Last LMWH dose:
  - **24 h before (once-daily dosing)**
  - **12 h before (twice-daily dosing)**

- **After Procedure Resume LMWH**
  - **24 h (low bleeding risk)**
  - **48-72 h (high bleeding risk)**
  - **Restart VKA simultaneously**
  - **Stop LMWH once INR is therapeutic**

Transitioning from a DOAC to warfarin (VKA)

- **overlap ("bridging") is needed,** because warfarin has a **delayed onset**, while DOACs have a **short half-life**. Warfarin takes **5–7 days** to become fully therapeutic. DOACs wear off within **12–24 hours. Without overlap, patients are under-anticoagulated.**

- **General Principles**

✓ **Start warfarin while the patient is still on the DOAC.**
✓ **Continue DOAC until INR is therapeutic.**
✓ **Check INR just *before* the next DOAC dose** (to avoid DOAC interference).

- **Step-by-Step Protocol**

Day 0

Start warfarin (usual starting dose 5 mg, adjust for age, comorbidities, liver disease)

Days 1–5

Continue DOAC at full therapeutic dose

Monitor INR **just before DOAC dose**

Stopping the DOAC

Stop DOAC when INR ≥ 2.0 (≥ 2.5–3.0 for mechanical valves) **on two consecutive measurements.**

After stopping DOAC, continue warfarin alone.

Transitioning from a DOAC to warfarin (VKA)

Step	Action
1	Start warfarin
2	Continue DOAC
3	Check INR before DOAC dose
4	Stop DOAC when INR ≥ 2
5	Continue warfarin