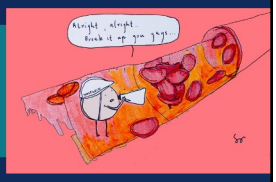
Practical Aspects and Updates for Anticoagulation Therapy

for Nurse Practitioners



Clinical Pharmacology Update | Evidence-Based Practice Lecture

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Disclosures

I have no relevant financial relationships to disclose.

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Learning Objectives

1. Select appropriate anticoagulants across key indications using current guideline recommendations
2. Apply DOAC-specific dosing adjustments for renal function, weight, and patient-specific factors with confidence
3. Identify and manage bleeding complications — and select the correct reversal agent for each anticoagulant class
4. Navigate anticoagulation in high-stakes special populations: cancer, CKD, obesity, and elderly patients
5. Apply current perioperative management guidance, including the evidence against routine bridging therapy

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Session Roadmap

Opening — Anticoagulation Basics, DOAC revolution & setting the stage	5 min	**Special Populations** — Cancer, CKD, Obesity Elderly	8 min
Current Oral Anticoagulant Options — Vitamin K Antagonist, Direct Thrombin Inhibitor, Factor Xa Inhibitors, Factor XIa (coming soon)	8 min	**Bleeding & Reversal** — Management & reversal agents	4 min
Guideline Updates — Atrial Fibrillation, VTE (DVT & PE)	10 min	**Perioperative Management** — BRIDGE trial & hold protocols	5 min
DOAC Selection — Decision Matrix; Renal Dosing	10 min	**Cases + Takeaways** — Rapid-fire clinical cases	5 min

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Anticoagulation Basics

- Hemostatic system controls 2 major functions
  - Maintains blood in fluid state for maintenance of circulation
  - Clot formation at site of vascular injury
- Generally, this process involves 3 distinct stages
  - Primary hemostasis (vascular injury —> weak platelet plug)
  - Secondary hemostasis (coagulation cascade —> stable fibrin mesh)
  - Tertiary hemostasis (fibrinolysis to prevent thrombosis)
- The interplay between key components (platelets, endothelial cells, clotting factors, and fibrinolytic agents) work to stabilize vascular integrity

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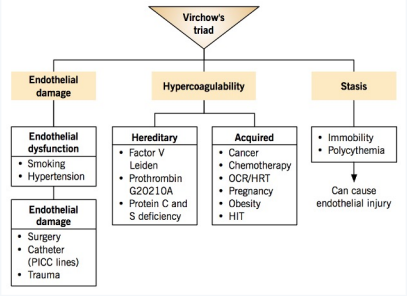
Anticoagulation Basics



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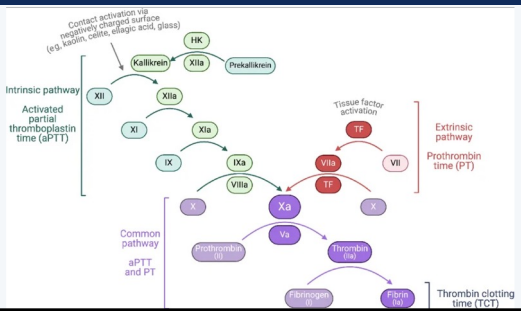
Anticoagulation Basics



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Why Do I Care?

- 1 in 50 patients take long-term anticoagulation (1)
  - >2% of non-institutionalized adults, almost 8 million Americans
- ~1 in 10 patients taking anticoagulation undergo surgery or an invasive procedure yearly (2)
  - All procedures/surgeries require balancing risk of serious bleeding and clotting
- Love it or hate it, you will need to know it

1. Alkhezi OS, Buckley LF, Fanikos J. Trends in Oral Anticoagulant Use and Individual Expenditures Across the United States from 2014 to 2020. Am J Cardiovasc Drugs. 2024 May;24(3):433-444
2. Wagner J, Lock JF, Kastner C, Klein I, Krajinovic K, Löb S, Germer CT, Wiegering A. Perioperative management of anticoagulant therapy. Innov Surg Sci. 2019 Jul 18;4(4):144-151

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SECTION 1

The Anticoagulation Landscape

Warfarin Era

1954 – 2010s

- INR monitoring
- Drug & food interactions
- Narrow therapeutic index
- Frequent dose adjustments

Direct Oral Anticoagulant (DOAC) Revolution

2010 – Present

- Fixed dosing
- No routine monitoring
- Fewer interactions
- Generally safer

- Why this matters: DOACs now dominate most guidelines — but warfarin isn't dead

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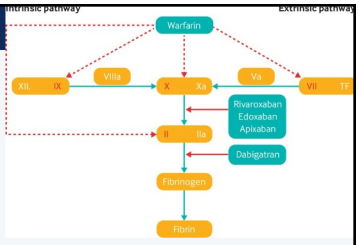
Current Oral Options



- Vitamin K Antigonist
  - Warfarin (Coumadin)
- Direct Thrombin Inhibitor
  - Dabigatran (Pradaxa)
- Factor Xa Inhibitors
  - Apixaban (Eliquis), Rivaroxaban (Xarelto), Edoxaban (Savaysa)
- Factor XIa Inhibitors (coming soon)
  - Asundexian, Milvexian, Abelacimab

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Oral Anticoagulants

- **Warfarin (Coumadin®)**
  - Originally discovered when spoiled sweet clover was eaten by cows —> discovery of prothrombin reduction 2/2 bihydroxycoumarin ⍰ synthetic rodenticide "warfarin" (Wisconsin Alumni Research Foundation)
  - Typical starting dose is 5 mg daily
    - Lower in elderly, malnourished, hepatic impairment
    - Think weekly dosing
  - Limitations
    - Narrow therapeutic range
    - Pharmacokinetics
    - Variable dosing/genetic polymorphisms
  - Strengths
    - Monitoring available
    - No renal adjustments
    - Studied in almost all prothrombotic disease states
    - Over 70 years of experience and data
    - Inexpensive tablet cost

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Oral Anticoagulants

- Time to activity is based upon factor half-lives

Factor VII – 6 hours
Factor IX – 24 hours
Factor X – 36 hours
Factor II – 50 hours

Protein C – 8 hours
Protein S – 30 hours

It takes ~ 5 days after initiating warfarin to see a more complete rise in INR (antithrombotic state)

Early inhibition of protein C can lead to warfarin's initial *procoagulant* effect, thus necessitating bridge therapy

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Oral Anticoagulants

- Warfarin monitoring
  - International Normalized Ratio (INR)
    - INR = $(PT_{patient}/PT_{reference})^{ISI}$
    - Frequency
      - Baseline, then after the initial 2 or 3 doses
      - Inpatients: Daily for inpatients till therapeutic for 2 days, then 2-3 times weekly for 1-2 weeks, then less often
      - Outpatients: Every few days till therapeutic. May be tapered to a maximum of every 4 weeks once a stable dose is achieved.
        - Target INR is primarily 2.5 (2 – 3) or 3 (2.5 – 3.5)
  - CBC, LFT, albumin, renal function

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DOAC Highlights

- **Apixaban (Eliquis)**
  - Can use in iHD
  - Dose adjustments only for AF, not VTE
  - Most contemporary data shows best safety with equal/greater efficacy
- **Rivaroxaban (Xarelto)**
  - Only approved DOAC for CAD/PAD (Generic available for low-dose)
  - Once daily
  - Must take with high fat meal
- **Edoxaban (Savaysa)**
  - Once daily
  - Better safety profile than Riva
  - Never gained significant traction

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DOAC Highlights

- **Dabigatran (Pradaxa)**
  - First DOAC to go generic
  - Dedicated reversal agent available (PraxBind)
  - Must keep in original manufacturer bottle due to moisture-related degradation

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Guideline Updates — Atrial Fibrillation

AHA/ACC 2023

CHA_2DS_2-VASc | Current Thresholds	
Score ≥ 2 (men), ≥ 3 (women)	Anticoagulation recommended
Score 1 (men), 2 (women)	Consider* anticoagulation
Score 0 (men), 1 (women)	No antithrombotic therapy

General Workflow
Determine need for AC (>2% yearly risk)
Determine bleed risk (HAS-BLED/Hemorrhages/Atria)
For those with intermediate risk; differ to cardiology
AC recs remain the same regardless of type (parox, persistent, permanent, even flutter)

Valvular AF Exception

Mechanical heart valves → Warfarin mandatory (DOACs contraindicated)
Bioprosthetic valves, moderate-to-severe mitral stenosis → evidence still evolving; let the specialists manage

HAS-BLED in Practice: Use it to identify and address modifiable bleeding risk factors — NOT as a reason to withhold anticoagulation therapy

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Guideline Updates — Atrial Fibrillation

AHA/ACC 2023

Table 8. Three Validated Risk Models for Stroke

* 8 points if age <65 y; 4 points if age 65-74 y; 2 points if age 75-84 y; and 3 points if ≥85 y.

TIA indicates transient ischemic attack.

Risk Factor	CHA_2DS_2-VASc	ATRIA	GARFIELD
Age ≥85 y		6	0.98
Age ≥75 y	2	5	0.59
Age 65-74 y	1	3	0.20
Female sex	1	1	
Hypertension	1		0.16
Renal disease		1	0.35
Diabetes	1	1	0.21
Current smoking			0.48
Congestive heart failure	1	1	0.23
Previous stroke or TIA	2	2 .8*	0.80
Vascular disease	1		0.20
Dementia			0.51
Previous bleeding			0.30
Proteinuria		1	
Low risk score	0	0 -5	0 -0.89
Intermediate risk score	1	6	0.90 -1.59
High risk score	≥2	7–15	≥1.60
C-index (11)	0.63	0.66	-
C-index (13)	0.67	-	0.71

ATRIA indicates Anticoagulation and Risk Factors in Atrial Fibrillation: anemia, renal disease, elderly (age ≥75 y), any previous bleeding, hypertension; CHA_2DS_2-VASc, indicates congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 y, sex category; GARFIELD-AF, Global Anticoagulant Registry in the FieldAtrial Fibrillation; and TIA, transient ischemic attack.

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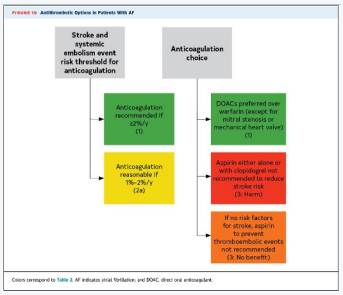
Guideline Updates — Atrial Fibrillation

AHA/ACC 2023



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Guideline Updates — VTE (DVT & PE)

ASH 2020 (2022)
AHA/ACC/CHEST 2026

KEY CHANGE: DOACs are now preferred for acute VTE — no LMWH lead-in required for most patients
PE initial agent selection changes based upon clinical risk

Uncomplicated VTE Framework

Clinical Prediction Rules/Scores	Wells Score (Leg DVT) Constans Score (UE DVT) Wells PE or Revised Geneva (PE)
Initial Management (First Week)	Determine Home vs hospital (↓ recurrent DVT/PE if uncomplicated)
Primary Treatment	Determine Risk Factors Decide need for 2 prevention
Secondary Prevention	Extended therapy — consider indefinitely (specialists to help determine need)

PE Risk Stratification

- **Massive**
  Systemic thrombolysis or catheter-directed Rx; ICU
- **Submassive**
  RV strain, consider catheter-directed therapy if deteriorating
- **Low-Risk**
  Outpatient DOAC therapy appropriate

Unprovoked VTE = always evaluate for underlying malignancy or thrombophilia before deciding on duration

Multiple guidelines exist for VTE/PE… Chest, ASH, ISTH, ACC… Double check to ensure you're up to date but know there can be nuance differences between these

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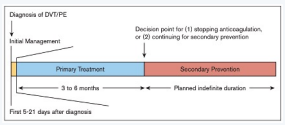
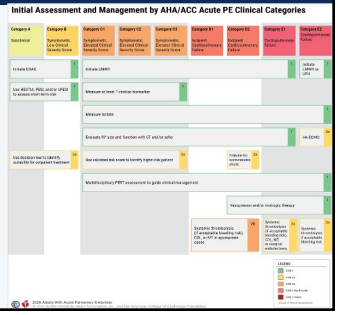
Guideline Updates — VTE (DVT & PE)

ASH 2021

Duration Decision Framework

Provoked VTE (major transient)	3 months then stop
Provoked VTE (minor/ongoing)	3–6 months, reassess
Unprovoked VTE	Extended therapy — consider indefinitely
Risk tools	DASH score, Vienna Prediction Model





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Current Oral Options

Drug	Dose Range	Indications	T ½	Efficacy vs Warfarin	Safety vs Warfarin
Warfarin (Coumadin)	Titrated to INR 2–3 (for most) Typically 2–10 mg PO daily	NVAF, VTE tx/prevention, mechanical heart valves, valvular AF (mitral stenosis), antiphospholipid syndrome	**36–42 h**		
Apixaban (Eliquis)	2.5 - 10 mg PO BID	NVAF, VTE tx & prevention, post-op DVT prophylaxis (hip/knee)	~12 h	**Superior** for stroke/SE prevention in NVAF (ARISTOTLE)	**Superior** — lower major bleeding, lower ICH, lower all-cause mortality. Only DOAC superior on **both** efficacy and safety
Rivaroxaban (Xarelto)	10 - 20 mg PO daily (2.5 mg PO BID for CAD/PAD)	NVAF, VTE tx & prevention, ortho prophylaxis, **CAD/PAD risk reduction**	5–13 h	**Non-inferior** for stroke/SE in NVAF (ROCKET AF)	**Mixed** — lower ICH and fatal bleeding, but **higher GI bleeding**; major bleeding overall similar
Dabigatran (Pradaxa)	75 - 150 mg PO BID	NVAF, VTE tx & prevention	12–17 h	**Superior** at 150 mg dose for stroke/SE (RE-LY); 110 mg dose non-inferior	**Mixed** — lower ICH but **higher GI bleeding** at 150 mg; 110 mg dose has lower overall major bleeding. I
Edoxaban (Savaysa)	30 - 60 mg PO daily	NVAF, VTE tx	10–14 h	**Non-inferior** for stroke/SE in NVAF (ENGAGE AF-TIMI 48)	**Superior** — lower major bleeding, lower ICH, lower CV mortality

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DOAC Selection — The Clinical Decision Matrix

Clinical Factor	Best Choice	Avoid / Caution	Clinical Punchline
Renal Impairment (CKD)	Apixaban	Dabigatran	Use Cockcroft-Gault (not eGFR) for all DOAC dosing
High GI Bleed Risk	Apixaban	Dabigatran, Rivaroxaban	Apixaban had lowest GI bleed in RCTs
GI Tolerability	Any DOAC except Dabigatran	Dabigatran	Dabigatran: highest GI SE — take with food
Adherence Concern	Rivaroxaban (once daily)	Dabigatran, Apixaban	BID dosing → higher missed-dose risk
Drug Interactions (P-gp)	Apixaban (least affected)	Dabigatran, Rivaroxaban	Review P-gp & CYP3A4 inhibitors/inducers
Mechanical Heart Valve	Warfarin	All DOACs contraindicated	Non-negotiable — DOACs cause harm here

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Renal Dosing Deep Dive — Where Errors Happen Most

Always use Cockcroft-Gault CrCl — NOT eGFR — for DOAC dosing decisions. eGFR underestimates clearance in elderly, low-muscle-mass patients.

Apixaban: Dual Dose-Reduction Criteria

Reduce to 2.5 mg BID if ≥ 2 of 3:

- Age ≥ 80 years
- Weight ≤ 60 kg
- Serum creatinine ≥ 1.5 mg/dL

NPs most commonly under-apply this rule

When to Avoid or Switch

Dabigatran	CrCl < 15 mL/min	*Contraindicated*
Rivaroxaban	CrCl < 15 mL/min	*Avoid*
Apixaban	ESRD/Dialysis	*Limited evidence; use with caution*
Edoxaban	CrCl > 95 mL/min	*Paradoxically less effective — use alternative*

Warfarin remains preferred in severe hepatic disease & mechanical valves

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Special Populations

Cancer-Associated Thrombosis — ASCO/ITAC 2023

- DOACs now PREFERRED over LMWH (ADAM VTE, SELECT-D, Caravaggio)
- Apixaban & rivaroxaban are first-line
- Exceptions: GI/GU malignancy, thrombocytopenia, drug interactions → LMWH
- NCCN Guidelines

Obesity (BMI > 40 or > 120 kg) — ISTH Guidance

- Accumulating real-world data support standard DOAC dosing
- Do NOT independently adjust doses — no validated weight-based regimen exists
- In general, Xa monitoring (DOAC or LMWH) not recommended

ESRD / Dialysis — AXADIA • RENAL-AF

- No clearly superior option exists — this is shared decision-making territory
- Apixaban: most studied in dialysis but evidence is limited and non-definitive
- Warfarin risks: calciphylaxis, unstable INRs in ESRD

Elderly Patients — ARISTOTLE Data

- Fall risk ALONE does not justify withholding anticoagulation — address this myth directly
- Apixaban: most favorable safety profile in elderly
- Vigilance required: this group is most likely to be incorrectly dosed

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Bleeding Management & Reversal Agents

Stratify First: Minor → Hold drug, supportive care, check last dose timing
Major/Life-Threatening → Initiate reversal immediately — do not wait for labs

Anticoagulant	Reversal Agent	Year Approved	Key Notes
Warfarin	Vit K + 4F-PCC (Kcentra)	Long-standing	FFP less preferred; for urgent reversal use PCC
Dabigatran	Idarucizumab (Praxbind)	2015	Highly specific; use it — do not substitute PCC
Factor Xa Inhibitors (Apixaban, Rivaroxaban)	Andexanet Alfa (Andexxa)	2018	4F-PCC is cost-effective alternative when Andexxa unavailable
All DOACs	Ciraparantag (pipeline)	Not yet approved	Promising universal reversal agent — watch this space

🔑 **Often overlooked: When do you RESUME anticoagulation after a major bleed? This decision is frequently more consequential than reversal itself.**

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Perioperative Anticoagulation Management

BRIDGE Trial (NEJM, 2015) — Practice-Changing Evidence

LMWH bridging was non-inferior to placebo for stroke prevention in AF patients — and caused significantly MORE major bleeding. Routine bridging is now DISCOURAGED for most AF patients.

Bridge ONLY When:

- Mechanical heart valves
- VTE within the past 3 months
- Highest-risk AF — case by case (consult hematology)

Do NOT Bridge:

- Most non-valvular AF patients
- VTE > 3 months ago
- Lower-risk patients on warfarin

DOAC Interruption Standard:
Hold 24–48 hrs for low-bleed-risk procedures | Hold 48–96 hrs for high-bleed-risk procedures | Adjust for renal function (especially dabigatran) | Use ACC perioperative calculator

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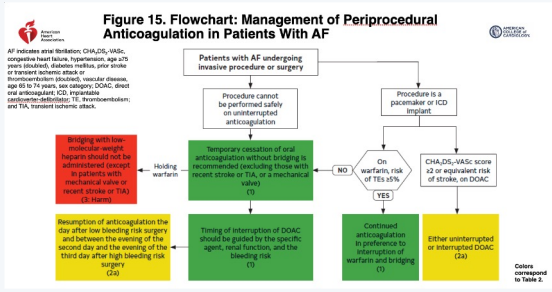
Perioperative Anticoagulation Management



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Rapid-Fire Clinical Cases

CASE 1
Scenario: 74-year-old woman with AF, CrCl 22 mL/min, history of GI bleed. Which agent? Which dose?
Answer: Apixaban 2.5 mg BID (meets 2 of 3 dose-reduction criteria: age ≥80 may not apply, but CrCl + GI history strongly favor apixaban at reduced dose)

CASE 2
Scenario: Active pancreatic cancer, new submassive PE, currently on immunotherapy. DOAC or LMWH?
Answer: Apixaban or rivaroxaban first-line per ASCO 2023 — UNLESS GI/GU bleed risk is prohibitive or significant drug interaction with targeted therapy exists → LMWH

CASE 3
Scenario: Patient on warfarin for Atrial Fibrillation, INR 2.4, elective knee arthroscopy scheduled next week. Bridge or hold?
Answer: Hold warfarin — do NOT bridge. Per BRIDGE trial + AHA/ACC guidelines, bridging increases major bleeding without reducing stroke risk in most AF patients

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5 Things to Take Back to Practice Tomorrow

1. Stop bridging routine AF patients perioperatively — BRIDGE trial data is clear
2. Use Cockcroft-Gault CrCl (not eGFR) for every DOAC dosing decision
3. For cancer-associated thrombosis, reach for apixaban or rivaroxaban first — unless GI/GU malignancy
4. Fall risk alone is NOT a reason to withhold anticoagulation in elderly patients
5. Always have a plan for RESUMING therapy after a bleed — not just reversing it

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Recommended Resources & References

Guidelines

- AHA/ACC 2023 Atrial Fibrillation Guidelines
- ASH 2021 VTE Guidelines
- ASCO 2023 Cancer-Associated Thrombosis Guidelines

Clinical Tools

- MDCalc.com — CHA_2DS_2-VASc, HAS-BLED, Cockcroft-Gault
- ACC Perioperative Anticoagulation App
- Anticoagulation Forum: acforum.org

Key Trials

- BRIDGE Trial (NEJM 2015) — perioperative bridging
- ARISTOTLE — apixaban in AF
- Caravaggio, ADAM VTE, SELECT-D — cancer VTE

CHEST Guidelines

- CHEST Antithrombotic Guidelines (latest edition)
- ISTH Guidance on DOACs in Special Populations

Always consult your institution's anticoagulation pharmacist for patient-specific guidance

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Questions

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