DOACs: A Review and Updates

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Disclosures

- No financial disclosures

Most Common Indications

- Venous thrombus embolism (VTE)
- Atrial fibrillation (AF)
- Acute coronary syndrome (ACS)
  - Usually within heparin/bivalirudin or fondaparinux

Direct Thrombin Inhibitors

- Parenteral options
  - Bivalirudin
  - Argatroban
- Oral options
  - Dabigatran

Direct Factor Xa Inhibitors

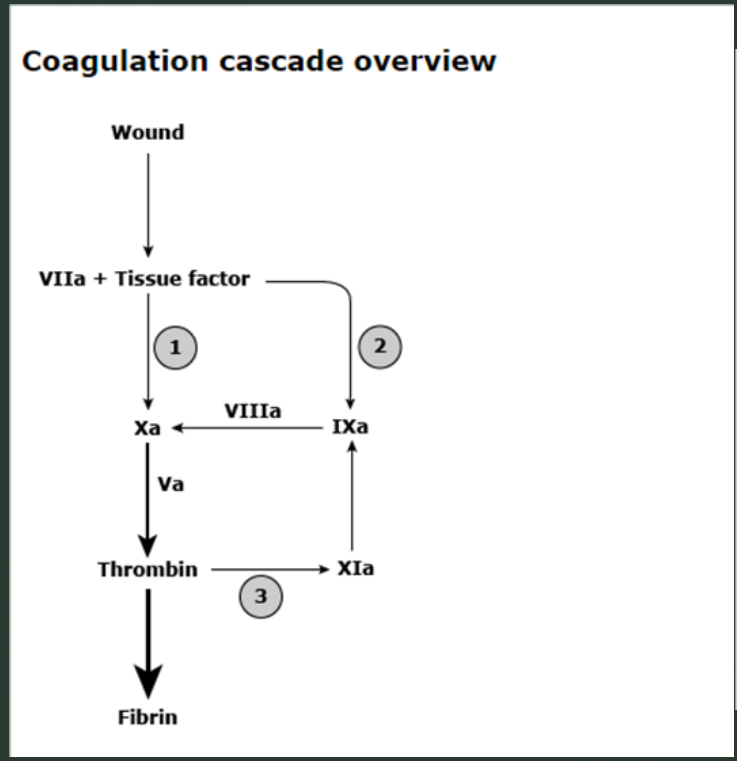
- Rivaroxaban
- Apixaban
- Edoxaban

Examples of Alternatives:

- Heparin/Warfarin

Review of Direct Oral Anticoagulants (DOACs)

- Mechanism of action
  - Essentially inhibit factors along the clotting cascade
    - Direct thrombin inhibitors
    - Direct factor Xa inhibitors



This schematic shows a revised version of the coagulation cascade that emphasizes the importance of pathways for hemostasis in vivo. Coagulation factors are shown as Roman numerals. Only the activated forms (with the suffix "a") are shown in this diagram for simplicity. Thrombin is activated factor II (factor IIa); unactivated factor II is prothrombin.

Tissue factor exposed at a wound interacts with factor VIIa and initiates clotting by two pathways:

- (1) – Activation of factor X to factor Xa (the extrinsic ten-ase complex).
- (2) – Conversion of factor IX to factor IXa, which activates factor X to factor Xa (the intrinsic ten-ase complex).

Pathways 1 and 2 are equally important.

In a third pathway (3), thrombin also activates factor XI to factor XIa, which can lead to further generation of factor IXa; it serves as an amplification pathway required during severe hemostatic challenges.

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Comparison Warfarin vs DOACs

	Warfarin	DOACs
Dosing:	Daily	Most > 1x daily
Monitoring:	Frequent PT/INR checks	Not required
Drug Interactions:	Numerous	Few
Reversal Agents:	+	+
Presence of Co-Morbidities:	Possibility of increased fracture risk	Dose adjustment for renal disease
Overall Bleeding Risk:	Higher	Lower
Cost:	More affordable	Less affordable

When is heparin/warfarin used/preferred over DOACs?

- Mechanical prosthetic heart valves
- Rheumatic heart disease
- Pregnancy
- Antiphospholipid syndrome
- Caution CKD – more data suggestive that efficacy of DOACs is equivalent not dependent on CrCl
- Caution severe liver disease – depends on Child-Pugh class

Updates

- Periprocedural management of DOACs
- Low-dose DOACs for extended VTE
- Restarting DOACs after ICH

PAUSE trial published 2019, data collected 2014-2018

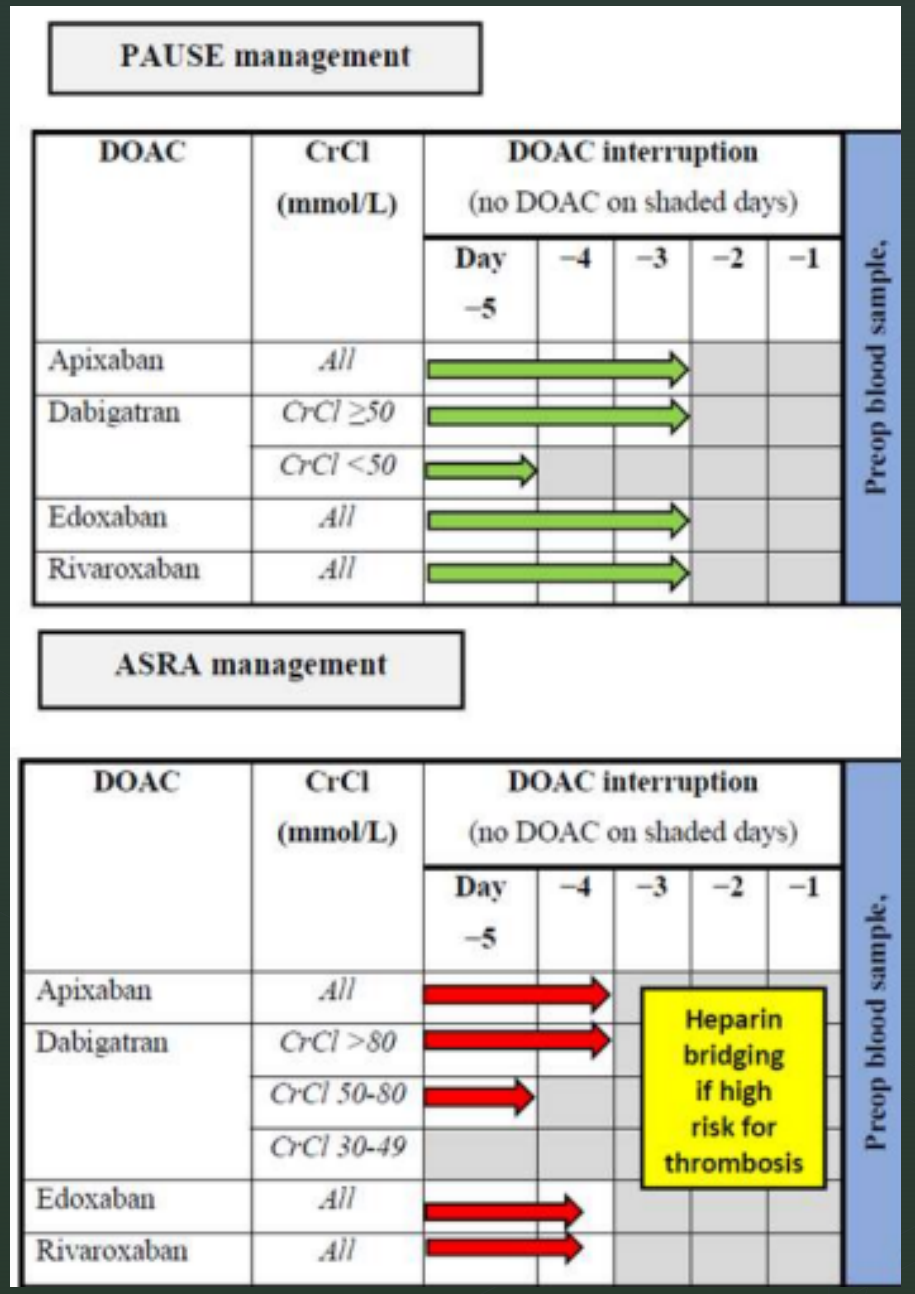
- Standardized system for periprocedural DOAC management
  - Hold 2 days prior to major surgery
  - Hold 1 day prior to minor surgery
  - Low complication rates
  - Limitations: few high-bleeding risk surgeries or neuraxial procedures
- American Society of Regional Anesthesia (ASRA) guidelines recommend longer hold times for DOACs (~3 days)

PAUSE-2 pilot trial published 2025, data collected 2020-2024

- Proof-of-concept randomized trial
- 159 people currently on DOACs (majority apixaban n=86) undergoing elective procedures with high-bleeding risk or neuraxial anesthesia
- Patients randomized to PAUSE vs. ASRA guidelines for holding DOACs

PAUSE-2 Pilot Trial

- Primary outcomes
  - Pre-procedural DOAC levels
- Secondary outcomes
  - Bleeding, thrombosis within 30 days



Outcomes

	PAUSE-approach	ASRA-approach
	N=80	N=79
DOAC interruption, median hrs	64 hrs	87 hrs
DOAC level pre-procedure, median	20	19
Residual DOAC level (ng/mL)		
<30	94.4%	95.6%
30-50	2.8%	1.4%
>50	2.8%	2.9%
Clinical outcomes		
Bleeding	1 non-major	1 major
Thrombosis	1 DVT	0

Key Points

- Pre-op DOAC levels similarly low (<30 ng/mL) between PAUSE and ASRA guidelines
- Not conclusive but leads to the idea that PAUSE approach (shorter pre-procedure hold duration) may still be reasonable even in higher risk patients
- Further/additional studies needed

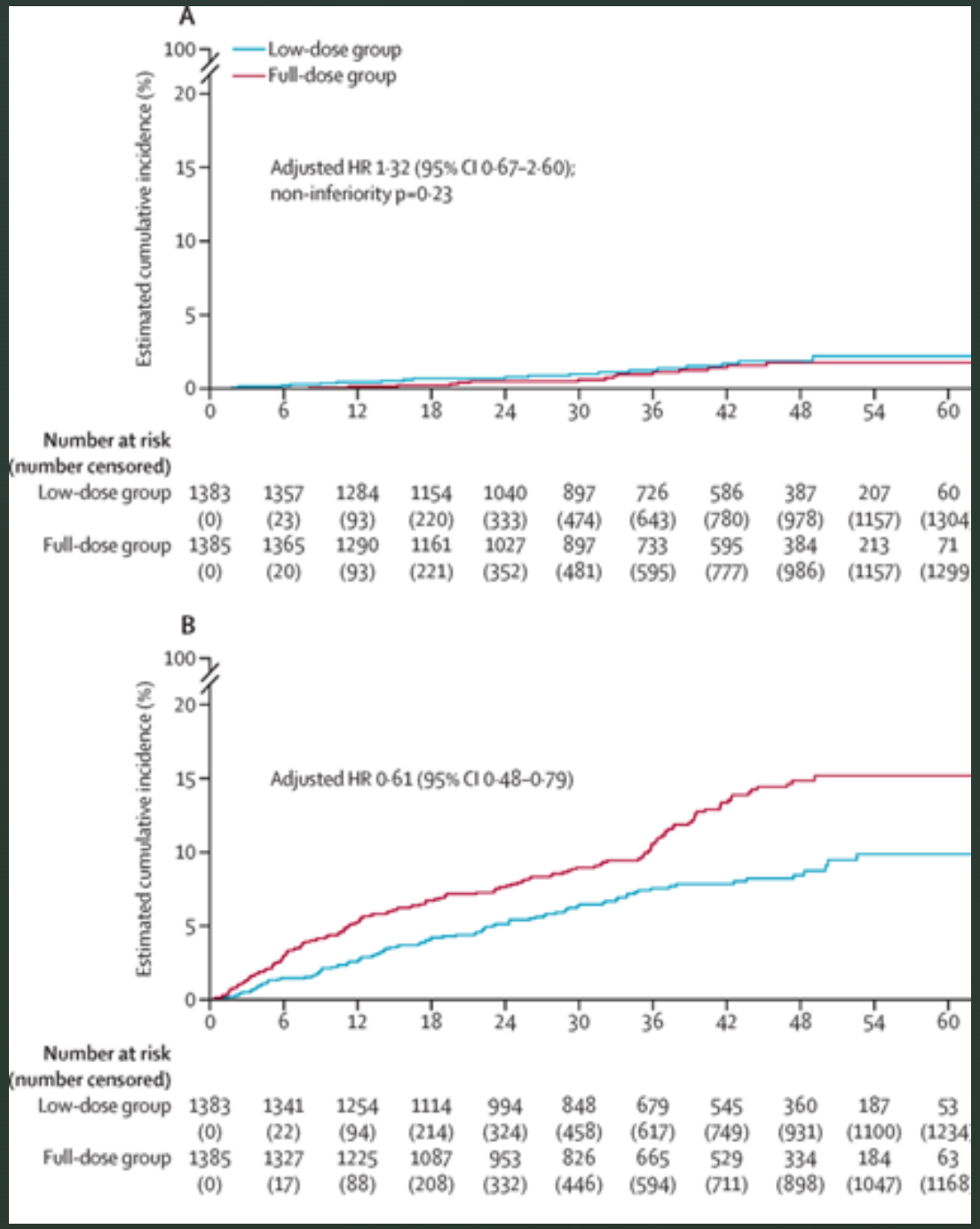
Extended AC Use for VTE

- Life-long AC recommended for pts with unprovoked VTE, persistent risk factors, or active cancer
- Two recent studies comparing full vs low-dose DOACs
  - RENOVE trial in high risk of recurrent VTE
    - Published 2025
  - API-CAT trial in cancer associated VTE
    - Published 2025

RENOVE and API-CAT

- Design: multicentered, randomized, non-inferiority trials
- Purpose: assess if reduced DOAC dosing is non-inferior to full dose in high-risk pts with VTE

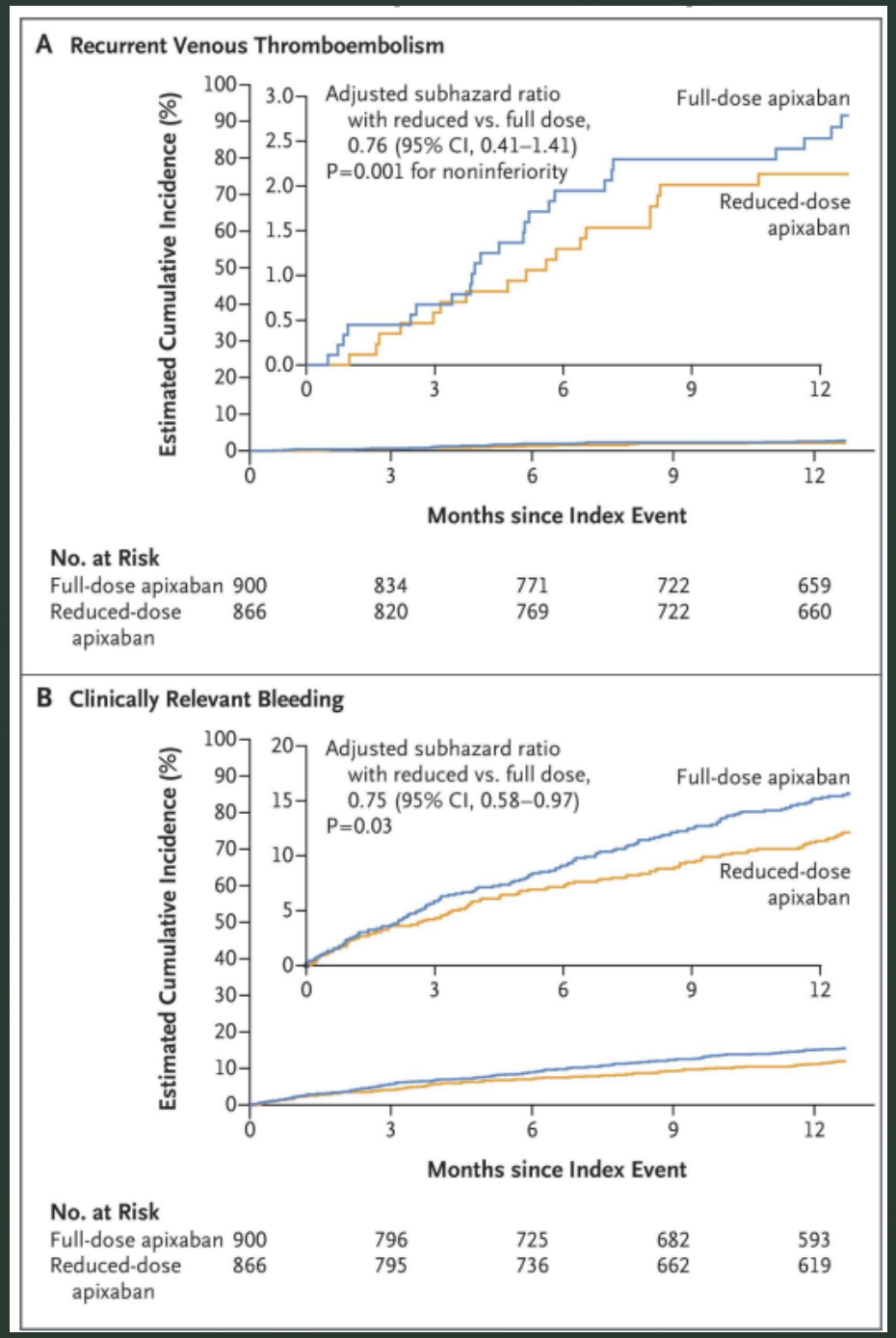
	RENOVE, n=2768	API-CAT, n=1766
Patients	Acute VTE and high risk for recurrence, anticoagulated 6-24 mo	Acute VTE and active cancer, anticoagulated ≥6 mo
Intervention	Reduced-dose vs. Full-dose DOAC (apixaban or rivaroxaban)	Reduced-dose vs. Full-dose apixaban
Follow-up	5 yrs	12 months
Outcomes	Recurrent VTE, bleeding, death	



RENOVE Trial

Reduced-dose vs. full-dose
Recurrent VTE: 2.2% vs. 1.8% over 5 yrs
HR 1.32 [0.7-2.6]
Did not meet criteria for noninferiority

Bleeding risk: 9.9% vs 15.2% over 5 yrs
HR 0.61 [0.5-0.8]
Reduced-dose superior to full dose



API-CAT Trial

Reduced-dose noninferior to full dose in preventing recurrent VTE 2.1% vs. 2.8%
HR 0.76 [0.41-1.41]

Reduced-dose superior to full dose for bleeding risk 12.1% vs 15.6%
HR 0.75 [0.58-0.97]

Key Points

- Reduced-dose DOACs are a reasonable option for people with high VTE recurrence risk, even in patients with cancer
- Reduced-dose DOACs are associated with significantly *lower* bleeding complications

DOACs in Patients with ICH

- ICH is a major co-morbid condition why ACs are avoided
- DOACs have lower risk of ICH than warfarin
- Observational studies/meta-analyses have shown a low risk of recurrent ICH and a net benefit to resuming ACs
  - Usually selected for lower risk patients

PRESTIGE-AF Trial

- Design: Multicenter, randomized, noninferiority trial
- Inclusion Criteria: Age 18+ with atrial fibrillation and spontaneous intracerebral hemorrhage
- Exclusion Criteria: ICH due to trauma or vascular malformations
- N: 319 Patients with ICH
- Methods: Eligible for enrollment from 14 days to 12 months after index ICH

PRESTIGE-AF Trial

- Intervention: Randomized to DOAC vs. no AC
- Primary outcomes: Ischemic stroke, recurrent ICH
- Secondary outcomes: Death, cardiovascular events, bleeding
- Follow-up: Up to 36 months

PRESTIGE-AF Trial

	DOAC	No DOAC
	N=158	N=161
Age, yrs	78	79
Female	35%	35%
CHA_2DS_2-VASC stroke risk	4	4
ICH type		
Lobar	34%	26%
Non-lobar	66%	74%
Prior anticoagulation	85%	83%
Mean time to enrollment	48 days	49 days

PRESTIGE-AF Trial Outcomes

	DOAC	No DOAC	HR
	N=158	N=161	
Ischemic stroke	1	20	0.05 [0.01-0.38]
Recurrent ICH	11	1	11.2 [2.0-62.9]
Major bleeding	21	5	4.5 [1.8-13.4]
All cause death	16	21	0.8 [0.4-1.6]

NNT = 13 NNH = 24

Key Points

- AC use:
  - Reduced risk of ischemic stroke
  - Increased risk of recurrent ICH
- Should we use AC after ICH?
  - Cautiously, recommend shared decision making as well as discussion with neurosurgery
  - Other options (left atrial appendage occlusion)

Conclusion

- PAUSE-based approach over ASRA-based approach to perioperative DOAC management (2 day hold) is reasonable
- Reduced-dose DOACs can be used after the first 6 months of therapeutic AC, even in people with cancer-associated VTE
- Restarting AC after ICH lowers stroke risk but increases ICH risk

References

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- PAUSE-based approach over ASRA-based approach to perioperative DOAC management (2 day hold) is reasonable
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