Advances in Target Specific Oral Anticoagulants 2015

CHOICES AFTER 60 YEARS!

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- No disclosures to report

Objectives

- Describe the basic pharmacology, clinical indications, and the pro's and con's of TSOAC's.
- Utilize knowledge to select patients for TSOAC's.
- Appreciate the paradigm shifts in Anticoagulation management in 2015.

History

History

- University of Wisconsin 1940, Karl Link, dicumarol (hydroxycoumarin)
- Mayo Clinic 1950's warfarin used clinically
- WARF-arin
- Only orally used anticoagulant for last 60 years

Oral Anticoagulants

Comparison of Oral Anticoagulants

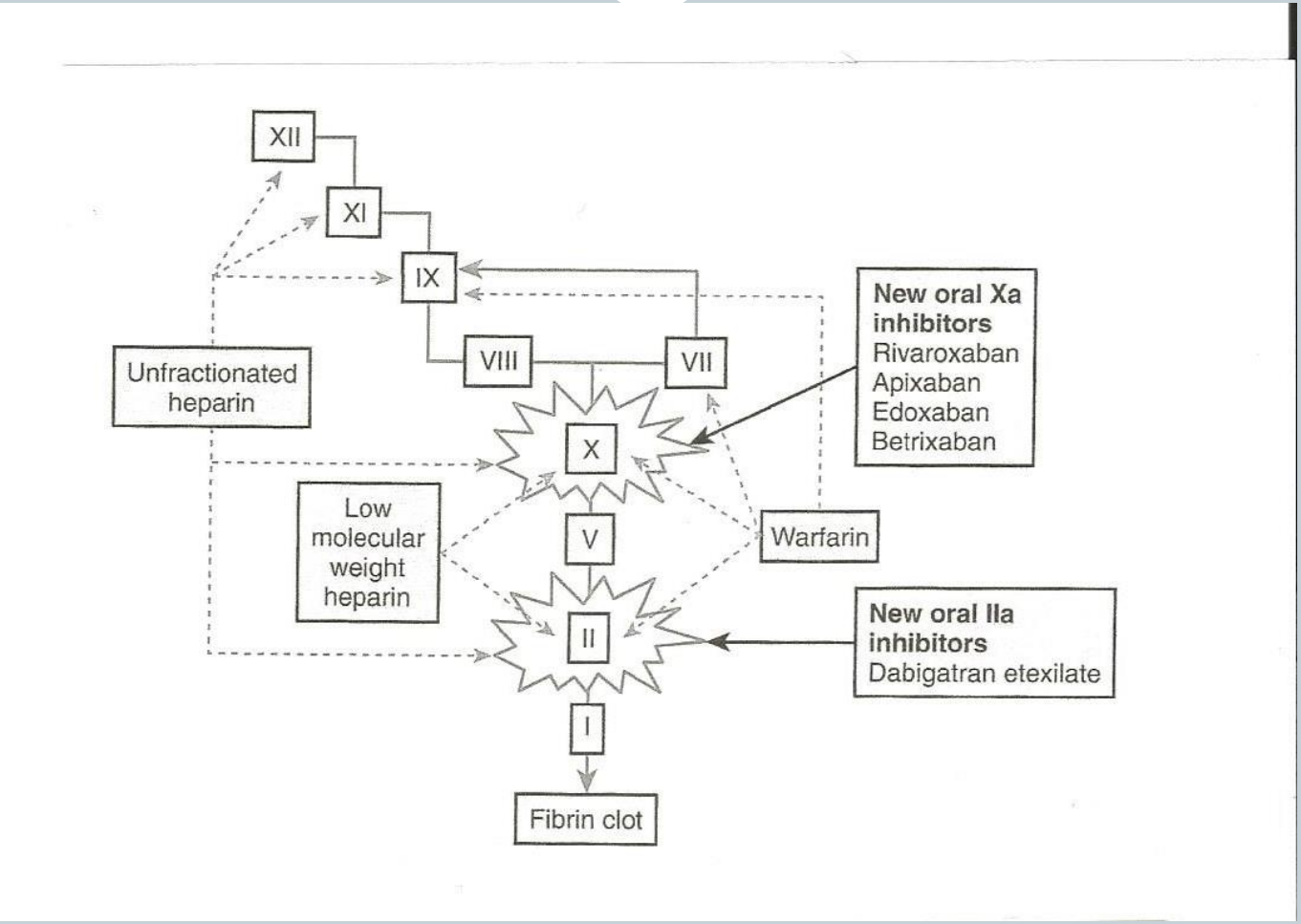
Agent	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa, VIIa, IXa, Xa	IIa	Xa	Xa	Xa
Dosing frequency	Once daily	BID	Once daily	BID	Once daily
Peak effect	4-5 days	1.5-3 h	2-4 h	1-3 h	1-2 h
Half-life	40 h	12-17 h	5-9 h	9-14 h	9-11 h
Renal elim.	None	80%	33%	25%	35-50%
Dialyzable	No	Yes	No	No	No
Interactions	Many	P-gp	3A4, P-gp	3A4, P-gp	3A4, P-gp
Monitoring	Yes	No	No	No	No
Antidote	Vitamin K	No	No	No	No
Lab measure	INR	aPTT (qual)	PT (qual)	No data	PT (qual)

P-gp = p glycoprotein
3A4 = cytochrome P450 3A4
qual = qualitative

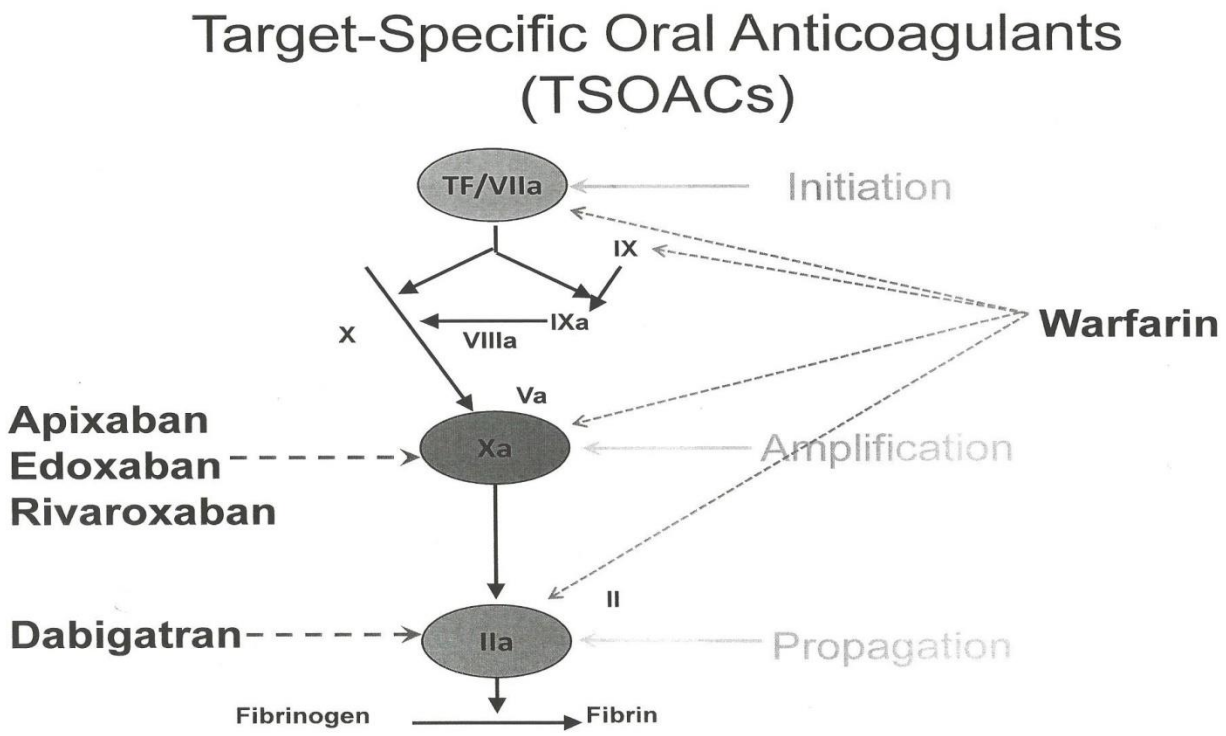
Cove CL, Hylek EM. J Am Heart Assoc. 2013; 2:e000136.


That's an old photo

Coagulation Cascade



Hemostasis


Target-Specific Oral Anticoagulants
(TSOACs)
TF/VIIa
Initiation
IX
IXa
VIIIa
X
Warfarin
Va
Apixaban
Edoxaban
Rivaroxaban
Xa
Amplification
II
Dabigatran
IIa
Propagation
Fibrinogen
Fibrin

What we know about Warfarin

- Extensive library of drug interactions
- Quality Metrics: TTR, %INR in range
- Anticoagulation Clinics reduce risk of thrombosis and bleeding by 50% from usual care
- Guidelines (not evidenced based, yet) on bridging to reduce risk of recurrent thrombosis and bleeding

What we know about Warfarin

- Can extend INR testing up to 12 weeks
- POC testing has allowed PST and PSM
  - Mixed results in meta analyses in end points
  - Improved TTR and patient satisfaction
  - Potential for improved risk/benefit ratio
- Indications: Mechanical Heart Valves, cancer, strong thrombophilia (APS), noncompliance, cardiac thrombus, valvular HD , AF, VTE, post cardiac surgery

What else do we know ?

- Warfarin still accounts for majority of ER visits for ADEs in US .
- Narrow Therapeutic Index still is difficult to maintain with 35% in clinical studies TTR 50% or better.
- Inconvenience of monitoring/bridging and cost.
- Clinical Perception and bias
  - Only 2/3 of patients who were retrospective good candidates received warfarin.

What we know about TSOAC's

- No monitoring of coagulation intensity.
- More convenient and satisfaction for those with active lives and no access to AC clinics.
- Fewer drug interactions but ABSOLUTE contraindications instead of "relative"
  - CY3A4, PPI, P-gp inducers/inhibitors
- There may be new side effects – GI, Skin Rash

What are TSOAC's

- TSOAC's, DOAC's, ODI's, NOAC's
- Highly target specific: **IIa** or **Xa**
- One DTI: Dabigatran (Pradaxa)
- Three Direct Xa Inhibitors: Rivaro**Xaban** (Xarelto) Api**Xaban** (Eliquis), and Endo**Xaban** (Savaysa)

Dabigatran Specifics

- BID dosing
- Highly sensitive to **renal effects, GI issues, Storage issues**
- P-gp inhibitors (increased) **verapamil** and inducers **rifampin** (decreased)
- Indications: **NVAF, VTE treatment (after heparin bridge/warfarin)**

Apixaban Specifics

- **BID** dosing
- Dose adjustment recommended in **age ≥ 80, Weight less than or equal to 60 kg, or Creatinine ≥ 1.5**
- **CYP-3A4 and P-gp Inhibitors:** Ketoconazole, azoles, ritanovir
- FDA Indications: **VTE prophylaxis hip/knee, VTE management, NVAF**
- Renal Treshold: <15cc/ml (AF), <30 cc/ml VTE

Rivaroxaban Specifics

- **Daily** dosing (Except VTE Rx 21 d BID)
- Indications: **NVAF (evening meal), VTE prophylaxis, VTE treatment**
- **CYP-3A4 and P-gp inhibitors**
- Renal thresholds: <15 cc/min NVAF, <30 cc/min VTE

Endoxaban Specifics

- **Daily** dosing
- Moderate renal effect
- **CYP-3A4 and P-gp inhibitors**
- Indications: **NVAF/VTE treatment**

TSOAC's vs VKA/Heparins

- **Thromboembolism (Benefit)**
  - **Arterial/NVAF**: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI
  - Non inferiority and superiority (apixaban, dabigatran*)
  - End points: Stroke (Ischemic/hemorrhagic) and systemic embolism
  - Pooled Meta-analyses from FDA on trials is consistent

Pooled Meta-analyses

- Significant reduction in **end point** (stroke/systemic embolism)
  - OR 0.85 (0.74-0.99) ARR 0.7%
- Significant reduction in **Hemorrhagic stroke**
  - RR 0.48 (0.36-0.62)
- Significant reduction in **all-cause Mortality**
  - RR 0.88 (0.82-0.96)

TSOAC's vs. VKA/Heparins

Venous Thromboembolism

- Primary

- VTE Prophylaxis in Major Orthopedic Procedures: RE-MOBIZE, ADVANCE, RECORD: superiority in VTE to enoxaparin for rivaroxaban and apixaban and non inferiorty to dabigatran.

- VTE prophylaxis in medical illness: ADOPT, MAGELLAN non inferiority to enoxaparin

TSOAC's vs. VKA/Heparins

- **VTE secondary prevention**:
- EINSTEIN-DVT/PE/EXT, RECOVER, AMPLIFY-EXT, RESONATE:
  - non inferiority to enoxaparin/VKA in recurrent VTE/mortality
  - Meta-analyses show consistent trend similar efficacy and better safety
  - Xa may be preferred over dabigatran due to bleeding/renal effects
  - ACP 2012 does NOT endorse as first line treatment
  - RCT's did NOT include hemodynamically unstable patients
- Dabigatran/Endoxaban requires previous treatment
- Apixaban has superiority in safety (major bleeds)

TSOAC's vs. VKA/Heparins

- **Bleeding: (Risk/Safety)**
  - **Meta- analysis 12 trials/over 100 K patients in NVAF/VTE (Chai-Adisaksopha et. al., Blood 2014)**
    - **Lower risk of major bleeds/GI RR 0.72 (0.62-0.85)**
    - **fatal bleeds RR 0.53 (0.43-0.64)**
    - **intracranial bleeds RR 0.43 (0.37-0.50)**
    - **Trend toward less serious bleeding**
  - **Lower risk of annual bleeds:**
    - **VKA 3-5% vs. TSOAC's 1-3%**
  - **No difference in renal failure or older age**
  - No specific Antidote **to TSOAC's (Factor 4 PCC)**

TSOAC's vs. VKA/Heparins

- **Adherence**: No difference in meta analysis 18 trials 13 % VTE and 22 % NVAF.
- **Monitoring**: Anticoagulation monitoring not needed for TSOAC's. Close Monitoring needed for both.
- **Drug Interactions:** Relative with VKA/heparins but ABSOLUTE with TSOAC's.

TSOAC Indications

- NVAF
- VTE Primary Prevention in Major Orthopedic Procedures
- VTE Secondary Prevention
- HIT
- ?ACS
- ?Protein C deficiency

TSOAC's vs. VKA/Heparins

- **Cost:** Direct vs. Indirect.
- **Compliance:** Short vs. Long T ½, Daily vs. BID, health literacy
- **Availability/ Barriers:** Insurance, pharmacy stock, AC clinic, rural settings.

TSOAC Contraindications

- Prosthetic Heart Valves
- Pregnancy/breastfeeding
- Cancer
- thrombophilia
- pediatric patients
- severe renal impairment
- GI disease/bleeding
- Antithrombic therapy ASA/clopidogrel
- Noncompliance (BLACK BOX)
- spinal/epidural procedures (BLACK BOX).

TSOAC's vs. VKA/Heparins

- **Bridging:** Dependent on T1/2. Not recommended for TSOAC.
  - Perioperative management is similar based on renal function, bleeding risk of procedure, risk of thromboembolism, and drug.
- **Transitions:** Protocols exist to transition patients from one drug to another.
- **Patient Education:** TSOAC's are not widely known, **last dose**, Medic Alert, Black Box warning, no specific antidote, compliance.

Bottom Line

- **CAREFUL PATIENT SELECTION**

Favorable use of TSOAC's

- Patients with labile INR on warfarin despite excellent compliance
- Poor access to monitoring/ active life style
- No severe hepatic or renal dysfunction
- Able to understand compliance and risks
- Warfarin contraindication

Poor Candidates for TSOAC's

- Triple therapy and/or drug interaction
- Noncompliance/poor health literacy
- Severe renal dysfunction or/and unstable hepatic function
- Reservations about reversibility
- Cost and availability

Take Home Points

- VKA's are still the "drug of choice" for most conditions.
- TSOAC's are increasingly establishing themselves as superior and safer anticoagulants for carefully selected patients
- Paradigm shifts will need to occur for full utilization of TSOAC's to occur (clinicians, patients, payers)

References and Resources

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