Cardiology Pharmacotherapy: Significant Updates for 2011

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Disclosures

- No financial interests to report
- No conflicts of interest to report
- Some off-label discussions will be held

Objectives

- Review key newly approved medications for cardiology
- Discuss defining characteristics for each
- Discuss therapeutic value for each
- Describe important changes to certain established cardiovascular medications

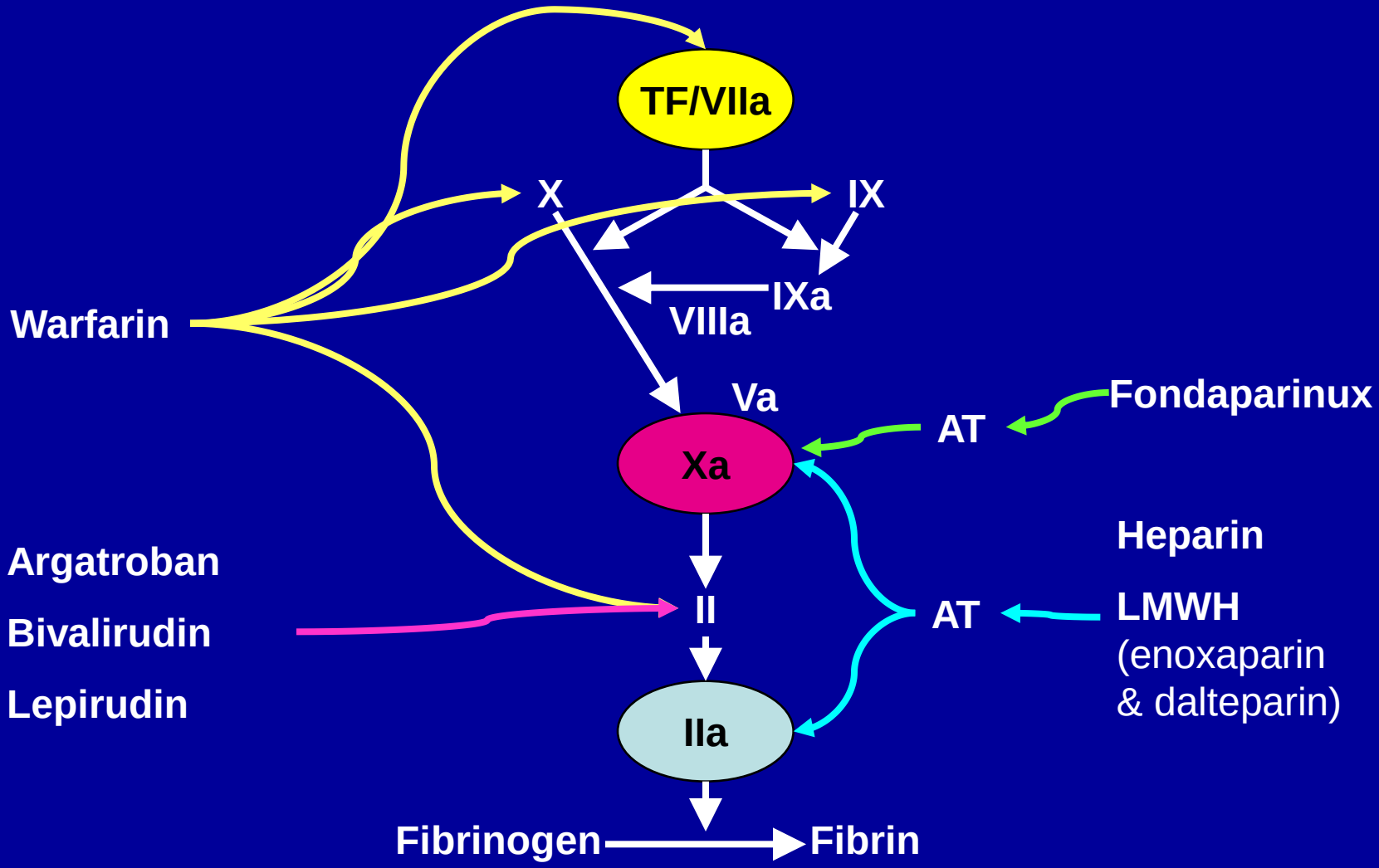
Abbreviations Used

- CrCl – Creatinine Clearance
- DVT – Deep Vein Thrombosis
- PE – Pulmonary Embolism
- $t_{½}$ – elimination half-life
- TF – Tissue Factor

New Oral Anticoagulants

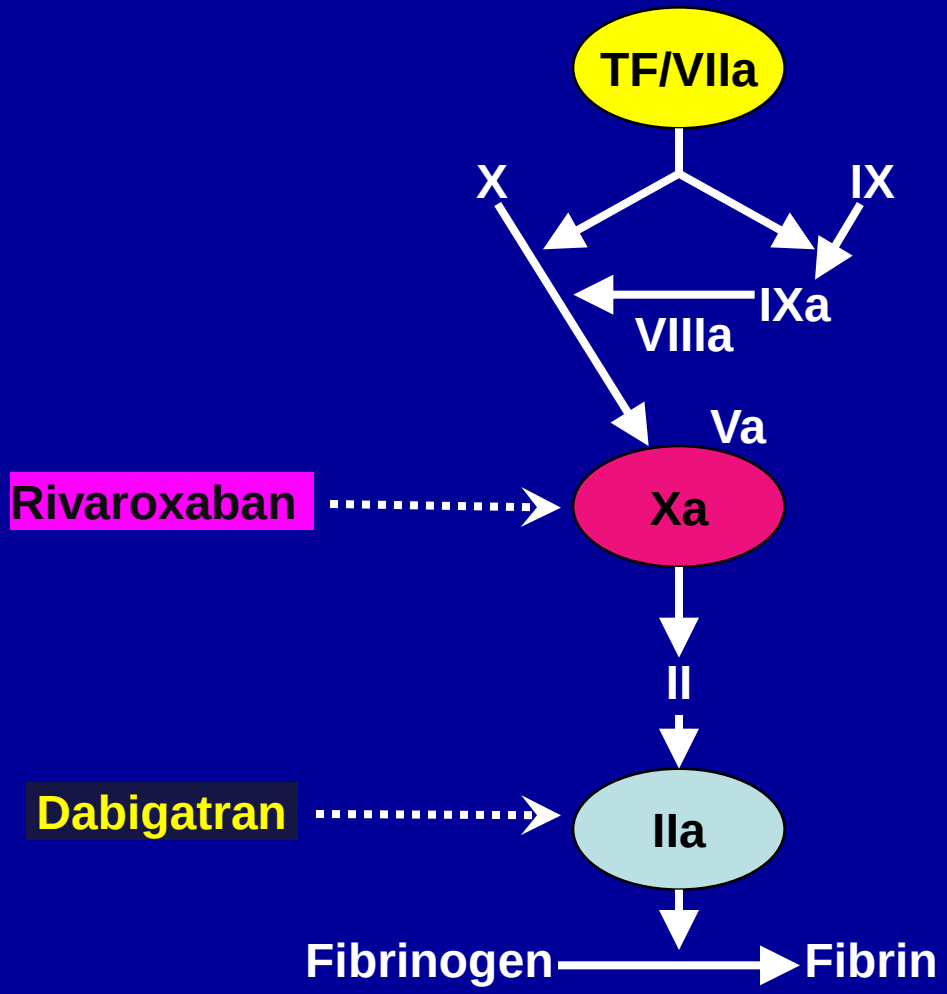
The beginning of a new era…

Existing Anticoagulants



Adapted from Weitz & Bates, J Thromb Haemost 2005

New Oral Anticoagulants



Adapted from Weitz & Bates, J Thromb Haemost 2005

Dabigatran (Pradaxa): Background

- Orally active direct thrombin inhibitor

  Thrombin is Factor IIa
- Does not require routine monitoring; dose is "fixed"
- Quick onset (~ 2 hours); $t_{1/2}$ ≈ 12-17 hrs
- No need to bridge!

  Exception: transitioning to warfarin

Eriksson BI et al. J Thromb Haemost 2007; 5:2178–2185

Dabigatran (Pradaxa): FDA Labeling

- **FDA indication:**

  Reduce the risk of stroke and systemic embolism in patients with non-valvular A-fib

- **Contraindications:**
  - **Active pathological bleeding**
  - **H/O serious hypersensitivity reaction**
- **Dose:**
  - **CrCl > 30 mL/min: 150 mg PO twice daily**
  - **CrCl 15-30 mL/min: 75 mg PO twice daily**

Pradaxa package insert (October 2010 edition). Boehringer Ingelheim, Inc. Ridgefield, CT

Dabigatran Characteristics[1,2]

- **Absorption: 3-7%**

  Note: capsule design aids absorption
- Distribution- 35% bound to proteins
- **Metabolism**
  - Activated by hydrolyis
  - **Substrate for p-GP**
  - **Not a substrate for CYP450**
- **Excretion- 80% renally eliminated**

1. Eriksson BI et al. J Thromb Haemost 2007; 5:2178–2185
2. Pradaxa package insert (October 2010 edition). Boehringer Ingelheim, Inc. Ridgefield, CT

Dabigatran (Pradaxa): Nursing Considerations

- **Administration:**
  - Capsule may be given ± food
  - Must be swallowed whole; cannot be opened
- **Missed doses:**
  - ≤ 6 hours since missed dose: administer now
  - > 6 hours since missed dose: omit if next dose cannot be ≥ 6 hours later
  - Never "double up"

Pradaxa package insert (October 2010 edition). Boehringer Ingelheim, Inc. Ridgefield, CT

Transitioning TO Dabigatran

- **FROM SQ inj (e.g. Lovenox, Arixtra)**
  - Give 1st dose of dabigatran when "next dose" of injection would have been given
- **FROM heparin infusion**
  - Stop heparin and give 1st dose of dabigatran at the same time (do both simultaneously)
- **FROM warfarin (Coumadin)**
  - Stop warfarin; and start dabigatran when INR is < 2

Pradaxa package insert (October 2010 edition). Boehringer Ingelheim, Inc. Ridgefield, CT

Transitioning FROM Dabigatran

- TO SQ inj (e.g. Lovenox, Arixtra)
  - Give 1st inj at the same time the "next dose" of dabigatran was to be given
- TO heparin infusion
  - CrCl ≥ 30 mL/min: start 12 hrs after last dose
  - CrCl < 30 mL/min: start 24 hrs after last dose
- TO warfarin (Coumadin)
  - See next slide

Pradaxa package insert (October 2010 edition). Boehringer Ingelheim, Inc. Ridgefield, CT

Transitioning FROM Dabigatran to Warfarin

Renal Function	Days of overlap
CrCl > 50 mL/min	3 days
CrCl 31 – 50 mL/min	2 days
CrCl 15 – 30 mL/min	1 day
CrCl < 15 mL/min	no recommendations

Pradaxa package insert (October 2010 edition). Boehringer Ingelheim, Inc. Ridgefield, CT

Dabigatran & PLANNED Surgery

- **Time to "hold" is related to renal function (eliminated by kidneys)**
  - **CrCl ≥ 50 mL/min: stop 1-2 days pre-op**
  - **CrCl < 50 mL/min: stop 3-5 days pre-op**
- **Note found in PI:**

  "Consider longer times for major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required"

Pradaxa package insert (October 2010 edition). Boehringer Ingelheim, Inc. Ridgefield, CT

Dabigatran & UNplanned Surgery

- If no delay is possible, bleeding risk is weighed against the urgency of surgery
- Bleeding risk can be assessed by:
  - Ecarin clotting time (ECT)

    First choice, but may be limited in availability
  - Activated partial thromboplastin time (aPTT)
  - Prothrombin time (PT)/INR
  - Thrombin time (TT) *best ECT alternative*

These tests are <u>NOT</u> for traditional (routine) monitoring!

Pradaxa package insert (October 2010 edition). Boehringer Ingelheim, Inc. Ridgefield, CT

Persistence of Dabigatran Effect

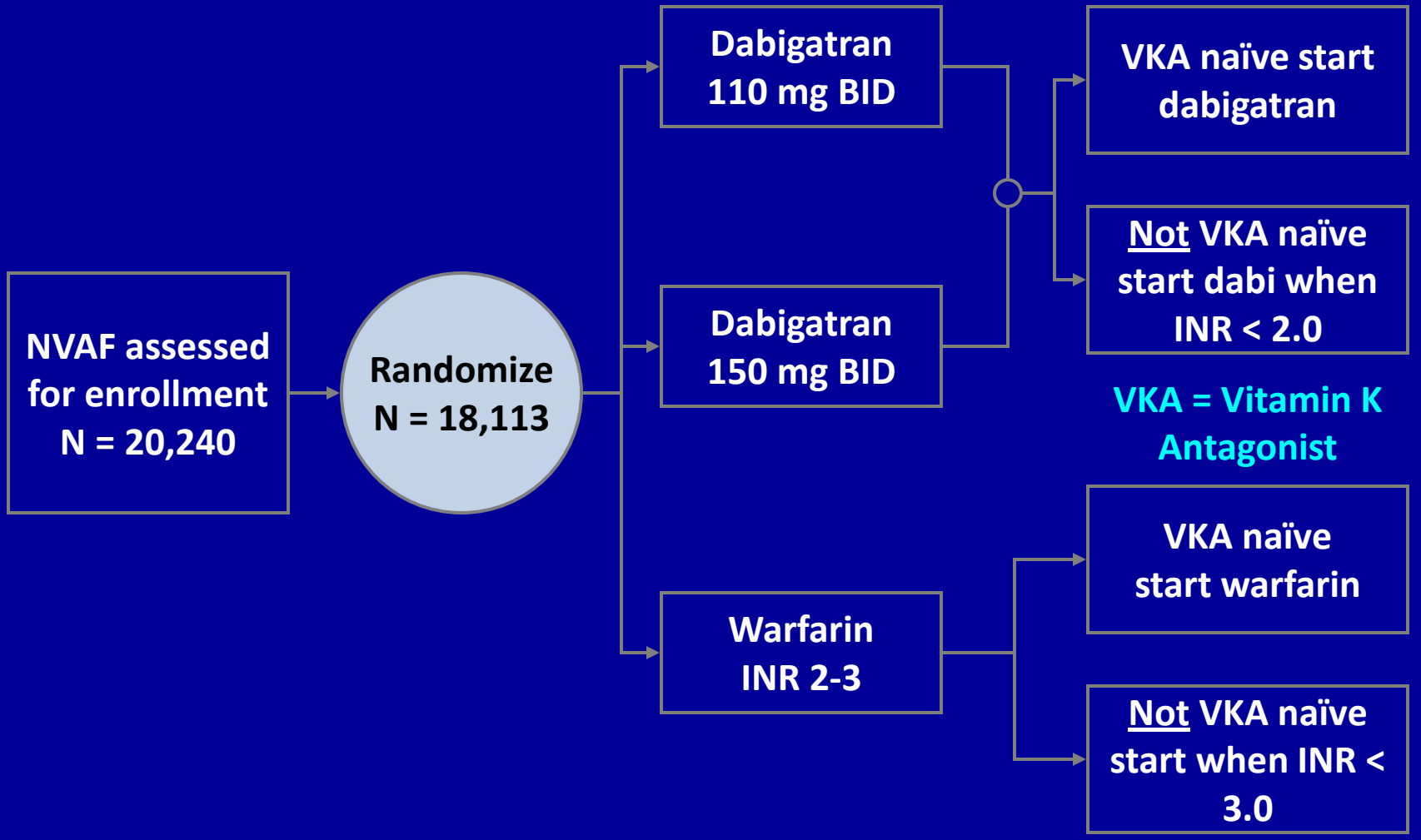
- No known antidote
- Natural "decay" of function is related to $t_{½}$ (12-17 hours)
- Dialysis may be effective, if available
- Uncertain role of other modalities
  - Blood products???

    fresh frozen plasma, cryoprecipitate
  - Factor VIIa???

    rFVIIa (NovoSeven®)

van Ryn, Stangier et al. Thromb Haemost 2010; 103: 1116–1127

RE-LY Study Flow



Connolly SJ, et al. Rationale and design of RE-LY. Am Heart J. 157 (5); 805-810.e2

RE-LY Study: Dabigatran use in A-Fib

- Tested against warfarin (18,000+ patients)

  2 doses tested; only 1 became FDA-approved

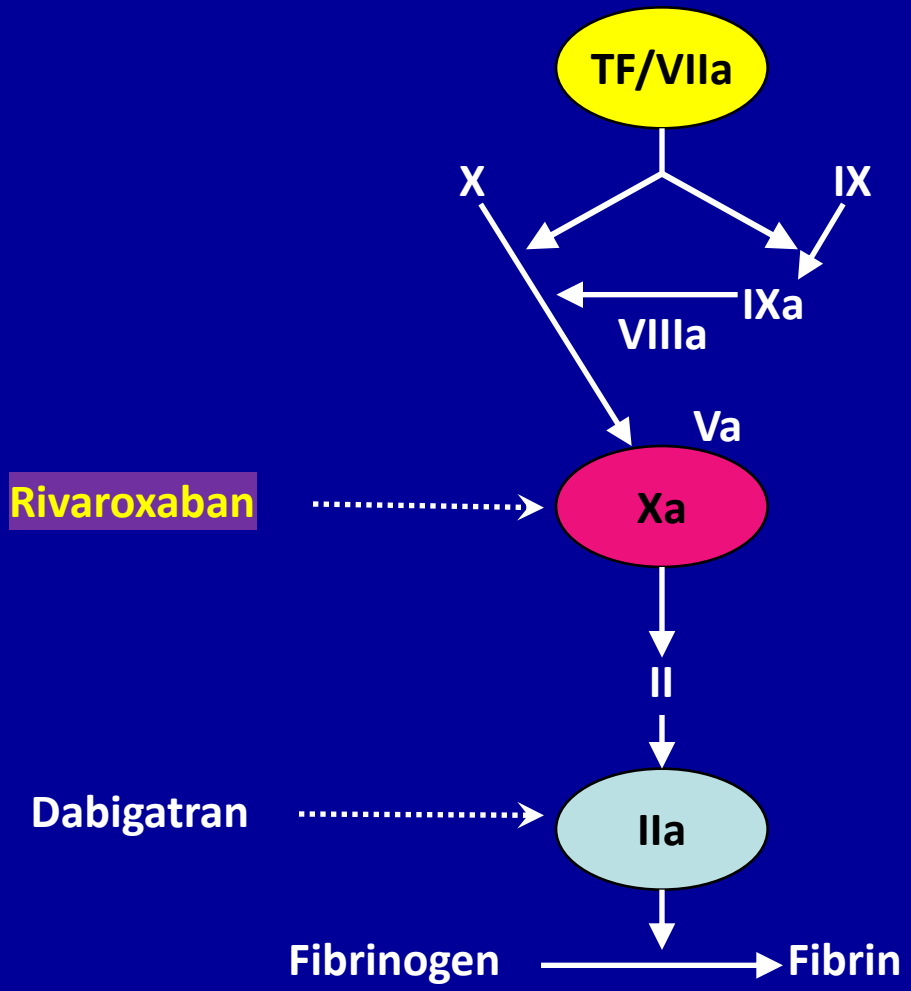
- Compared to warfarin (INR 2-3):
  - Dabigatran 150 mg PO BID
    - Superior efficacy (fewer strokes, etc)
    - Equal major bleeding events

    ~ ⅓ fewer clots, same # of bleeds
  - Dabigatran 110 mg PO BID
    - Equal efficacy (same rate of strokes, etc)
    - Fewer major bleeding events

    ~ ⅕ fewer bleeds, same # of clots

Connolly SJ et al. NEJM 2009; 361:1139–1151.

New Anticoagulants



Adapted from Weitz & Bates, J Thromb Haemost 2005

Rivaroxaban (Xarelto): Background[1,2]

- Orally active, direct Factor Xa inhibitor

  First step in the "common pathway"
- Does not require routine monitoring; dose is "fixed"
- Quick onset (~ 2½ hours); $t_{½}$ ≈ 9 hrs

1. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—after multiple dosing in healthy male subjects. Kubitza, Becka, Voith, Zuehlsdorf. Eur J Clin Pharmacol (2005) 61: 873–880
2. Xarelto prescribing information (July 2011 edition). Janssen, Inc.

Rivaroxaban (Xarelto): Characteristics[1,2]

- Absorption- 80-100% absorbed
- Distribution- ~95% plasma protein bound
- Metabolism- CYP3A4/5, CYP2J2, hydrolysis
- Excretion
  - Urine- 66%
  - Feces- 28%
  - Also substrate for efflux pumps p-GP, ABCG2

1. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—after multiple dosing in healthy male subjects. Kubitza, Becka, Voith, Zuehlsdorf. Eur J Clin Pharmacol (2005) 61: 873–880
2. Xarelto prescribing information (July 2011 edition). Janssen, Inc.

Rivaroxaban (Xarelto): Labeling

- **FDA indication:**

  Prophylaxis of DVT which may lead to PE in patients undergoing knee or hip replacement

- **Contraindications:**
  - **Active pathological bleeding**
  - **H/O hypersensitivity reaction**
- **Dose: 10 mg PO daily ± food**

  CrCl < 30 mL/min: not recommended

Xarelto prescribing information (July 2011 edition). Janssen, Inc.

Rivaroxaban (Xarelto): Nursing Implications

- **Administration:**
  - May be crushed; if administered via tube, tube placement (in stomach) is important
  - Start ≥ 6 hrs post-op & hemostasis assured
- **Duration (recommended):**
  - Hip Replacement Surgery: 35 days
  - Knee Replacement Surgery: 12 days
- **Missed Dose: take same day, if able**

Xarelto prescribing information (July 2011 edition). Janssen, Inc.

Rivaroxaban use with Other Anticoagulants

- **Approved for use in prophylaxis only**
  - ***Not typically a situation for "bridging"***
- **Use with other anticoagulants is likely to increase risk of bleeding**
- **No evidence to support increased efficacy**

Xarelto prescribing information (July 2011 edition). Janssen, Inc.

Rivaroxaban Orthopedic Studies

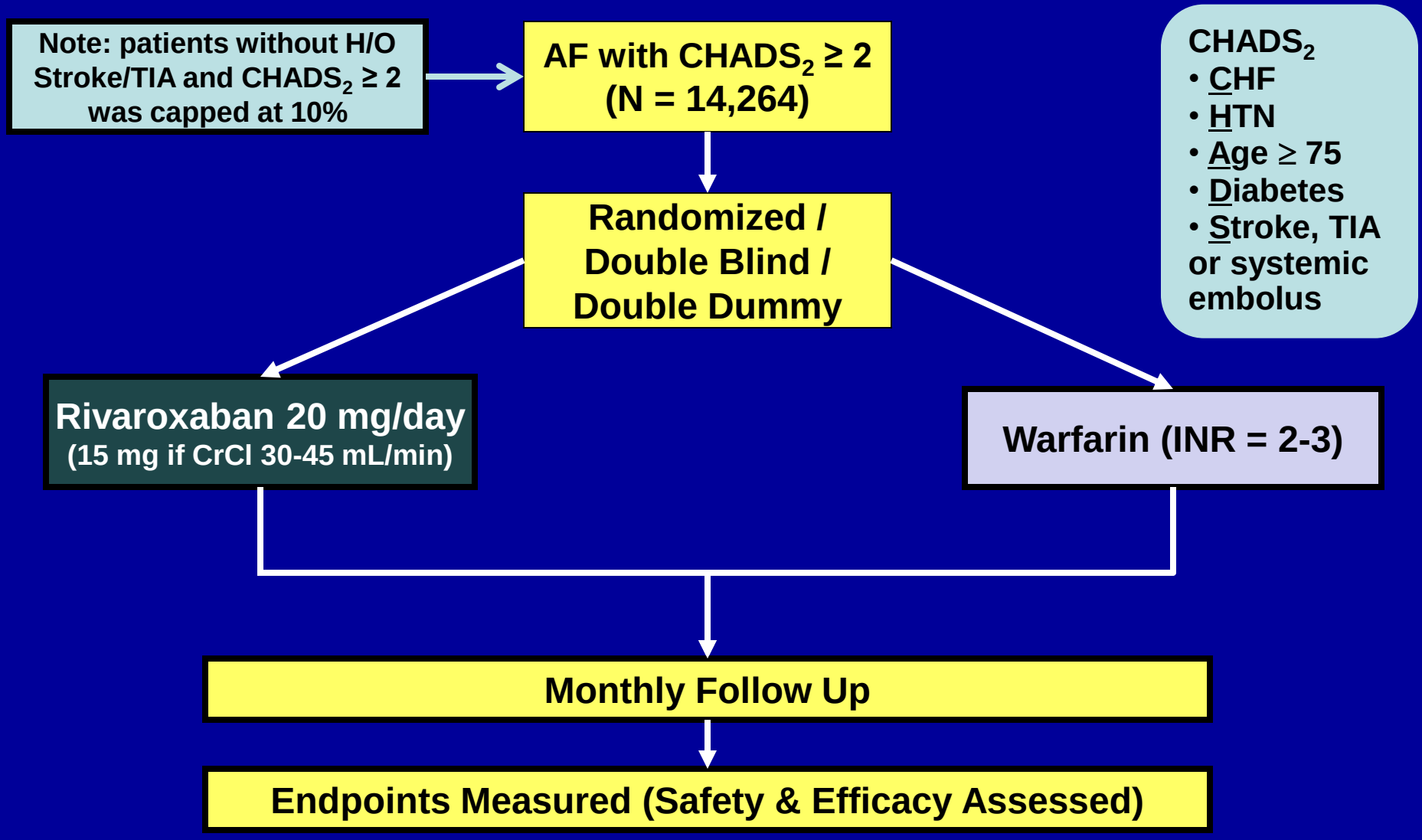
- RECORD 1 (THR)
  - Riva 10 mg daily 6-8 h post op x 35 days
  - Enox 40 mg daily 12 h pre op x 35 days
- RECORD 2 (THR)
  - Riva 10 mg daily 6-8 h post op x 35 days
  - Enox 40 mg daily 12 h pre op x 10-14 → placebo
- RECORD 3 (TKR)
  - Riva 10 mg daily 6-8 h post op x 10-14 days
  - Enox 40 mg daily 12 h pre op x 10-14 days
- RECORD 4 (TKR)
  - Riva 10 mg daily 6-8 h post op x 10-14 days
  - Enox 30 mg q 12 hrs, 12h post op x 10-14 days

P < 0.05

Riva = rivaroxaban (Xarelto), Enox = enoxaparin (Lovenox)

THR = Total Hip Replacement, TKR = Total Knee Replacement

Rivaroxaban in AF (ROCKET-AF)



Patel MR, et al for ROCKET-AF Investigators. 10.1056/nejmoa1009638. August 10, 2011

ROCKET-AF Outcomes

- **Safety: composite of major and non-major clinically relevant bleeding events**
- **Efficacy**
  - **Primary: Composite of stroke (ischemic or hemorrhagic) and systemic embolism**
  - **Secondary:**
    - **Composite of primary + CV Death**
    - **Composite of primary + CV Death + MI**
    - **Individual components of the composites**

Patel MR, et al for ROCKET-AF Investigators. 10.1056/nejmoa1009638. August 10, 2011

ROCKET-AF Primary Outcomes

	Rivaroxaban		Warfarin		HR (95% CI)	P-Value	
	# events # pts	Rate (#/pt yr)	# events # pts	Rate (#/pt yr)	*<1 favors rivaroxaban*	Non-Inferior	Superior
Efficacy as treated	188 6958	1.7	241 7004	2.2	0.79 (0.66-0.96)	<0.001	NR
Safety as treated	189 7061	1.7	243 7082	2.2	0.79 (0.65-0.95)	NR	0.02
Intent-to-treat	269 7081	2.1	306 7090	2.4	0.88 (0.75-1.03)	<0.001	0.12

Patel MR, et al for ROCKET-AF Investigators. 10.1056/nejmoa1009638. August 10, 2011

Future Status

- FDA approval for A-Fib pending

  Expect AF decision November 2011
- Dosing for AF may be different than orthopedic surgery
  - Ortho: 10 mg daily
  - A-Fib: varies with renal function (℞ clearance)
    - 20 mg daily (CrCl > 45 mL/min)
    - 15 mg daily (CrCl 30-45 mL/min)

New Oral Antiplatelet

News from the other half of clot formation

Ticagrelor (Brilinta): Background

- **Orally active $P2Y_{12}$ antagonist** (blocker)
  - **$P2Y_{12}$ is activated by ADP**
  - **$P2Y_{12}$ is responsible for prolonged platelet activation signaling**
  - **Same receptor as clopidogrel (Plavix) and prasugrel (Effient), but has "reversible" binding**
- **Onset:**
  - **Rapid onset (~ 2 hrs); C_{max} by 2-3 hrs**
  - **Not a pro-drug (administered as active form)**

Tantry US, Bliden KP, Gurbel PA. AZD6140. Expert Opin Investig Drugs 2007; 16:225–229

Ticagrelor Characteristics

- **Reversible binding**
  full recovery of platelet upon withdrawal
- **Pharmacokinetics**
  - **Absorption- 36%**
  - **Distribution- >99% protein bound**
  - **Metabolism- CYP3A4**
  - **Excretion- 58% feces, 26% urine**

Tantry US, Bliden KP, Gurbel PA. AZD6140. Expert Opin Investig Drugs 2007; 16:225–229

Ticagrelor: Labeling

- **FDA Indication:**
  - ***Reduce rate of CV death, MI, or stroke in patients with Acute Coronary Syndromes***
  - **Also reduces the rate of stent thrombosis**
- **Contraindications:**
  - **History of intracranial hemorrhage**
  - **Active pathological bleeding**
  - **Severe hepatic impairment**

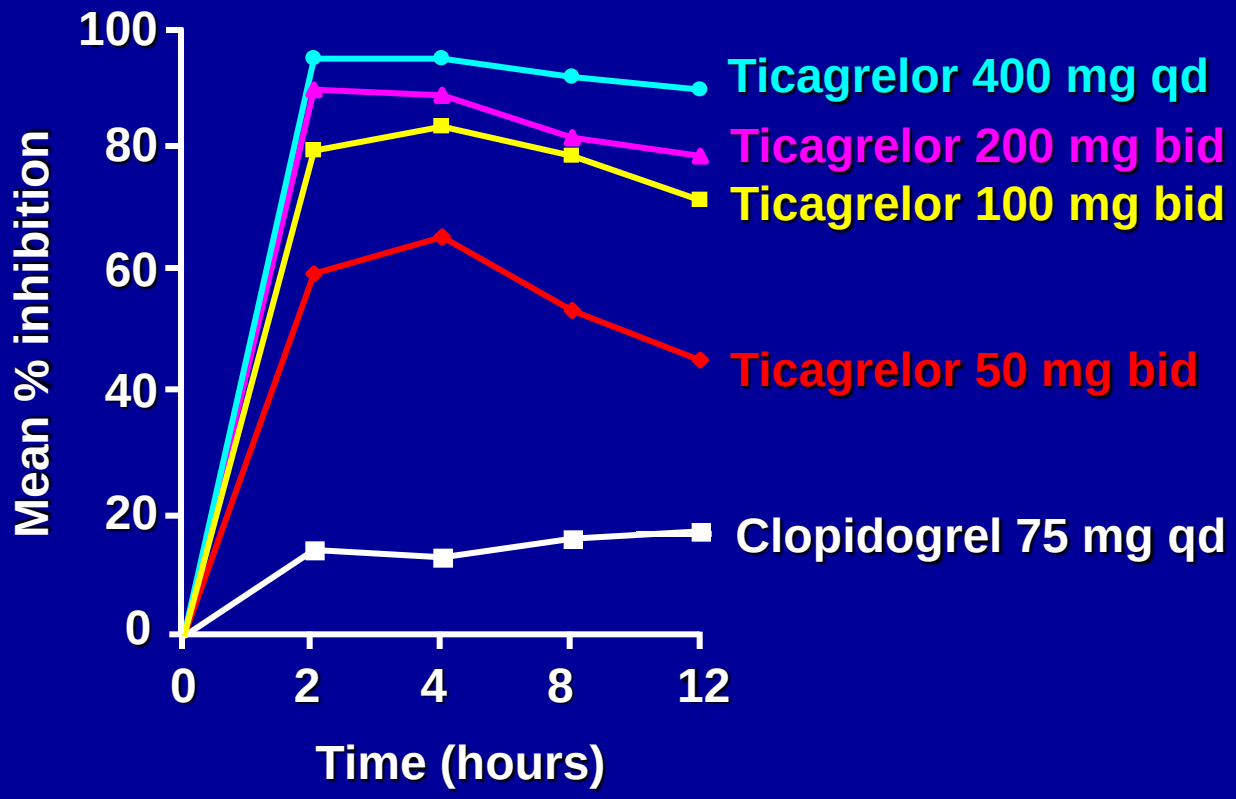
Brilinta package insert. Astra Zeneca, Inc

Ticagrelor: Nursing Implications

- Dosing
  - Two 90 mg tabs (180 mg) x 1, then 90 mg BID
  - Reduce / limit aspirin to 100 mg/day
  - “Plavix-treated" patients are dosed the same
- Administration: ± food
- Missed Dose: “Take next dose at scheduled time”

Brilinta package insert. Astra Zeneca, Inc

Inhibition of Platelet Aggregation



Husted S et al. Eur Heart J. 2006;27:1038-47.

PLATO

PLATO

Moderate to high-risk ACS patients (UA/NSTEMI/STEMI, PCI, medically managed, or CABG)

(N=18,000)

ASA + Clopidogrel
300 mg LD/75 mg QD
600 mg LD allowed in PCI

ASA + Ticagrelor
180 mg LD/90 mg BID

12-month maximum exposure
(Min = 6 mo, Max = 12 mo, Mean = 11 mo)

Primary endpoint:	**CV Death (CVD) + MI + stroke**
Secondary endpoint:	CVD/MI/stroke/revascularization with PCI; CVD/MI/stroke, severe recurrent ischemia

ASA = acetylsalicylic acid; bid = twice daily; CVD = cardiovascular disease; ld = loading dose; MI = myocardial infarction; NSTEMI = non-ST-segment elevation MI; qd = once daily; STEMI = ST-segment elevation MI; UA = unstable angina.

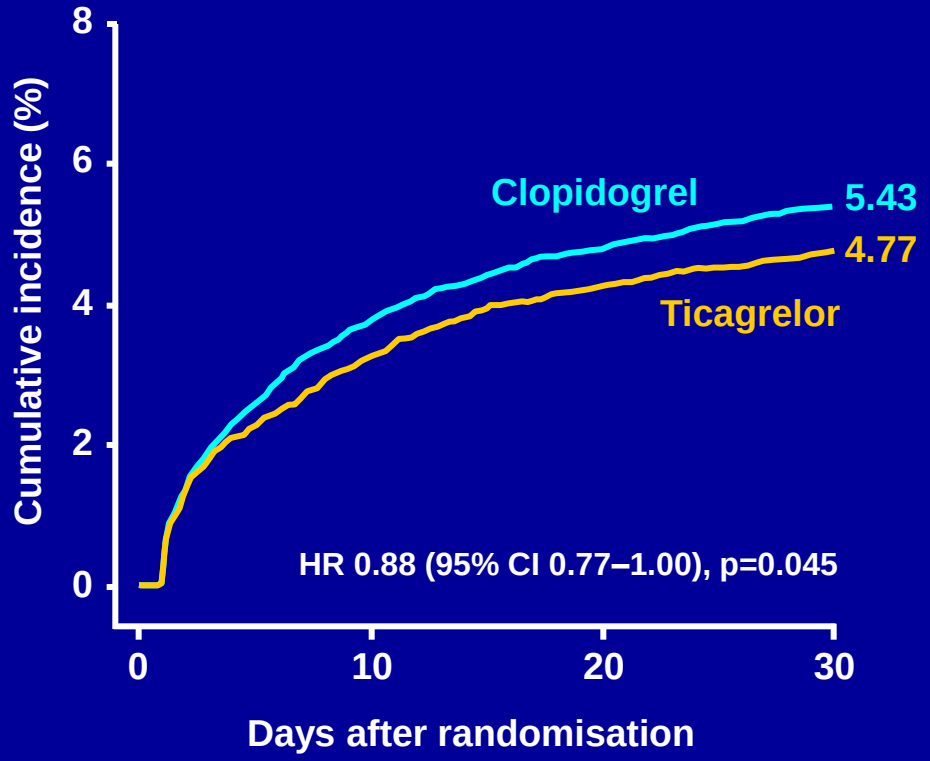
PLATO Primary Outcomes

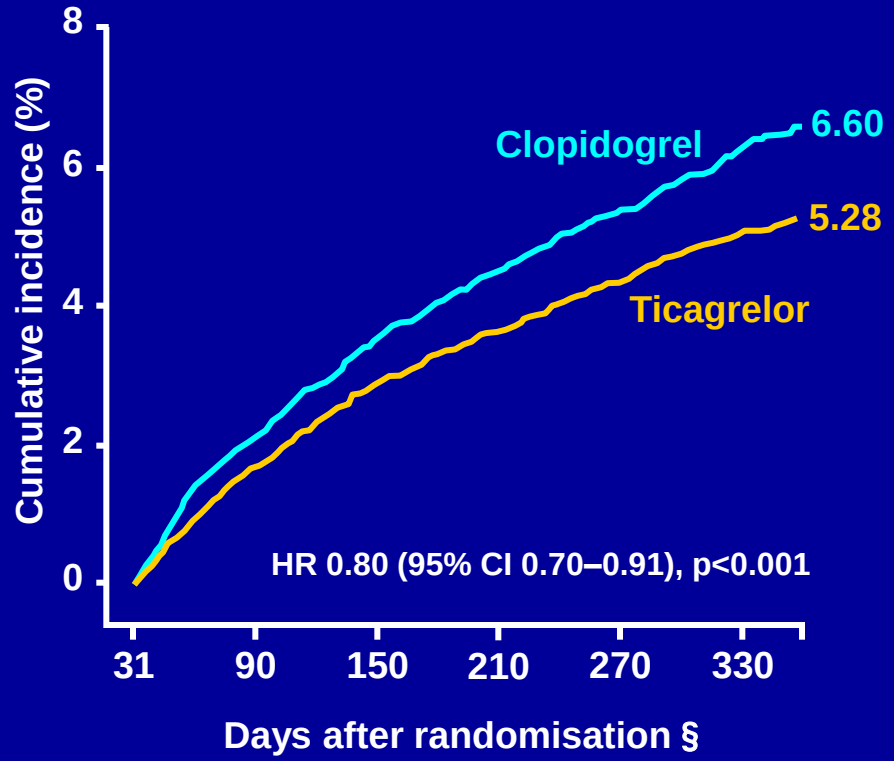
End Point (Efficacy Outcome)	Ticagrelor N = 9,333 N (%)	Clopidogrel N = 9,291 N (%)	HR for Ticagrelor (95% CI)
Primary Endpoint (Composite) NNT = 53	864 (9.8)	1,014 (11.7)	0.84 (0.77-0.92)

Wallentin L, et al. N Engl J Med 2009;361

Primary Efficacy Endpoint Over Time

PLATO





No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

§ Excludes patients with any primary event during the first 30 days

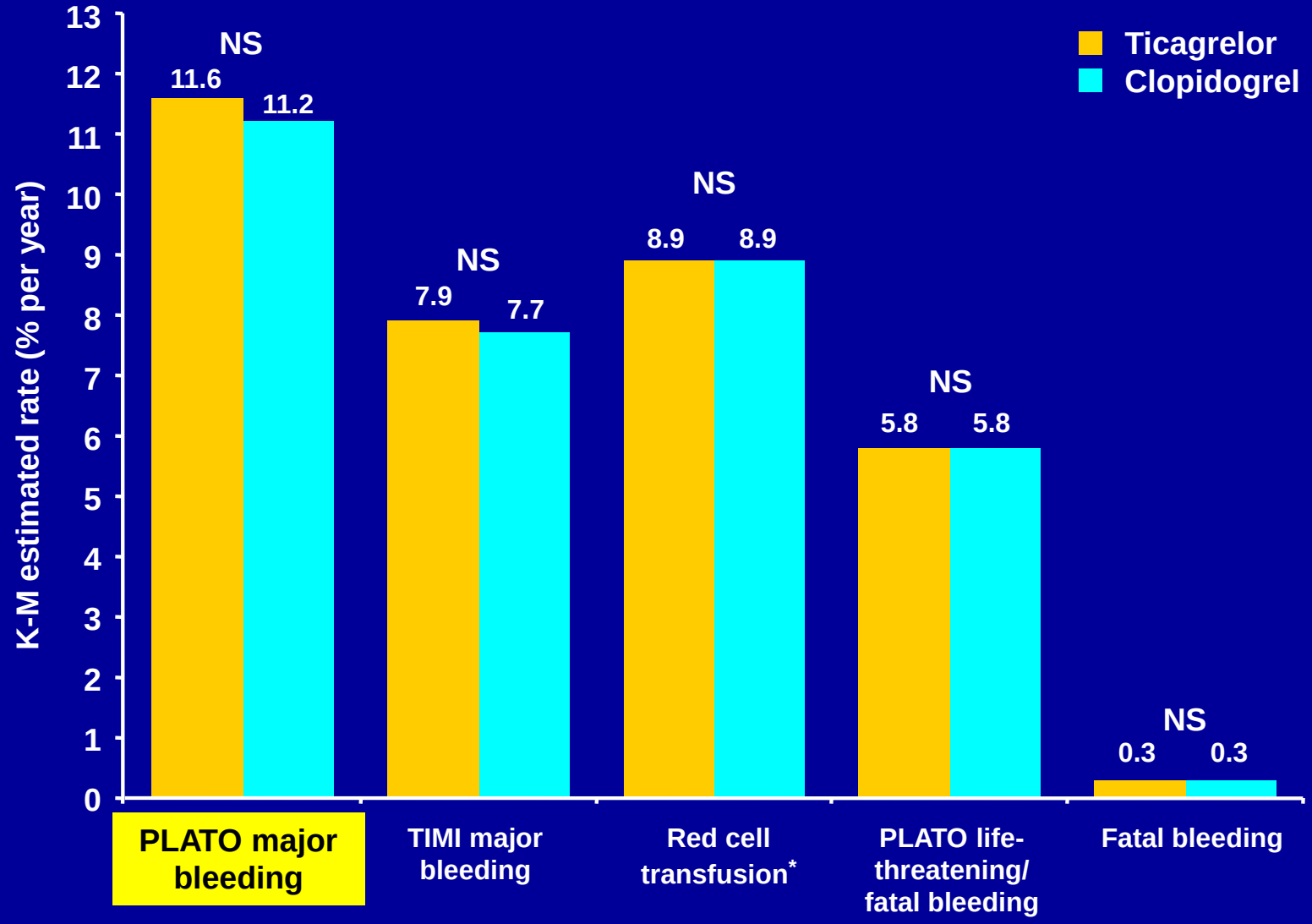
PLATO Safety Outcomes

Variable (Bleeding Outcome)	Ticagrelor N = 9,235 N (%)	Clopidogrel N = 9,186 N (%)	HR for Ticagrelor (95% CI)
Major Bleed (PLATO)	961 (11.6)	929 (11.2)	1.04 (0.95-1.13)

Wallentin L, et al. N Engl J Med 2009;361

Total Major Bleeding

PLATO



Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. NEJM 2007;357:2001–15;
*Proportion of patients (%); NS = not significant

Ticagrelor Side Effects

- **Dyspnea**

  Ticagrelor is an ATP analog metabolized to adenosine, which can trigger dyspnea

  NNH = 17 – **Any dsypnea: 13.8% (tica) -v- 7.8% (clop); p < 0.001**

  NNH = 250 – **Required D/C: 4.4% (tica) -v- 4% (clop); p < 0.001**

- **Bradycardia:**

  4.4% (ticagrelor) -v- 4% (clopidogrel) (p = 0.21)

- **Fluid retention**
- **↑ uric acid levels**

Wallentin L, et al. N Engl J Med 2009;361

Updates to Existing Medications

Teaching Old Dogs New Tricks

Simvastatin (Zocor)

- **Hepatically metabolized by "CYP3A4"**

  CYP3A4 is one of many liver enzymes responsible for metabolizing substances

- **Simvastatin inhibits CYP3A4 activity (℞ interactions)**
- **Labeling revised with more stringent dose limits & contraindications**
- **See next slide for summary table**

www.fda.gov/Drugs/DrugSafety/ucm256581.htm, retrieved July 8, 2011

Old Simvastatin Label	New Simvastatin Label
Avoid with: itraconazole, ketoconazole, nefazodone, erythromycin, telithromycin, clarithromycin, HIV PI's	***Contraindicated with***: ℞ in left "avoid with" column, PLUS posaconazole, gemfibrozil, cyclosporine, danazol
NTE 10 mg/Day with: gemfibrozil, cyclosporine, danazol	**NTE 10 mg/Day with:** amiodarone, verapamil, diltiazem
NTE 20 mg/Day with: amiodarone or verapamil	**NTE 20 mg/Day with:** amlodipine, ranolazine
NTE 40 mg/Day with diltiazem	**NTE 40 mg/Day with:** ticagrelor (from ticagrelor PI)
Avoid large quantities of grapefruit juice (> 1 qt/day)	**No change**

NTE = Not to Exceed (maximum 24 hour dose)

www.fda.gov/Drugs/DrugSafety/ucm256581.htm, retrieved July 8, 2011

Dronedarone (Multaq)

- Anti-arrhythmic similar to amiodarone, except no Iodine[1]

  May not exhibit organ toxicity over time
- FDA approved to reduce hospitalizations in non-permanent AF[1]
- Trial in permanent AF halted early due to increased events[2]

1. Multaq Prescribing Information. Sanofi-Aventis, Inc
2. www.fda.gov/Drugs/DrugSafety/ucm264059.htm, retrieved August 8, 2011

Emerging Dronedarone Issues

- Cardiovascular Outcomes (July 2011)[1]
  - Double the ***composite rate*** of CV Death, MI, Stroke, and Systemic Embolization
  - Data breakdown on next slide
- Hepatoxicity (January 2011)[2]
  - Presumably on-label use
  - ≈ 492 K prescriptions dispensed to ≈ 147 K out patients (July 09 - Oct 10)
  - 2 reported cases out of 492,000 = 0.00004%

1. www.fda.gov/Drugs/DrugSafety/ucm264059.htm, retrieved August 8, 2011
2. www.fda.gov/Drugs/DrugSafety/ucm240011.htm, retrieved August 8, 2011

Dronedarone Safety Data

Data from PALLAS	Multaq N=1572 n (%)	Placebo N=1577 n (%)	Hazard Ratio	p-value
Primary Composite Endpoint #1 CV Death, Myocardial Infarction, Stroke, Systemic Embolism	32 (2)	14 (0.9)	2.3	0.009
Co-Primary Endpoint #2 Death, Unplanned CV Hospitalization	118 (7.5)	81 (5.1)	1.5	0.006
Death	16 (1)	7 (0.4)	2.3	0.065
Myocardial Infarction	3 (0.2)	3 (0.2)	1.0	1
Stroke	17 (1.1)	7 (0.4)	2.4	0.047
Heart Failure Hospitalization	34 (2.2)	15 (1)	2.3	0.008

Note: These are preliminary data provided by the manufacturer; therefore, the data have not undergone quality assurance procedures and have not been completely adjudicated.

www.fda.gov/Drugs/DrugSafety/ucm264059.htm, retrieved August 8, 2011

FDA's Take on PALLAS

- **Do NOT use in permanent atrial fibrillation**
- **FDA is evaluating preliminary PALLAS results**

  Evaluating potential impact on paroxysmal or persistent AF/Flutter
- **The PALLAS are yet to undergo peer review & publication process**

www.fda.gov/Drugs/DrugSafety/ucm264059.htm, retrieved August 8, 2011

Rosiglitazone (Avandia)

- 9/23/2010 – FDA announced increased rates of MI in rosiglitazone patients
- 2/3/2011 – FDA announced restrictions
  - Patients already tolerating rosiglitazone
  - Patients unsuccessful on other medications and do not wish to use pioglitazone (Actos)
  - Special program (REMS) requires enrollment by physician, patient, and pharmacist
- Data derived from multiple sources

www.fda.gov/Drugs/DrugSafety/ucm241411.htm, retrieved August 8, 2011

Review

- Two new anticoagulants have arrived
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
- Ticagrelor (Brilinta) – new anti-platelet
- Increased FDA scrutiny of existing meds
  - Simvastatin (Zocor, others)
  - Dronedarone (Multaq)
  - Rosiglitazone (Avandia, others)

Ticagrelor "PLATO Bleeding"

PLATO Term	Description	Associated ↓↓ in hemoglobin	X-Fusion (whole blood or PRBC)
Major: Life-threatening	• Fatal • ICH • Intra-pericardial w/ tamponade • Hypovolemic shock • Hypotension requiring pressors or surgery	5 g	≥ 4 Units
Major: Other	Significantly disabling (e.g. intraocular with vision loss)	3-5 g	2-3 Units
Minor bleed	Requires intervention	N/A	N/A
Minimal bleed	All others not requiring intervention or treatment	N/A	N/A

PLATO Trial Design. Am Heart J 2009;157:599-605