



New Oral Anticoagulants

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Overview

- Why we need alternatives to warfarin
- Review of the 3 new oral anticoagulants
- Results from major trials:
 - Thromboprophylaxis in orthopedic surgery
 - Treatment of VTE
 - Stroke prevention in afib
- Cost effectiveness
- Monitoring/effects on anticoagulation tests
- Review advantages/disadvantages



What's wrong with warfarin?

- Narrow therapeutic range
- Slow onset of action
- Slow offset of action (long duration of action, long elimination half life)
- Multiple drug and dietary interactions
- Monitoring required to maintain in therapeutic range



What's wrong with warfarin?

- Difficult to manage for invasive procedures
- Impaired quality of life for the patient
- Labor intensive for health care provider
- Under-use of therapy due to fear of adverse events and complexity of management



What's wrong with warfarin?

- Efficacy is dependent upon infrastructure
 - Time in therapeutic range (TTR) is associated with improved safety and efficacy
 - TTR is improved with AC management programs
 - TTR is greater in countries with more sophisticated health care infrastructure



What are the attributes of the ideal anticoagulant?

- Oral administration
- Rapid onset of action/rapid offset of action
- Wide therapeutic range
- Predictable therapeutic effect with fixed or weight-based dosing
- No food or drug-drug interactions



What are the attributes of the ideal anticoagulant?

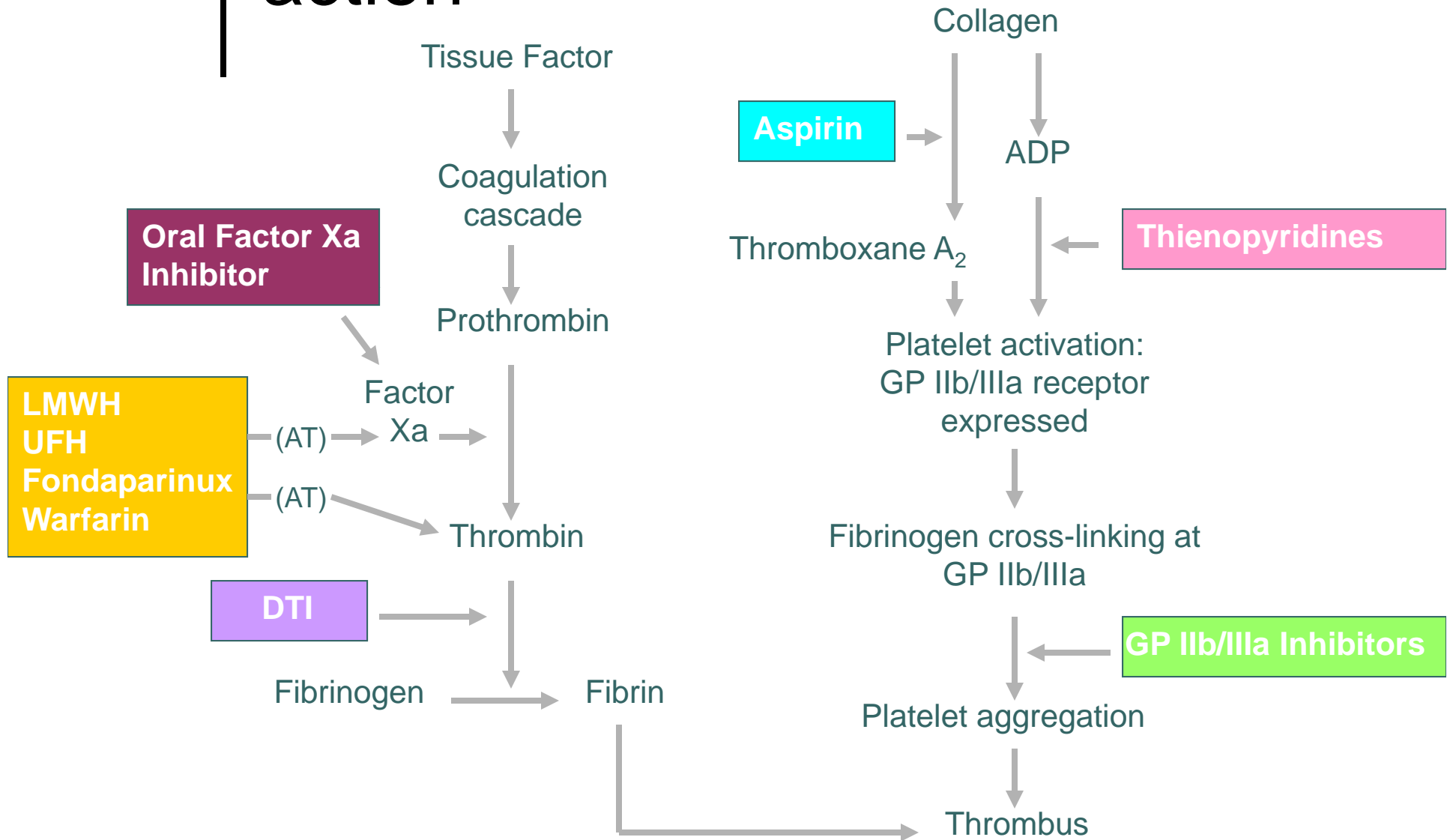
- No monitoring required (but the ability to monitor if desired)
- Well defined pharmacokinetics in presence of renal or hepatic disease
- Easily reversible
- Cost effective



New oral anticoagulants

- Direct thrombin (IIa) inhibitor
 - Dabigatran (Pradaxa)
- Factor Xa inhibitors
 - Rivaroxaban (Xarelto)
 - Apixaban

Coagulation cascade and sites of action





Dabigatran--basics

- Direct thrombin (factor IIa) inhibitor
- Max anticoag activity 2-3 hours after ingestion
- Half life 7.1-17 hours
- Metabolism--conjugation
- Elimination--renal (80%), remainder excreted in bile
 - Contraindicated in patients with CrCl <30 ml/min
- Main side effect--dyspepsia (10%)



Dabigatran--basics

- Drug-drug interactions--least likely to have drug interactions
 - No P450 interactions
 - P glycoprotein substrate
 - Amiodarone (increases level by 60%), verapamil, rifampin, clarithromycin, quinidine (contraindicated)
 - Proton pump inhibitors
 - Reduce absorption by 20-30%
- No drug-food interactions
 - Food delays absorption, not clinically significant
- No antidote
- Dialyzable



Dabigatran--basics

- Unstable if not store in original bottle (desiccant in lid) or blister pack
- Must be used within 60 days (if maintained in original bottle or blister packs)
- No pill boxes



Dabigatran--approvals

- FDA indication:
 - Non-valvular atrial fibrillation
 - October 2010
 - 10/2010-1/2011 128,000 prescriptions to 86,000 patients
- Canada/EU
 - Approved for post-operative thromboprophylaxis



Rivaroxaban--the basics

- Direct factor Xa inhibitor
- Peak plasma concentration 2.5-4 hours after administration
- Half life--3.2-9.1 hours
- Metabolism: oxidation (via CYP3A4 and CYP2J2) and hydrolysis
- Elimination--2/3 renal, 1/3 fecal



Rivaroxaban--the basics

- Drug interactions--most likely to have interactions
 - CYP 3A4 and P glycoprotein substrate
 - Drugs that are substrates for both may cause more significant interaction
 - Ketoconazole, ritonavir, clarithromycin, erythromycin (increase levels 30-100%)
 - Rifampicin (decrease levels 50%)
- Drug-food interactions
 - Recommended to be taken with food
 - H2blockers, antacids no effect; no info on PPIs



Rivaroxaban--approvals

- Canada/EU--post operative thromboprophylaxis
- Not yet approved by the FDA
 - Delayed due to concerns in reporting of bleeding rates
 - Excluded surgical site bleeding from major bleeding category and reported it separately



Apixaban--the basics

- Direct factor Xa inhibitor
- Time to peak AC effect 3-3.5 hours
- Half life--8-15 hours
- Metabolism--oxidation (via CYP3A4) and conjugation
- Elimination--25% renal, 75% fecal
- Drug-drug interactions
 - Likely CYP3A4 interactions, but no data available
- Drug-food interactions
 - No information



Apixaban--approvals

- Not yet approved for clinical use or commercially available in the US or abroad
- Nearing EU approval for post operative thromboprophylaxis



Oral Anticoagulants

Drug	Warfarin	Rivaroxaban	Apixaban	Dabigatran
Target	Vitamin K epoxide reductase	Factor Xa	Factor Xa	Thrombin
Half-life (hours)	40	3.2-9.1	8-15	7.1-17
Monitoring	INR-adjusted	Not needed	Not needed	Not needed
Administration	Once daily	Once daily	Once-twice daily	Once-twice daily
Metabolism	CYP450	66% fecal; 33% renal	75% fecal; 25% renal	20% fecal; 80% renal
Antidote or treatment of bleeding	Vit K + FFP, APCC, or recombinant FVIIa	Recombinant Factor Xa derivative, APCC, recombinant FVIIa	Recombinant Factor Xa derivative	No antidote
Assay	PT/INR	Antifactor Xa, PiCT, HepTest	Antifactor Xa	Ecarin Clotting time
Drug Interactions	CYP 2C9, 1A2, 3A4	CYP 3A4 Inhibitor	CYP 3A4 Inhibitor	PPI decrease absorption



VTE prevention--dabigatran

- RE-MODEL and RE-NOVATE
 - Non-inferiority trials
 - TKA (RE-MODEL) THA (RE-NOVATE)
 - Dabigatran 150 mg or 220 mg daily vs. enoxaparin 40 mg SQ pre op (EU dosing regimen)
 - Dabigatran non-inferior; no difference in bleeding
- RE-MOBILIZE
 - TKA
 - Dabigatran 150 mg or 220 mg daily vs. enoxaparin 30 mg BID post op (NA dosing regimen)
 - Dabigatran failed to show non-inferiority; no difference in bleeding

J Thromb Haemost 2007;5:2178-85, Lancet 2007;370:949-56, J Arthroplasty 2009;24:1-9



VTE prevention--rivaroxaban

- RECORD-1, 2, 3
 - Rivaroxaban 10 mg daily vs. enoxaparin 40 mg daily
 - Rivaroxaban superior to warfarin*
 - No difference in bleeding complications
 - RECORD-4
 - Rivaroxaban 10 mg vs. enoxaparin 30 mg BID
 - Rivaroxaban superior to warfarin*
 - No difference in bleeding complications
- *Composite outcome: VTE and all-cause mortality

NEJM 2008;358:2765-75, Lancet 2008;372:31-9, NEJM 2008;358:2776-86, Lancet 2009;373:1673-80



VTE prevention--apixaban

- ADVANCE-1
 - Total knee arthroplasty
 - Apixaban 2.5 mg BID vs. enoxaparin 30 mg BID
 - Treatment for 12 days
 - Failed to show non-inferiority*
 - ADVANCE-2
 - Total knee arthroplasty
 - Apixaban 2.5 mg BID vs. enoxaparin 40 mg daily
 - Treatment for 12 days
 - Apixaban superior to enoxaparin*
 - No difference in bleeding in either study
- *Primary outcome composite VTE and all cause mortality



VTE prevention--apixaban

- ADVANCE-3
 - Total hip arthroplasty
 - Apixaban 2.5 mg BID vs. enoxaparin 40 mg daily (apixaban post op, enoxaparin pre op)
 - Treatment for 35 days
 - Primary outcome asymptomatic or symptomatic DVT, PE or death
 - 27 apixaban, 74 enoxaparin; RR 0.36 (0.22-0.54) for non-inferiority and superiority
 - No difference in bleeding



VTE treatment--dabigatran

○ RE-COVER

- Dabigatran 150 mg BID vs. adjusted dose warfarin x 6 months (after initial IV anticoagulation)
- Acute VTE (proximal DVT or PE)
- Primary outcome: recurrent, symptomatic objectively confirmed VTE and related deaths
 - 2.4% dabigatran, 2.1% warfarin (HR 1.10 (0.65-1.84))
 - Dabigatran non-inferior to warfarin; failed to meet superiority
- Safety:
 - Major bleeding: 1.6% dabigatran, 1.9%warfarin
 - Any bleeding: 16.1% dabigatran, 21.9% warfarin



VTE treatment--rivaroxaban

○ EINSTEIN

- Symptomatic DVT
- Rivaroxaban 15 mg BID x 3 weeks, followed by 20 mg daily vs. enoxaparin followed by VKA
- Continued treatment arm: rivaroxaban vs. placebo for an add'l 6-12 months
- Non-inferior compared to VKA for recurrent VTE; superior to placebo for continuation arm
- No difference in bleeding



Stroke prevention in afib-- dabigatran

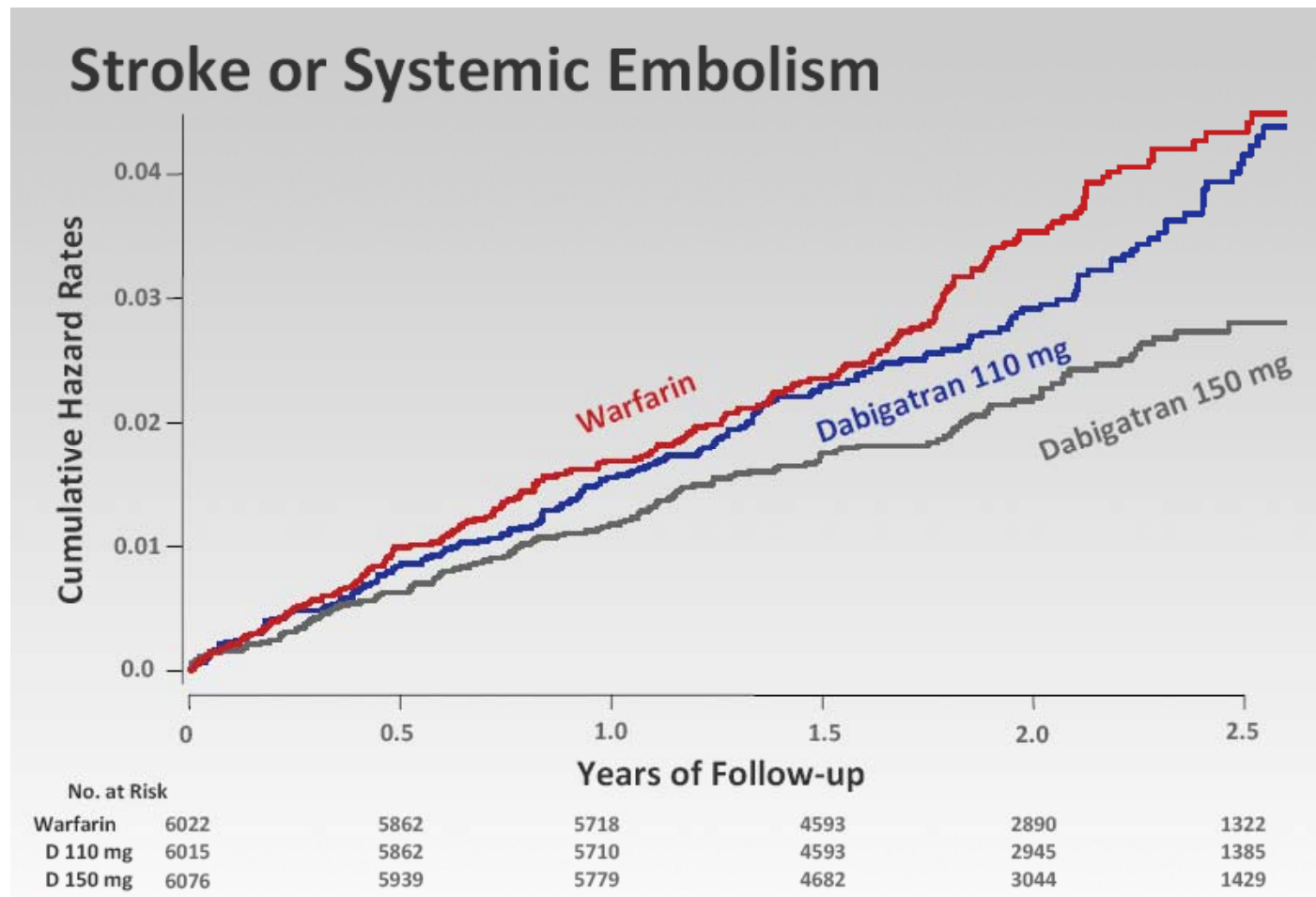
○ RE-LY

- Non-valvular afib
- 18,113 patients, 951 sites, 44 countries
- Mean CHADS₂ score 2.1
- Mean TTR 64%
- 110 or 150 mg BID dabigatran vs. adjusted dose warfarin
- Results:
 - 110 mg BID non-inferior to warfarin (182 vs. 199 events 1.53%/yr vs. 1.69% p<0.001) with significantly less major bleeding
 - 150 mg BID superior to warfarin (134 vs. 199 events; 1.11%/yr vs. 1.69% p<0.001) with no difference in major bleeding, however significantly less ICH
 - Rates MI higher on dabigatran (0.53%/yr warfarin, 0.72%/yr 110 mg, 0.74%/yr 150 mg p=0.048)
- Long term follow up ongoing

NEJM 2009;361:1139-51



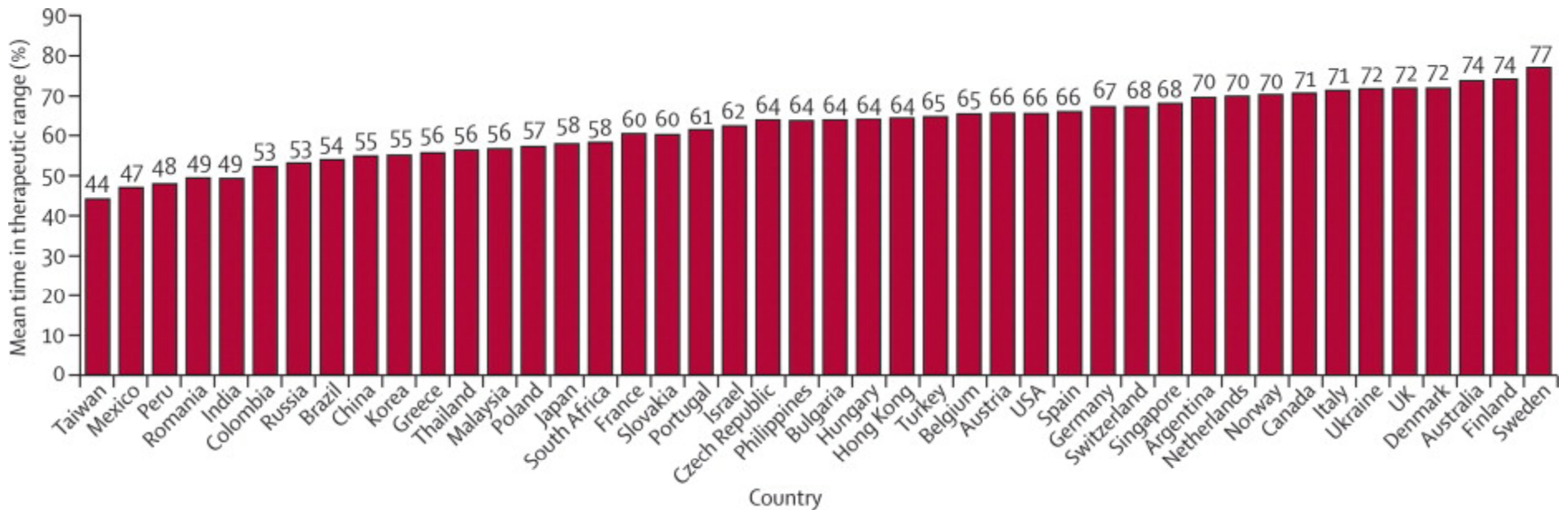
RE-LY: Dabigatran



Modified from *NEJM* 2009;361:1139-51.



TTR in RE-LY by country



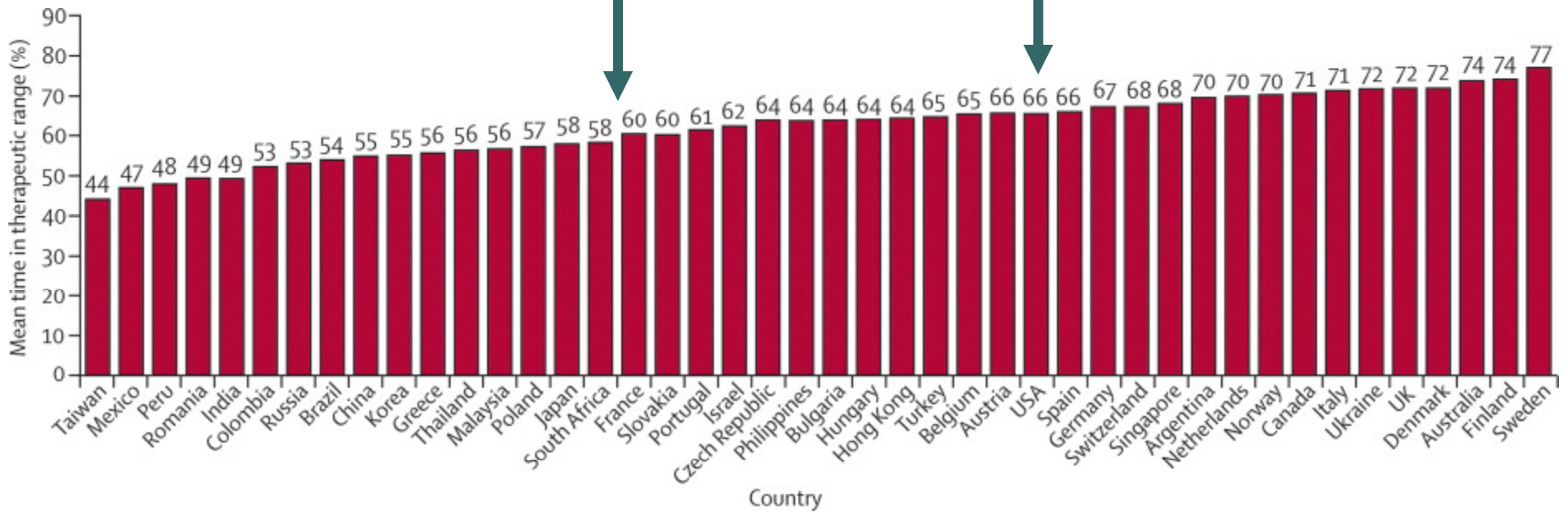
Lancet 2010;376:975-83



TTR in RE-LY by country

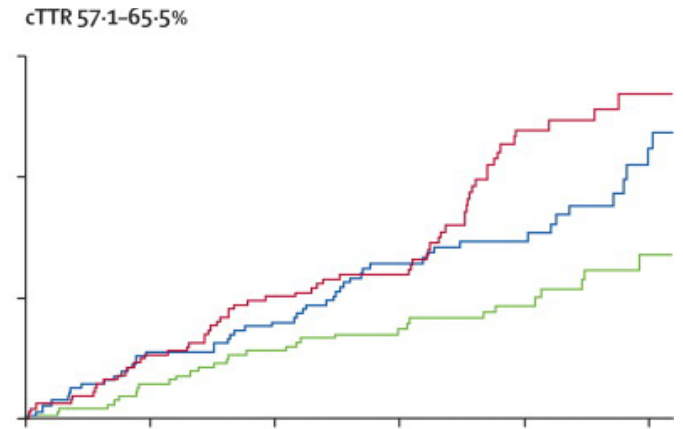
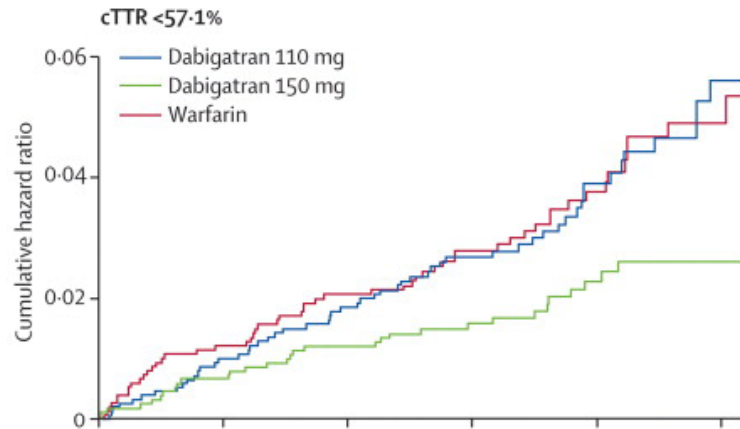
Threshold above warfarin
superior to dual antiplatelet Rx

US: 66%



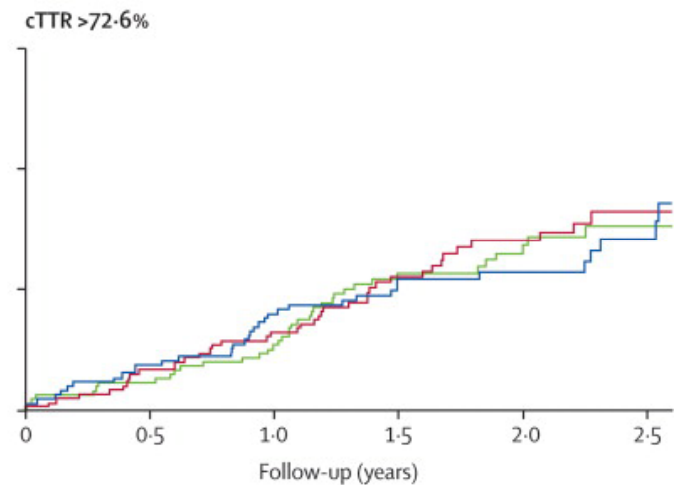
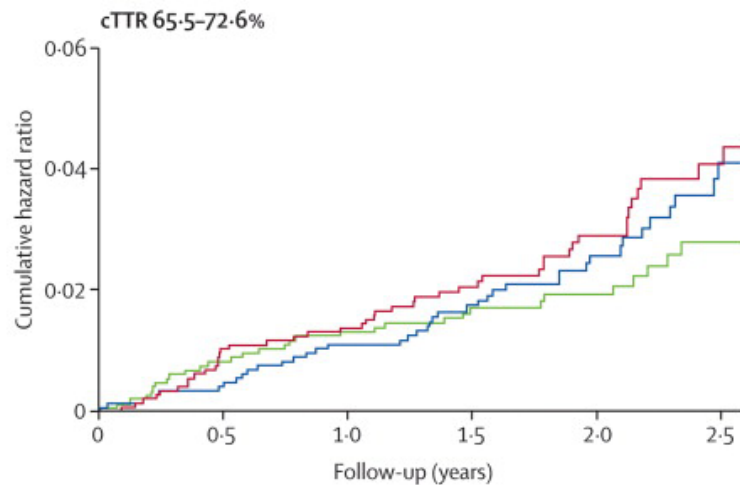
Lancet 2010;376:975-83

Time to primary outcome in each quartile of center's mean TTR



Number at risk

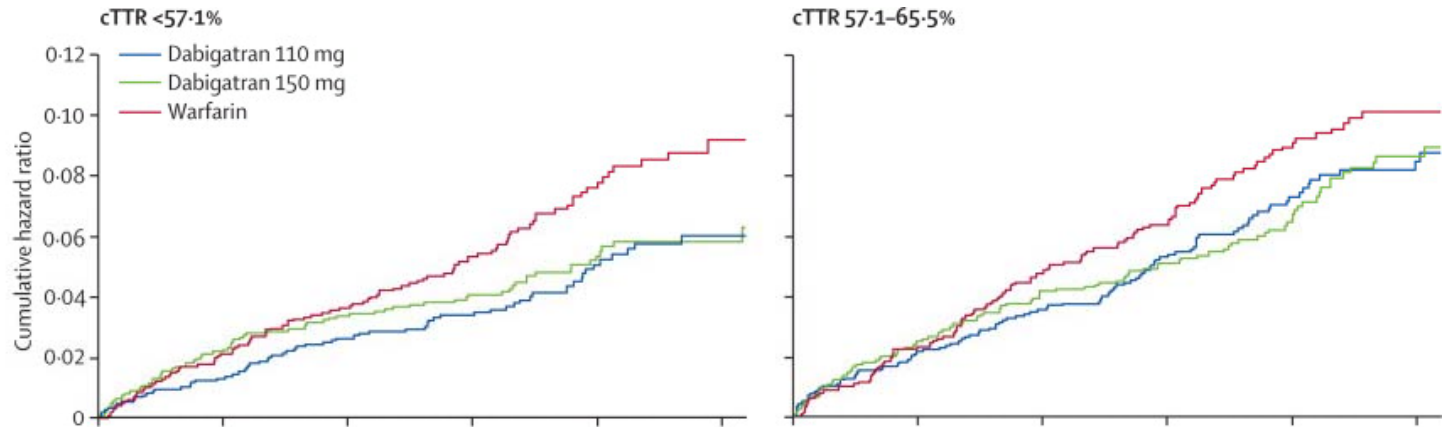
Dabigatran 110 mg	1497	1450	1411	1144	649	274	1524	1477	1440	1169	783	379
Dabigatran 150 mg	1509	1469	1427	1164	699	283	1526	1493	1453	1192	801	394
Warfarin	1504	1445	1395	1094	640	242	1514	1476	1438	1175	752	351



Number at risk

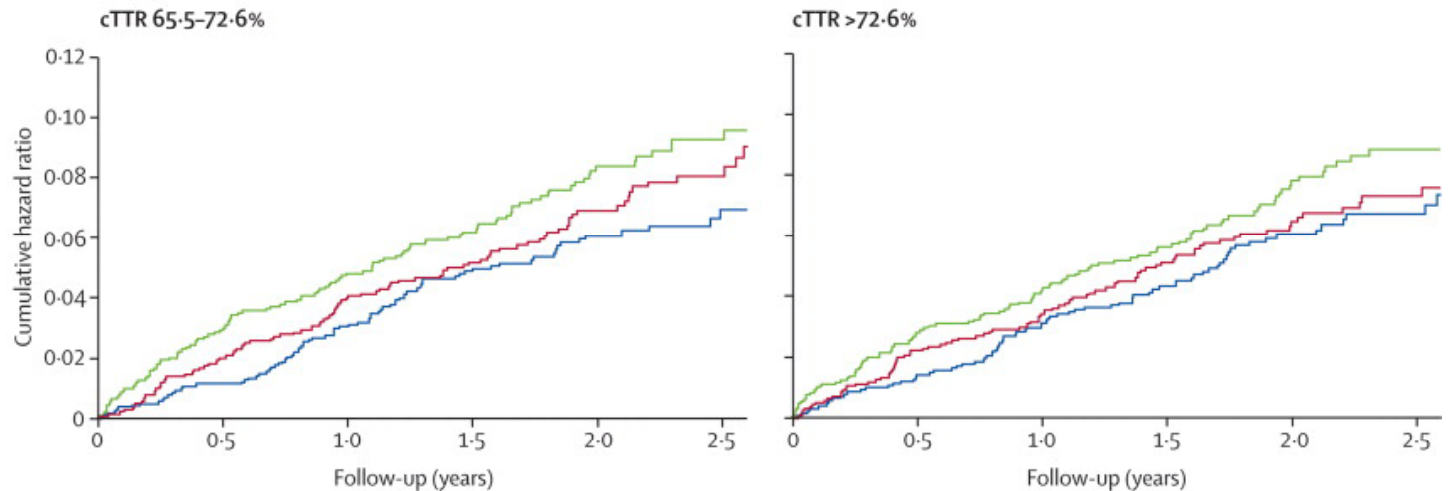
Dabigatran 110 mg	1474	1456	1420	1142	760	370	1482	1444	1405	1108	730	347
Dabigatran 150 mg	1484	1445	1419	1153	761	369	1514	1487	1437	1135	750	367
Warfarin	1487	1458	1436	1150	755	359	1509	1476	1440	1166	737	366

Time to major bleeding event in each quartile of center's mean TTR



Number at risk

Dabigatran 110 mg	1497	1443	1398	1135	647	274	1524	1465	1416	1139	753	362
Dabigatran 150 mg	1509	1448	1399	1135	680	276	1526	1467	1416	1160	774	377
Warfarin	1504	1430	1371	1065	614	231	1514	1460	1403	1140	729	333



Number at risk

Dabigatran 110 mg	1474	1445	1392	1108	736	364	1482	1438	1385	1087	706	336
Dabigatran 150 mg	1484	1415	1372	1105	715	343	1514	1455	1399	1109	716	350
Warfarin	1487	1445	1398	1121	725	344	1509	1452	1411	1129	714	354



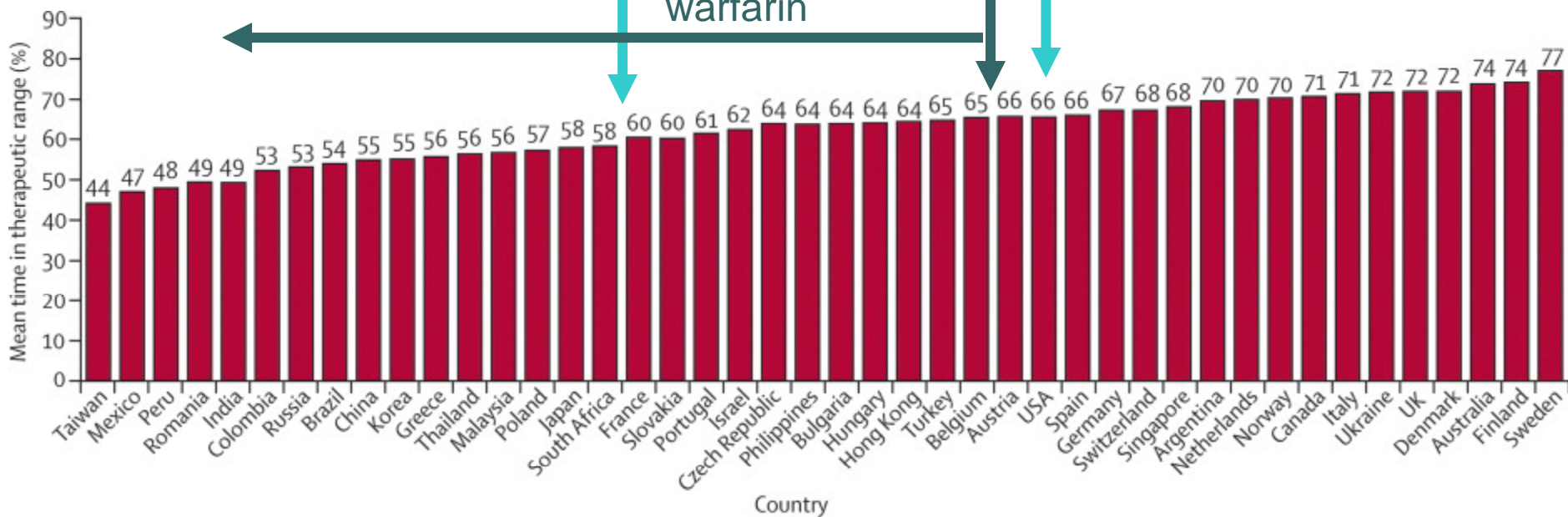
TTR in RE-LY by country

Threshold above warfarin
superior to dual antiplatelet Rx

US: 66%

Below dabigatran
superior to
warfarin

Above no difference



Lancet 2010;376:975-83



Pharmacist Run Anticoagulation Clinical Data

Measures of Anticoagulation Control			
Measure	Usual Care Model	Nurse Model	Pharmacist Model
INR time in range (%) [*]	57.4	71.8	83.6
INR values in range (%) [*]	49.4	67.3	74.9
INR > 5.0 (%) [*]	2.9	2.0	1.2
Hospitalizations			
Rate (#/100) [*]	13.9	12.3	5.4
Relative Risk (95% CI) [†]	2.59 (1.29-5.18)	2.29 (1.23-4.25)	----
ED visits			
Rate (#/100) [*]	5.6	5.6	1.2
Relative Risk (95% CI) [†]	4.40 (1.24-15.59)	4.45 (1.42-13.98)	----

* p < 0.05 for all comparisons vs pharmacist

† p < 0.01 for all comparisons vs. pharmacists



Stroke prevention in afib-- rivaroxaban

○ ROCKET AF

- Rivaroxaban 20 mg daily (15 mg daily for CrCl 30-49) vs. adjusted dose warfarin 2.0-3.0
- Mean CHADS₂ score 3.48 (rivaroxaban), 3.46 (warfarin)
- Median TTR 57.8
- Vascular death, stroke, embolism
 - On treatment event rate: rivaroxaban 3.11, warfarin 3.63; HR 0.86 (0.74-0.99)
 - ITT: rivaroxaban 4.51, warfarin 4.81; HR 0.94 (0.84-1.05)
- No difference bleeding rates

Presented at the AHA meeting, November 2010



TTR in RE-LY by country

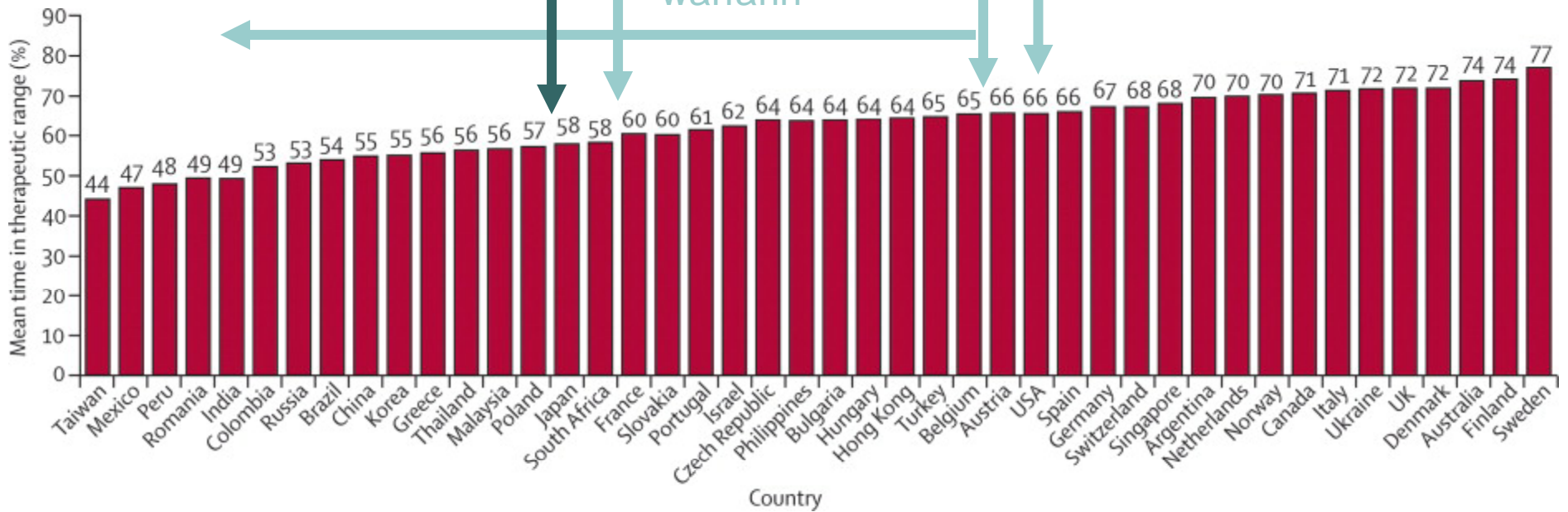
Threshold above warfarin
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TTR in ROCKET AF

Below dabigatran
superior to
warfarin

Above no difference





Stroke prevention in afib-- apixaban

- AVERROES
- Patients “unsuitable” for VKA
- Apixaban 5 mg BID vs. ASA 81-324 mg daily
- Mean CHADS₂ 2.0 (apixaban), 2.1 (ASA)
- Primary outcome stroke or systemic embolism
 - 51 apixaban, 113 ASA HR 0.45 (0.32-0.62)
- No difference in bleeding
- Terminated early due to benefit of apixaban



Stroke prevention in afib-- apixaban

- ARISTOTLE

- Apixaban vs. warfarin
- Ongoing



Cost effectiveness/utility

- Perspective
 - Society, patient, provider, payer
- What are the costs?
 - Cost of the drug
 - Costs of monitoring
 - Costs of events
- Effectiveness/utility
- Time horizon



Effectiveness vs. Utility

- Cost effectiveness
 - Dollars expended for particular benefit
 - I.e., life years gained
- Cost utility
 - Dollars expended for value gained
 - I.e., QALY



Cost effectiveness/utility-- dabigatran in afib

- Target population:
 - age ≥ 65 , non-valvular a fib, CHADS ≥ 1
- Perspective: society
- Time horizon: lifetime (35 years)
- Markov decision model
- Data from RE-LY
- Cost of dabigatran estimated based on UK pricing



Cost effectiveness/utility-- dabigatran in afib

- Assumptions:

- Costs:

- Drug treatment costs for warfarin included:
 - 14 INR tests (sensitivity analysis add'l 8 tests)
 - Medicare reimbursement for “anticoagulation management”
 - Costs of treatment for stroke, hemorrhage, MI, death

- Utility:

- Taking the medications (and associated monitoring)
 - Neurologic events, MI
 - Temporary states: major and minor bleeding



Cost effectiveness/utility-- dabigatran in afib

- Cost effectiveness sensitive to cost of drug:
 - No longer cost effective:
 - Above \$9.36 for 110 mg BID
 - Above \$13.70 for 150 mg BID
- Much benefit derived from lower rates of ICH with dabigatran (costly and low utility)
- Increasing risk of stroke or ICH, resulting in dabigatran being more cost effective
- Current US pricing \$7.90/day 150 mg dose



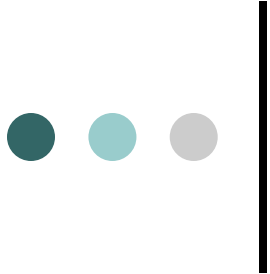
New oral anticoagulants--will they be cost effective?

- Cost utility of new agents dependent upon:
 - Cost of drug
 - Institution's TTR (higher TTR associated with better performance of warfarin)
 - Individual patient risk for clotting and bleeding (more cost effective for higher risk patients)
 - Confirmed performance of these new medications over warfarin



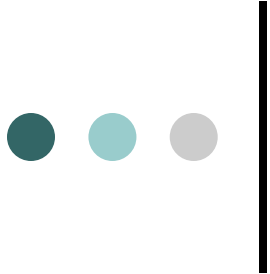
Need for monitoring

- Patients with low body weights or obese patients
- Pediatric patients
- Renal or hepatic impairment
- Accidental or deliberate overdose
- To measure adherence
- To evaluate patients with hemorrhagic or thrombotic complications



Monitoring/effects on coagulation tests--dabigatran

- Affect on coagulation assays dependent on timing of administration of the drug
- PTT--relationship non-linear (plateaus) can detect presence of AC activity, but not suitable to quantify AC effect
 - On chronic therapy median peak 2x, trough 1.5x
- PT--least sensitive, little effect at clinically relevant doses (INR 2 at supratherapeutic doses)
- ACT--similar to PTT, relationship curvilinear



Monitoring/effects on coagulation tests--dabigatran

- Thrombin time--sensitive, available, linear relationship, not standardized across labs
- Ecarin clotting time--best to assess bleeding risk, not widely available
- Hemoclot thrombin inhibitor assay--dilute thrombin time, sensitive, standard reagents; dabigatran specific assay in development



Monitoring/effects on coagulation tests--rivaroxaban

- PT/INR--effect of rivaroxaban on PT is transient and changes over time after administration
 - Therapeutic drug concentration 12-19 (trough) to 152-201 (peak) ng/mL
 - PT insensitive, lacks accuracy and precision at trough levels; can detect at concentrations 50-700 ng/mL
 - INR correction not appropriate for rivaroxaban (can exacerbate effects of different reagents with rivaroxaban and PT)



Monitoring/effects on coagulation tests--rivaroxaban

- aPTT--rivaroxaban has weaker affect on aPTT than PT
- Affect short lived
- Different reagents used in aPTT have different sensitivities to rivaroxaban
- No information on the affect on the ACT
- Hep Test (clot based anti-Factor Xa assay)-
-rivaroxaban has paradoxical affects
- Prothrombinase-induced Clotting time--
paradoxical effects



Monitoring/effects on coagulation tests--rivaroxaban

- Anti-Factor Xa assays:
 - sensitivity varies among available assays
 - One commercially available assay appears to be able to detect rivaroxaban in concentrations 0-500 ng/mL
 - To be useful, standard curves will need to be developed



Monitoring/effects on coagulation tests--apixaban

- Limited information available
- Minimal impact on PT and aPTT at therapeutic concentrations
- Factor Xa assays can detect the presence of drug



Potential advantages of new oral anticoagulants over VKAs

- Oral administration
- Rapid onset of action
 - May replace IV anticoagulants for certain indications
 - May eliminate need for 2 AC regimen (ie heparin and warfarin)
- Predictable therapeutic effect with fixed dosing
 - No routine coagulation monitoring



Potential advantages of new oral anticoagulants over VKAs

- Limited or no food or drug interactions
- Short half-life
 - Effect wears off more quickly than VKAs
- No need for bridging for invasive procedures
- More convenient for the patient
 - No routine monitoring, no dietary interactions, limited drug interactions
- More convenient for physician
 - No routine monitoring



Potential advantages of new oral anticoagulants over VKAs

- Potential for greater use
 - Barriers removed that limit more widespread use
- Potentially more cost effective
 - No routine monitoring
 - Fewer adverse events
- Possible superior efficacy
- Possible superior safety



Potential disadvantages of new oral anticoagulants over VKAs

- No routine coagulation monitoring
 - Cannot titrate dose
 - Determination of failure of therapy vs. poor compliance
- Short half-life
 - AC effect declines quickly if compliance poor
 - Poor compliance may affect efficacy more than with VKAs



Potential disadvantages of new oral anticoagulants vs VKAs

- No antidotes
- No monitoring lab marker available to measure drug activity if needed
- Potential dose adjustment for renal or hepatic dysfunction
- Cost