

# Factor Xa inhibitors in atrial fibrillation

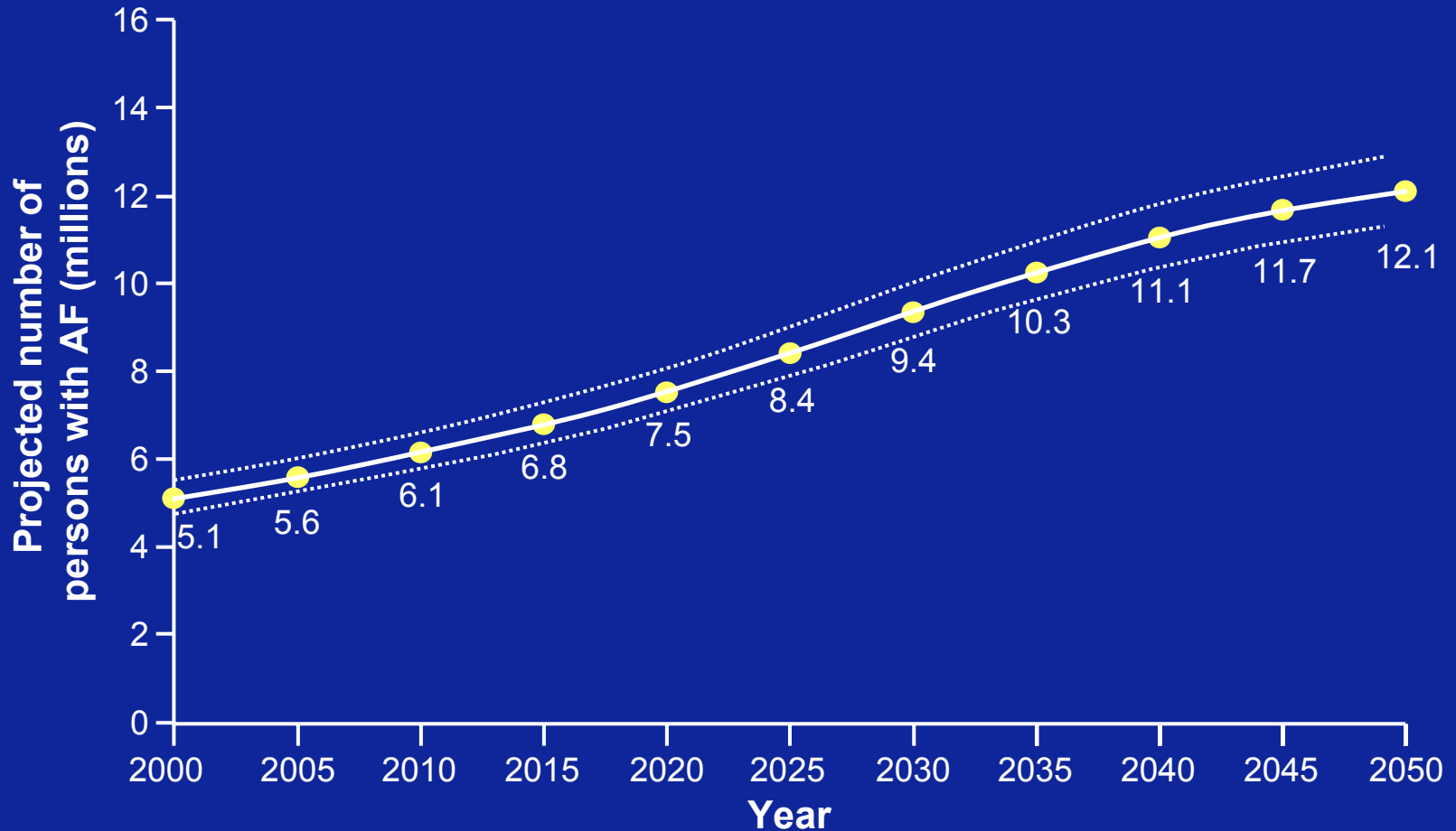
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Alexander G. G. Turpie  
Department of Medicine  
HHS-General Hospital  
Hamilton, Canada

# Atrial fibrillation (AF)

- AF – the most common significant cardiac arrhythmia
  - Estimated to affect 4.5 million people in the EU and 2.2 million people in the US
  - Incidence of 9.9 per 1000 person-years in a large European study (N=6432)
- Incidence of AF strongly age dependent – prevalence ~10% in those aged >80 years
- AF increases the risk of stroke 5-fold
  - AF is directly responsible for 15–20% of strokes
- AF is also a significant risk factor for stroke recurrence and severity
- The population is aging ...

# Projected prevalence of AF in the US



Assuming no further increase in age-adjusted AF incidence  
Miyasaka *et al. Circulation* 2006

# Guidelines – ACC/AHA/ESC 2006

Risk stratification	Therapy
<b>High risk of stroke</b> <ul style="list-style-type: none"><li>• Prior thromboembolism (stroke, TIA, systemic embolism)</li><li>• Rheumatic mitral stenosis</li><li>• <b>More than one of:</b> age <math>\geq 75</math> years, hypertension, heart failure, impaired LV systolic function, or diabetes mellitus</li></ul>	Oral VKA
<b>Moderate risk of stroke</b> <ul style="list-style-type: none"><li>• <b>Only one of:</b> age <math>\geq 75</math> years, hypertension, heart failure, impaired LV systolic function, or diabetes mellitus</li></ul>	Oral VKA or aspirin
<b>Low risk of stroke</b> <ul style="list-style-type: none"><li>• 'Lone' AF (no other risk factors)</li></ul>	Aspirin

Oral VKA target INR is 2.5 (range 2–3); aspirin is recommended at 81–325 mg/day

Fuster et al., *Circulation* 2006

# Vitamin K antagonists – efficacy and safety

- VKAs prevent the  $\gamma$ -carboxylation of vitamin K-dependent coagulation factors – prothrombin, Factors VII, IX and X
- Dose-adjusted warfarin was very effective at preventing stroke in patients with AF – RRR 68% (95% CI 50–79%; pooled analysis of five randomized controlled trials)
  - Reduced all-cause mortality by 33% (95% CI 9–51%)
- No significant increase in major bleeding in patients treated with dose-adjusted warfarin vs control
  - Annual rate of major bleeding: warfarin 1.3%; control 1.0%
  - Intracranial haemorrhage: warfarin 0.3%; control 0.1%

# Vitamin K antagonists – major limitations

- Unpredictable pharmacokinetics and pharmacodynamics, which are affected by:
  - Genetic factors (CYP 2C9 mutation)
  - Drug–drug interactions
  - Consumption of alcohol and foods containing vitamin K
- Monitoring and frequent dose adjustment required to maintain INR within therapeutic window
  - Monitoring is costly, and a burden on patients and society
- Slow onset and offset of action (e.g. if patient requires surgery), requiring bridging with heparin or LMWH

# The 'ideal' anticoagulant for patients with AF

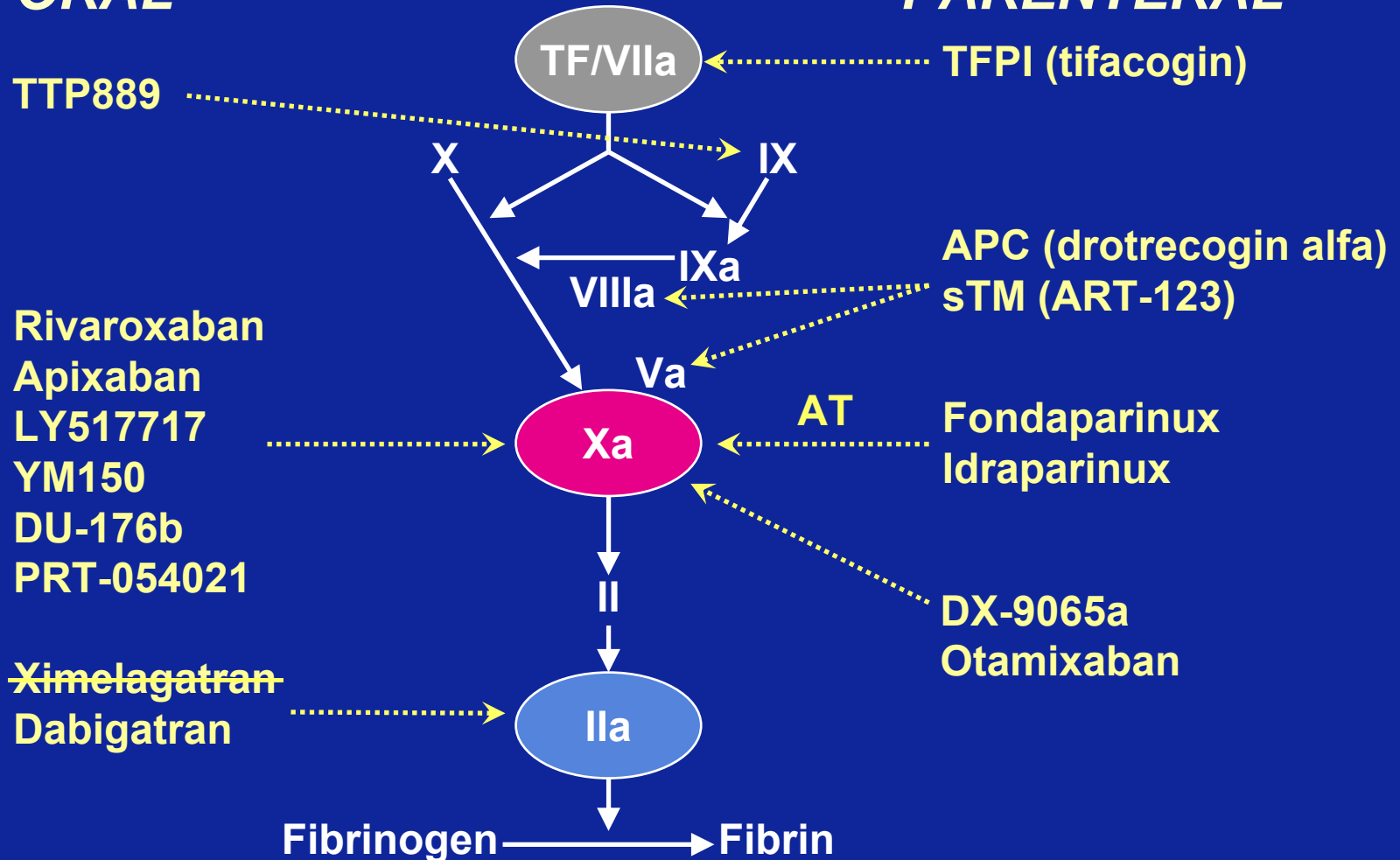
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- Oral
  - Rapid onset and offset of action
  - Predictable PK and PD
  - Low propensity for food and drug interactions
  - Fixed doses
  - Wide therapeutic window
- ⇒ No need for monitoring

# New anticoagulants

**ORAL**

**PARENTERAL**



# Direct thrombin inhibitors

- Ximelagatran: not approved for stroke prevention in patients with AF – withdrawn due to hepatotoxicity
- Dabigatran: phase II, dose-finding study in patients with AF completed – PETRO (50–300 mg bid and od)
  - Dabigatran 150 mg bid had similar efficacy and safety to warfarin and was chosen for the phase III programme
  - Concomitant treatment with aspirin increased risk of bleeding
- Phase III study with dabigatran for the prevention of stroke in patients with AF has begun – RE-LY
  - Target enrolment 15,000; comparator warfarin; treatment duration up to 3 years

# Direct Factor Xa inhibitors

- FXa may be a better target than thrombin
  - Has few functions outside coagulation (compared with thrombin)
  - Has a wider therapeutic window than thrombin (separation of efficacy and bleeding), *in vitro*
  - Thrombin inhibitors are associated with rebound thrombin generation – no evidence with FXa inhibitors
  - Efficacy of heparin-based anticoagulants improves as selectivity for FXa increases:  
UFH < LMWH < fondaparinux

# Paradigm for novel anticoagulant development

- Often first evaluated for prevention of VTE after major orthopaedic surgery
  - Allows proof-of-principle in an acute indication with high event rates, where bleeding can be monitored and controlled in a hospital environment
  - Small numbers of patients are needed to show an effect
  - Short-term indication (typically 5–9 days)
- VTE treatment studies usually come next
  - Longer term, chronic indication (~3 months therapy)
  - Often dose-finding for stroke prevention studies in AF
- Phase III stroke prevention studies in AF start after phase II VTE treatment studies are complete
  - Very long-term therapy (>1 year)
  - Large numbers of patients required to show significant effects vs warfarin/VKAs

# Factor Xa inhibitors in development

Indication	VTE prevention*	VTE treatment	Stroke prevention in patients with AF	Other?
Idraparinux	–	Phase III results expected soon	Phase III halted	–
Rivaroxaban	Phase III	Phase III	Phase III	–
LY517717	Phase IIb completed	–	–	–
YM150	Phase IIa completed	–	Planned	–
DU-176b	Phase IIa completed	–	Planned	ACS planned
Apixaban	Phase IIb completed; planned in cancer patients	Phase II underway	–	Post-ACS planned
PRT-054021	Phase II planned	Planned	Planned	Secondary prevention of stroke and MI planned

\*Prevention of VTE after major orthopaedic surgery, unless indicated

Subcutaneous, indirect Factor Xa  
inhibitor

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# Idraparinux (sanofi-aventis)

- Idraparinux is a hypermethylated, long-acting pentasaccharide, allowing once-weekly dosing

## VTE studies

- PERSIST study – randomized, phase II, dose-ranging study comparing idraparinux with warfarin for 12 weeks' treatment of DVT (after initial enoxaparin)
  - Efficacy with all idraparinux doses was similar to warfarin
    - No dose–response relationship for efficacy
  - Significant dose–response relationship for major bleeding
  - Lowest idraparinux dose (2.5 mg) to be tested further
- VAN GOGH (phase III for DVT/PE treatment) results expected late 2006

# Idraparinux: AF studies

- AMADEUS study – phase III, open-label, non-inferiority study comparing once-weekly idraparinux with VKA for prevention of thromboembolic events in patients with AF ⇒ **recruitment halted**
  - Lower incidence of events than expected
  - A very large number of patients would be required to show a significant effect

# SSR 126517 – biotinylated idraparinux

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- Allows rapid reversal of anticoagulant effect upon infusion of avidin
- A bioequipotency study vs idraparinux for DVT treatment is ongoing
- A phase III VTE treatment study is recruiting

# Oral direct Factor Xa inhibitors

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# LY517717 (Lilly)

- Only VTE prevention data currently available
- Randomized, double-blind, dose-escalation study comparing LY517717 with enoxaparin for prevention of VTE in patients undergoing TKR or THR

	LY517717 (mg od)						Enox 40 mg od 66/90
	25	50	75	100	125	150	
EP/SP*	26/32	20/34	22/32	69/106	80/110	77/103	66/90
VTE (DVT/PE), %	42	40	55	19	19	16	21
Major bleeding, %	0	0	0	0.9	0.9	1.0	3.3

\*Efficacy population (n)/safety population (n)

- Three lower doses were halted due to lack of efficacy
- 100, 125 and 150 mg od doses were non-inferior to enoxaparin
- No information is currently available regarding future plans

# YM150 (Astellas)

- Only VTE prevention data currently available
- Randomized, open-label, dose-escalation study comparing YM150 with enoxaparin for prevention of VTE in patients undergoing THR

	YM150 (mg od)				Enox 40 mg od 31/36
	3 27/34	10 31/35	30 31/36	60 27/34	
EP/SP*					
VTE (DVT/PE), %	52	39	23	19	39
Major bleeding	0	0	0	0	0
Clinically relevant, non-major bleeding, %	2.9	5.7	0	0	0

\*Efficacy population (n)/safety population (n)

- Significant dose–response relationship for efficacy ( $p=0.006$ )
- ONYX-2 is currently recruiting – double-blind, phase II, dose-ranging study of YM150 for VTE prevention in patients undergoing THR

# DU-176b (Daiichi Sankyo)

- Dose-dependently inhibits both venous and arterial thrombosis, in rat models
  - Antithrombotic doses were in the same concentration range
- Single 60 mg dose of DU-176b was given to healthy males:
  - Inhibited FXa activity, reduced thrombin generation, prolonged PT, aPTT and INR
  - Reduced venous thrombosis by 28% and arterial thrombosis by 26% in a Badimon chamber
- A phase IIa study (od or bid DU-176b) for VTE prevention after THR demonstrated proof of principle
  - No results are published yet
- Phase IIb studies in VTE prevention, stroke prevention in patients with AF, and in patients with ACS are planned or have been initiated

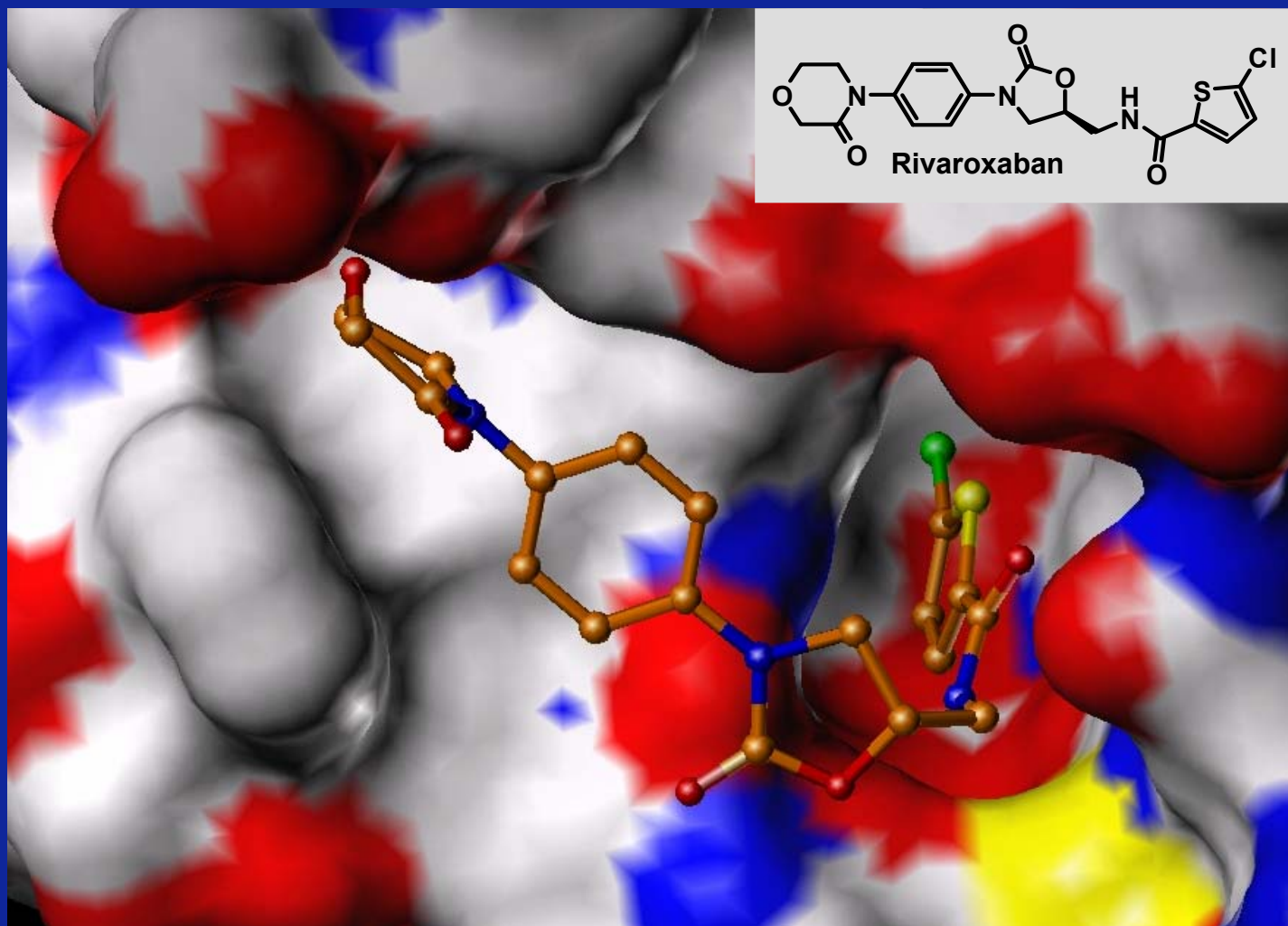
# Apixaban (Bristol-Myers Squibb)

- A highly potent, oral, direct FXa inhibitor ( $K_i$  0.08 nM)
  - Follow-up to razaxaban (development halted due to bleeding concerns)
- Phase II study for VTE prevention after TKR: completed
  - Double-blind; dose-ranging; three od and three bid apixaban doses; comparator enoxaparin and warfarin; target enrolment n=1202
- Phase II pilot study for VTE prevention in patients with advanced metastatic cancer: ongoing
- The Botticelli-DVT study for treatment of acute symptomatic DVT: ongoing – efficacy and safety of apixaban 5 mg bid, 10 mg bid and 20 mg od; comparators LMWH or fondaparinux followed by VKA
- Phase II study in patients with recent UA or MI: ongoing
  - Placebo-controlled; double-blind; target enrolment n=1800
- No details are available regarding plans in patients with AF

# PRT-054021 (Portola)

- Portola licensed compound from Millennium (MLN-1021)
- $K_i$  for FXa: 0.7 nM
- Bioavailability: 47%
- $t_{1/2}$ : 8.8 hours
- Well tolerated in a phase I study (N=64)
- Phase II study for the prevention of DVT: begun
- Portola intend to develop PRT-054021 for VTE prevention and treatment, stroke prevention in AF and secondary prevention of stroke and MI

# Rivaroxaban (BAY 59-7939)/human Factor Xa complex



# Rivaroxaban

(Bayer HealthCare AG and J&J/Scios, Inc.)

- Oral, direct FXa inhibitor;  $K_i$  for FXa 0.4 nM
- Potent antithrombotic effects for the prevention and treatment of venous thrombosis, in animal models
- Well tolerated in healthy subjects, with a rapid onset of action, and dose-proportional pharmacokinetics and pharmacodynamics
- Low propensity for clinically relevant drug–drug interactions
- In advanced clinical development for the prevention of VTE after major orthopaedic surgery, the treatment of VTE and the prevention of stroke in patients with AF

# Rivaroxaban for the prevention of VTE after major orthopaedic surgery

- Extensive phase II programme for the prevention of VTE after major orthopaedic surgery:
  - Phase IIa, open-label study in patients undergoing THR (od and bid dosing): demonstrated proof-of-principle of antithrombotic activity
  - Two phase IIb, double-blind studies (bid dosing) in patients undergoing THR or TKR: total daily rivaroxaban doses of 5–20 mg had similar efficacy and safety to enoxaparin
  - Based on these results, and a further study with od rivaroxaban in patients undergoing THR, rivaroxaban 10 mg od was selected as the dose to be studied in phase III
- Phase III RECORD studies have begun using rivaroxaban 10 mg od
  - Four studies; recruitment ongoing, target enrolment >10,000 patients worldwide; THR and TKR; comparator enoxaparin; short and extended prophylaxis

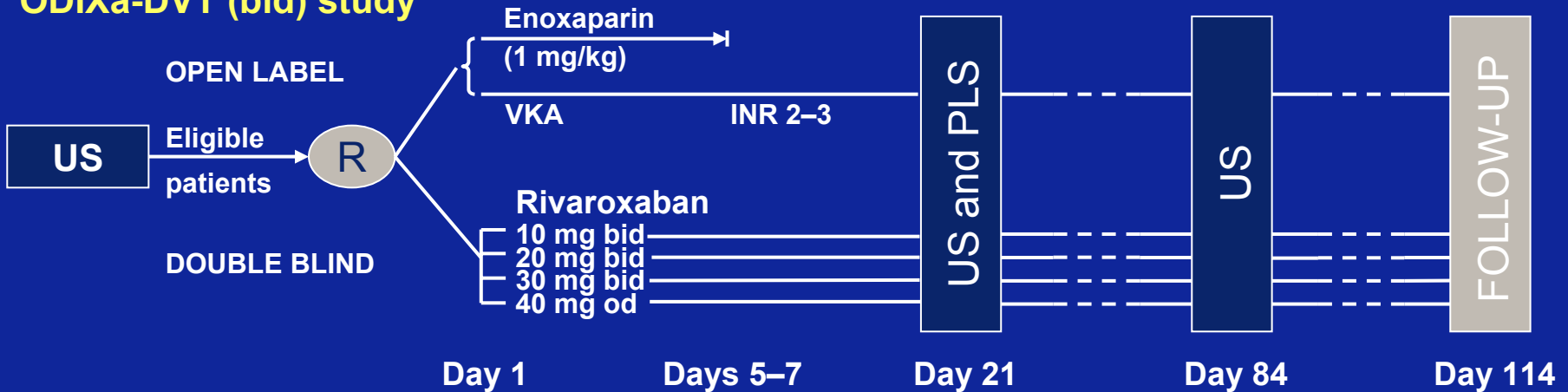
# Rivaroxaban phase IIb studies for DVT treatment

- ODIXa-DVT – rivaroxaban 10, 20, 30 mg bid or 40 mg od vs enoxaparin and VKA for 12 weeks
  - Primary efficacy endpoint: reduction in thrombus burden without recurrent VTE at day 21
- EINSTEIN-DVT – rivaroxaban 20, 30 or 40 mg od vs tinzaparin/enoxaparin/UFH and VKA for 12 weeks
  - Primary efficacy endpoint: composite of symptomatic, recurrent VTE and deterioration in thrombus burden at week 12

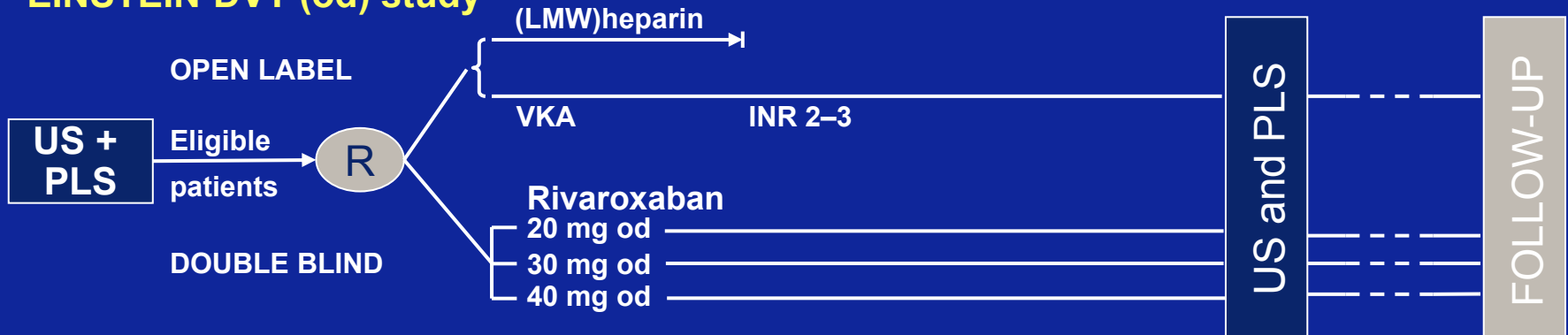
# ODIXa-DVT and EINSTEIN-DVT study designs

Eligible patients: those with symptomatic, proximal DVT at baseline

## ODIXa-DVT (bid) study



## EINSTEIN-DVT (od) study



US, ultrasound; PLS, perfusion lung scintigraphy

Agnelli *et al.*, *ESC/WCC* 2006; Büller *et al.*, *ESC/WCC* 2006

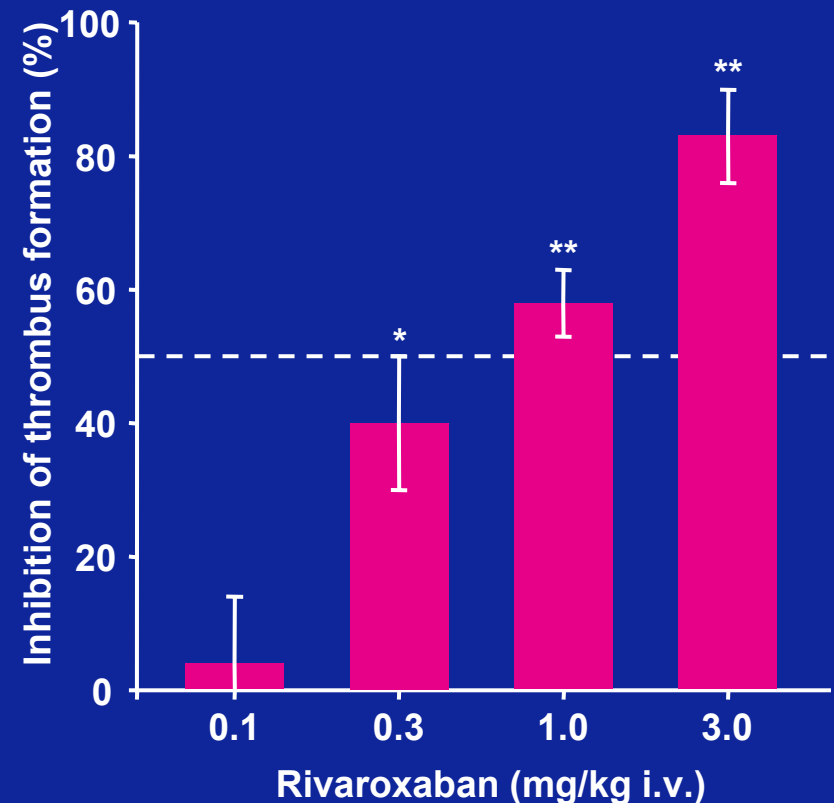
# Rivaroxaban DVT treatment studies – topline results

- Over 1150 patients with DVT enrolled
- All doses provided effective anticoagulation with a low incidence of recurrent VTE
- Favourable safety profile with low rates of any bleeding or adverse events
- No signal for liver toxicity
- Efficacy and safety of all rivaroxaban doses were similar to standard therapy
- Phase III studies with once-daily rivaroxaban for initial treatment and long-term secondary prevention of VTE have been initiated

# Rivaroxaban in arterial indications

- Animal models: rivaroxaban dose-dependently prevented arterial thrombosis
- Phase I studies: rivaroxaban may have a favourable safety profile in cardiovascular indications ...

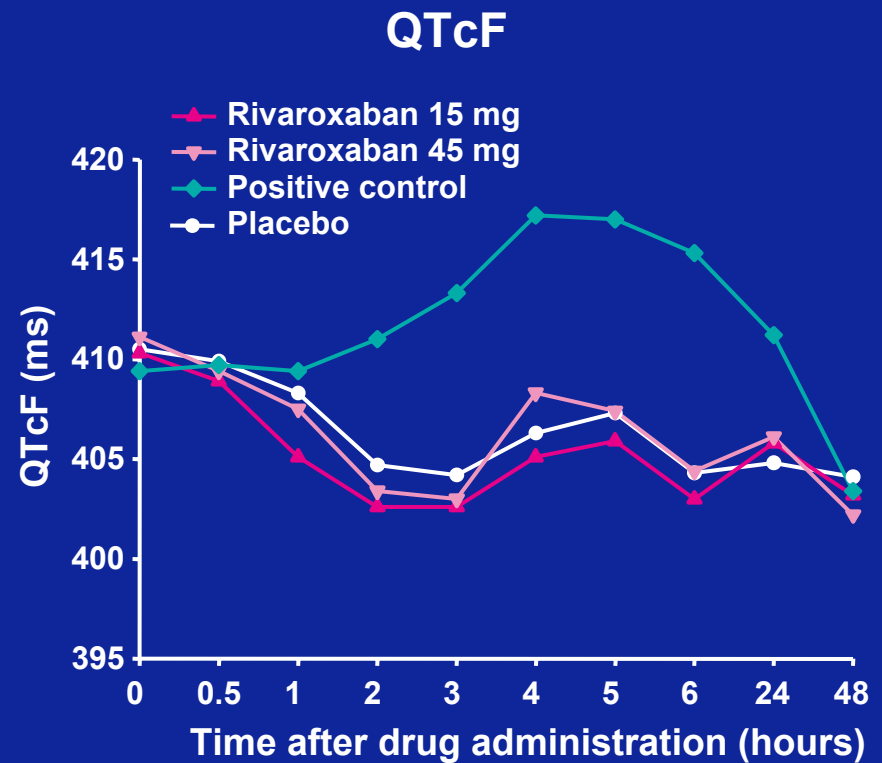
## Arterial thrombosis model: rabbit AV shunt



# Rivaroxaban has no effect on the QTc interval

Healthy subjects aged  $\geq 50$  years received rivaroxaban, positive control or placebo

- Rivaroxaban did not prolong the QTcF
- Incidences of outlying QTcF values  $>450$  ms were similar between rivaroxaban and placebo
- Rivaroxaban plasma concentrations and QTcF correlated with a slope of  $-0.003$  ms/ $(\mu\text{g/l})$
- This 'thorough' study proved that rivaroxaban does not prolong the QTc interval



# Rivaroxaban has a low propensity for drug–drug interactions

- No clinically relevant interaction with aspirin
  - No increase in adverse events
  - Bioavailability of rivaroxaban was unaffected
  - Bleeding time was prolonged, but small effect not considered clinically relevant
- No interaction with digoxin
  - No effect on the pharmacokinetics of digoxin
  - Co-administration slightly decreased bioavailability of a single dose of rivaroxaban
  - Digoxin did not influence the effect of rivaroxaban on inhibition of FXa activity or clotting tests
- Rivaroxaban can be taken with or without food – food increases the predictability of its effects

# Rivaroxaban dose-finding for AF – Japanese studies

- Two pilot, phase Ib studies to assess the safety, PK and PD of rivaroxaban in Japanese patients with AF are being conducted
- bid study: dose-escalation study assessing rivaroxaban 5, 10, 20 mg bid for 30 days; no comparator; ~25 patients per arm
- od study: parallel-group study assessing rivaroxaban 5, 10, 15 and 20 mg od vs warfarin (target INR 1.6–2.6)
- These studies will determine whether ethnic differences influence the safety, PK and PD of rivaroxaban in patients with AF, allowing a dose decision for Japanese phase III studies

# Concluding remarks

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- New anticoagulants that do not require frequent monitoring or dose adjustment are required to prevent stroke in patients with AF
- Drugs that inhibit FXa are attractive options
- Numerous oral, direct FXa inhibitors are in clinical development
- Rivaroxaban is the furthest advanced in its development programme
- Over the next 5 years, we could potentially see a paradigm shift in the way thromboembolic events are prevented in patients with AF ...