DRUGS AND THE HEART

NICK LINKER
JCUH, MIDDLESBROUGH
Resting membrane potential (phase 4) is -90mV. K⁺ channels open and K⁺ currents (I_K) high.

Fast Na⁺ channels and slow Ca²⁺ channels are closed.
Cells are depolarised e.g. by action potential in adjacent cell

Phase 0 depolarisation caused by increase in Na\(^+\) current (\(I_{Na}\))

\(I_K\) falls as K\(^+\) channels close
Phase 1 represents an initial repolarisation caused by special type of transient outward hyper-polarising $K^+$ current ($I_{K_{to}}$)
Because of increase in slow inward Ca\textsuperscript{2+} current (\(I_{CaL}\)) occurring at the same time as \(I_{Kt0}\), repolarisation is delayed and there is a plateau phase (phase 2). This phase distinguishes cardiac action potentials from those of nerves and skeletal muscle.
Repolarisation (phase 3) occurs when $K^+$ conductance (and $\therefore I_K$) increases along with inactivation of $Ca^{2+}$ channels.
SINO-ATRIAL NODE ACTION POTENTIAL - 1

- No true resting potential
- Generates regular spontaneous action potentials
- Depolarising current carried primarily by $\text{Ca}^{2+}$ current instead of $\text{Na}^{+}$ current
- No fast $\text{Na}^{+}$ channels
SINO-ATRIAL NODE ACTION POTENTIAL - 2

- At end of repolarisation, slow depolarising Na$^+$ currents ($I_f$) start (phase 4).
- When membrane potential reaches -50mV, transient Ca$^{2+}$ channels open ($I_{CaT}$).
- When membrane potential reaches -40mV $I_{CaL}$ opens.
- In addition, K$^+$ channels close.
Phase 0 depolarisation is primarily caused by inward Ca\(^{2+}\) current (\(I_{Ca,L}\)).

\(I_f\) and \(I_{Ca,T}\) gradually close.

As Ca\(^{2+}\) movement is not rapid, rate of depolarisation is slow.
**SINO-ATRIAL NODE ACTION POTENTIAL - 4**

❤ Repolarisation (**phase 3**) occurs as K\(^+\) channels open (**I\(_K\)**)

❤ At the same time, Ca\(^{2+}\) channels close, decreasing **I\(_{CaL}\)**
ANTI-ARRHYTHMIC DRUGS
VAUGHAN WILLIAMS CLASSIFICATION

❤ Introduced in 1970 by Vaughan Williams and Singh
❤ Classified antiarrhythmic drugs on the basis of their cellular electrophysiology into four classes
CLASS I ANTIARRHYTHMIC DRUGS

♥ Bind to fast Na\(^+\) channels responsible for phase 0 depolarisation
♥ Decrease amplitude of action potential
♥ Decrease conduction velocity in myocardium
♥ May effect action potential duration and effective refractory period (ERP)
CLASS IA ANTIARRHYTHMIC DRUGS

- Increase ERP (and APD) due to effects on K⁺ channels
- These effects can suppress arrhythmias
- Can also cause arrhythmias (pro-arrhythmic effect), specifically torsades de pointes
DISOPYRAMIDE

❤ Indicated for maintenance of sinus rhythm in patients with pAF; treatment of VT

❤ Adverse effects include proarrhythmic effect (exacerbated by hypokalaemia)

❤ Potent anticholinergic effect

❤ Negative inotrope
Indicated for treatment of VT
Adverse effects include proarrhythmic effect (exacerbated by hypokalaemia)
Only available as i.v. preparation
Long-term oral use associated with SLE-like syndrome in 25 – 30%
CLASS IB ANTIARRHYTHMIC DRUGS

♥ Decrease ERP (and APD)
LIDOCAINE AND MEXILETINE

❤ Indicated for treatment of VT
❤ Adverse effects include CNS side effects (lidocaine)
❤ Mexiletine can cause nausea and headache
CLASSIC ANTIARRHYTHMIC DRUGS

- Little effect on ERP (and APD)
- Significantly prolong intra-myocardial conduction
- Can also cause arrhythmias (pro-arrhythmic effect), specifically monomorphic VT
FLECAINIDE

❤ Indicated for treatment of SVT and VT (in patients without structural heart disease)
❤ Adverse effects include proarrhythmic effect
❤ CNS effects in 10-15% (headache, dizziness)
❤ Metallic taste
Propafenone

❤ Indicated for treatment of SVT and VT (in patients without structural heart disease)

❤ Adverse effects include proarrhythmic effect

❤ Also has β-blocking and Ca$^{2+}$ channel blocking activity
CLASS II ANTIARRHYTHMIC DRUGS (β-ADRENOCEPTOR ANTAGONISTS)

❤ Bind to β-adrenoceptors blocking binding of adrenaline and nor-adrenaline

❤ Some may partially activate the receptor (partial agonist with ISA)

❤ Some are relatively selective for β₁-adrenoceptors
CLASS II ANTIARRHYTHMIC DRUGS (β-ADRENOCEPTOR ANTAGONISTS)

CARDIAC EFFECTS

♥ Decrease contractility
♥ Decrease relaxation rate
♥ Decrease heart rate
♥ Decrease conduction velocity

VASCULAR EFFECTS

♥ Smooth muscle contraction
CLASS II ANTIARRHYTHMIC DRUGS
(β-ADRENOCEPTOR ANTAGONISTS)

ANTI-ARRHYTHMIC EFFECTS

❤ Decrease heart rate
❤ Decrease conduction velocity
❤ Increase action potential duration and ERP
<table>
<thead>
<tr>
<th>CLASS/DRUG</th>
<th>-HTN-</th>
<th>ANG</th>
<th>ARR</th>
<th>MI</th>
<th>CCF</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NON-SELECTIVE</strong> $\beta_1/\beta_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARTEOLOL</td>
<td>$\times$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISA; long acting; also used for glaucoma</td>
</tr>
<tr>
<td>CARVEDILOL</td>
<td>$\times$</td>
<td></td>
<td>$\times$</td>
<td></td>
<td></td>
<td>$\alpha$-blocking activity</td>
</tr>
<tr>
<td>LABETALOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td></td>
<td></td>
<td>ISA; $\alpha$-blocking activity</td>
</tr>
<tr>
<td>NADOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td>long acting</td>
</tr>
<tr>
<td>PENBUTOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>PINDOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td></td>
<td></td>
<td>ISA; MSA</td>
</tr>
<tr>
<td>PROPRANOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td>MSA; prototypical $\beta$-blocker</td>
</tr>
<tr>
<td>SOTALOL</td>
<td></td>
<td></td>
<td>$\times$</td>
<td></td>
<td></td>
<td>several other significant mechanisms</td>
</tr>
<tr>
<td>TIMOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>primarily used for glaucoma</td>
</tr>
<tr>
<td><strong>$\beta_1$-SELECTIVE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEBUTOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>ATENOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BETAXOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td></td>
<td>MSA</td>
</tr>
<tr>
<td>BISOPROLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESMOLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td></td>
<td></td>
<td></td>
<td>ultra short acting; intra or postoperative HTN</td>
</tr>
<tr>
<td>METOPROLOL</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>$\times$</td>
<td>MSA</td>
</tr>
</tbody>
</table>

Abbreviations: HTN, hypertension; Ang, angina; Arr, arrhythmias; MI, myocardial infarction; CCF, congestive cardiac failure; ISA, intrinsic sympathomimetic activity; MSA membrane stabilising activity
CLASS III ANTIARRHYTHMIC DRUGS

- Bind and block $K^+$ channels responsible for repolarisation
- Increase in action potential duration
- Increase in effective refractory period
- QT interval increased on ECG

Delayed Repolarization by Potassium-Channel Blockade

Ventricular Action Potential
AMIODARONE – ELECTROPHYSIOLOGICAL & HAEMODYNAMIC EFFECTS

❤ Prolongs action potential duration and effective refractory period

❤ Non-competitive α- and β- inhibition

❤ 15-20% decrease in sinus rate

❤ 10% increase in PR and QT interval

❤ Reduces peripheral resistance & increases cardiac index

❤ No significant change in ejection fraction
AMIODARONE – PHARMACOKINETICS

- Variable oral absorption
- Grapefruit inhibits metabolism
- Onset of action often takes 1 – 3 weeks, even with loading doses
- Needs approx. 10g to load patient
- Extensive accumulation in adipose tissue, liver, lung and spleen
- Metabolised by liver to desethylamiodarone and is eliminated by hepatic metabolism
- Biphasic elimination with \( \frac{1}{2} \) reduction of plasma levels after 2.5–10 days with a long terminal plasma elimination phase avg. 40–55 days
AMIODARONE – SIDE EFFECTS

♥ Tend to be dose related

♥ Neurologic (20-40%)
  – Malaise, fatigue, tremor, involuntary movements, peripheral neuropathy

♥ Gastrointestinal (25%)
  – Nausea, constipation, anorexia

♥ Ophthalmic
  – Optic neuropathy, photosensitivity, lens opacities, (asymptomatic corneal deposits)

♥ Dermatological (15%)
  – Photosensitivity, blue-gray pigmentation
AMIODARONE – SIDE EFFECTS

❤ Respiratory
  – Pulmonary inflammation or fibrosis

❤ Thyroid
  – Hypo- or hyperthyrodisim

❤ Hepatic
  – Abnormal liver function tests
SOTALOL

❤ Racemic mixture of d- and l- isomers
❤ Both isomers possess class III antiarrhythmic effects
❤ 97% of β-blocking activity possessed by l-isomer
❤ Class III action not exhibited below doses of 80mg b.d.
❤ Pro-arrhythmic effect exacerbated by hypokalaemia
❤ Exhibits reverse use-dependence
Dronedarone

❤ Developed in 1992 as an alternative to amiodarone, lacking iodine molecules
❤ Blocks Na\(^+\) channels
❤ Prolongs the cardiac action potential and increases refractoriness
❤ Possesses Ca\(^{2+}\) antagonist properties
❤ Non-competitive anti-adrenergic action
Dronedarone - Trials

- Efficacy and safety of dRonedarone for The cOntrol of ventricular rate (ERATO)
- EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm (EURIDIS)
- ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity Decrease (ANDROMEDA)
- Dronedarone Atrial Fibrillation study after Electrical cardioversion (DAFNE)
- A Trial with dronedarone to prevent Hospitalization or dEath in patieNts with Atrial fibrillation (ATHENA)
- Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation (DIONYSOS)
- Permanent Atrial fibrillation outcome Study using dronedarone on top of standard therapy (PALLAS)
- American-Australian trial with DronedarONE In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS)
4628 high risk patients with paroxysmal or persistent AF or flutter were randomised to dronedarone 400mg bd or placebo.

Patients were followed for a mean of 21 months.

Primary end-point was first hospitalisation due to cardiovascular events or death.

Secondary end-points were death from any cause, death from cardiovascular causes and first hospitalisation due to cardiovascular events.

Haemodynamically stable patients ≥75 or ≥70 with at least one risk factor (hypertension, diabetes, prior CVA/TIA, ↑LA, or LVEF <40%)

DRONEDARONE - ATHENA

RESULTS

❤️ Dronedarone associated with a 24% reduction in death or cardiac hospitalisation vs placebo (p<0.001)

❤️ Overall mortality similar (p=0.18), cardiovascular mortality lower (p=0.03)

❤️ Higher GI side effects and increased creatinine with dronedarone; other side effects similar

CONCLUSION

❤️ Dronedarone reduced the incidence of hospitalisation due to cardiovascular events or death in patients with atrial fibrillation

Dronedarone - Andromeda

- 627 patients with symptomatic heart failure (NYHA class III or IV), randomised to dronedarone or placebo
- Terminated after 7 months
- 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (hazard ratio in the dronedarone group, 2.13; 95% confidence interval [CI], 1.07 to 4.25; p=0.03). The excess mortality was predominantly related to worsening of heart failure.

**DRONEDARONE - DIONYSOS**

- Comparison of efficacy and safety of dronedarone versus amiodarone for maintenance of sinus rhythm in 504 patients with persistent AF
- 7 month follow-up
- AF after cardioversion occurred in 36.5% of patients in the dronedarone arm vs. 24.3% of patients in the amiodarone arm
- A decrease of 20% favouring dronedarone vs. amiodarone (83 vs 107, p=0.1291) was seen in the predefined main safety endpoint
- Amiodarone – more effective in preventing recurrence of AF but with higher toxicity

ROLE OF DRONEDARONE

💖 Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation in patients:

- whose AF is not controlled by first-line therapy (usually including β-blockers) **AND**
- who have at least one of the following cardiovascular risk factors:
  - hypertension requiring drugs of at least two different classes
  - diabetes mellitus
  - previous transient ischaemic attack, stroke or systemic embolism
  - left atrial diameter of 50 mm or greater
  - left ventricular ejection fraction less than 40%, **or**
  - age 70 years or older **AND**
- who do not have unstable NYHA class III or IV heart failure
Up to Jan 26, 2011, 257 serious cases of new-onset or worsening heart failure have been reported worldwide.

The incidence of heart-failure events was 369 of 3282 (11.2%) in the dronedarone group and 312 of 2875 (10.9%) in the placebo group.

Case reports of liver injury, including two cases of liver failure requiring transplantation, have been reported in patients receiving dronedarone. Some of these cases have occurred shortly after start of treatment.
DRONEDARONE - PALLAS

♥ Trial comparing the efficacy of dronedarone to placebo in permanent AF patients

♥ Patients were age >65 with co-morbid conditions, such as systemic arterial embolism, myocardial infarction, documented coronary artery disease, prior stroke, symptomatic heart failure, or the combination of age above 75 years, hypertension and diabetes

♥ Exclusion criteria included NYHA Class IV heart failure or unstable NYHA Class III heart failure

♥ The trial had two composite co-primary endpoints: Major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death) and cardiovascular hospitalisation or death from any cause
CLASS IV ANTIARRHYTHMIC DRUGS (CALCIUM CHANNEL BLOCKERS)

❤ Block Ca\(^{2+}\) entry into cell
❤ Cause vascular smooth muscle relaxation
❤ Negative inotropic effect
❤ Negative chronotropic effect
❤ Decreased conduction velocity within the heart, particularly at the AV node
CLASSES OF CALCIUM CHANNEL BLOCKERS

DIHYDROPYRIDINES
- Amlodipine
- Felodipine
- Isradipine
- Nicardipine
- Nifedipine
- Nitrendipine

PHENYLALKYLAMINES
- Verapamil

BENZOTHIAZEPINES
- Diltiazem
VERAPAMIL / DILTIAZEM

❤️ Slow conduction through AV node
❤️ Caution in heart failure
❤️ Caution with concomitant β-blockers
❤️ Avoid in WPW syndrome with pre-excited AF
ADENOSINE

♥ Naturally occurring purine nucleoside
♥ Causes smooth muscle relaxation (via A_2 receptors)
♥ Via A_1 receptors & Gi proteins opens K^+ channels and ↓ cAMP which inhibits Ca^{2+} channels
♥ Also inhibits release of noradrenaline
ADENOSINE

- Half-life in blood is less than 10 seconds
- Rapidly transported into red blood cells
- Decreases heart rate and reduces conduction velocity, particularly in the AV node
- Main use is to terminate SVT involving AV node and in helping to diagnose other arrhythmias
- Avoid in patients with severe asthma
- Use with caution in patients on dipyridamole
- Caffeine and theophyllines antagonise adenosine
CARDIAC GLYCOSIDES (DIGOXIN)

- Potent inhibitor of cellular Na⁺/K⁺-ATPase
- Causes ↑ in intracellular Ca^{2+}
- Results in smooth muscle contraction & vasoconstriction
- Increases vagal efferent activity in the heart
**DIGOXIN**

- Relatively useful in controlling ventricular rate in patients with atrial fibrillation
- High levels produce atrial arrhythmias and heart block
- Contra-indicated in AF with WPW syndrome
- Many drug interactions
**Vaughan Williams Classification of Antiarrhythmic Drugs**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>EXAMPLES</th>
<th>IA</th>
<th>IB</th>
<th>IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Na⁺ channel blockers</td>
<td>Quinidine, Procainamide, Disopyramide</td>
<td>Depress phase 0, Slow conduction</td>
<td>Depress phase 0 in abnormal more than normal tissue</td>
<td>Flecainide, Propafenone*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolong repolarisation</td>
<td>Shorten repolarisation</td>
<td>Marked depression of phase 0 and slowing of conduction (QRS may increase)</td>
</tr>
<tr>
<td>II Beta blockers</td>
<td>Propranolol, Metoprolol, Atenolol</td>
<td></td>
<td>Sinus node, AV node depression</td>
<td></td>
</tr>
<tr>
<td>III K⁺ channel blockers</td>
<td>Amiodarone**, Sotalol*, Bretylium, Dofetilide</td>
<td></td>
<td>QT prolongation</td>
<td></td>
</tr>
<tr>
<td>IV Ca²⁺ channel blockers</td>
<td>Verapamil, Diltiazem</td>
<td></td>
<td>Sinus node, AV node depression</td>
<td></td>
</tr>
</tbody>
</table>

* Propafenone and sotalol also have class II effects
** Amiodarone has activity in all 4 classes
OTHER (DRUGS)
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*
DABIGATRAN: RE-LY

♥ Randomised trial of 18,113 patients
♥ All had AF (paroxysmal, persistent or permanent)
♥ AF documented within the last 6 months
♥ Plus:
  - Previous stroke or transient ischaemic attack
  - Left ventricular ejection fraction < 40%
  - New York Heart Association class II or worse within last 6 months
  - Age ≥ 75 or age 65 to 74 years plus:
    - diabetes mellitus
    - hypertension, or
    - coronary artery disease
DABIGATRAN: RE-LY

♥ Compared to warfarin, 110mg b.d. of dabigatran was associated with similar rates of stroke and systemic embolism but lower rates of major haemorrhage.

♥ Compared to warfarin, 150mg b.d. of dabigatran was associated with lower rates of stroke and systemic embolism but with a similar rate of major haemorrhage.

♥ Both doses associated with a significant reduction in intracranial haemorrhage compared to warfarin.
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*
RIVAROXABAN: ROCKET AF

♥ EFFICACY
- Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism
- Rivaroxaban was superior to warfarin while patients were taking study drug
- By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority

♥ SAFETY
- Similar rates of bleeding and adverse events
- Less ICH and fatal bleeding with rivaroxaban

♥ CONCLUSION
- Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with AF
Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S.,
John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H.,
Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D.,
Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D.,
J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D.,
David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D.,
Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D.,
Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D.,
Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D.,
Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D.,
and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*
APIXABAN: ARISTOTLE

Treatment with apixaban as compared to warfarin in patients with AF and at least one additional risk factor for stroke:

♥ Reduces stroke and systemic embolism by 21% (p=0.01)
♥ Reduces major bleeding by 31% (p<0.001)
♥ Reduces mortality by 11% (p=0.047)

with consistent effects across all major subgroups and with fewer study drug discontinuations on apixaban than on warfarin, consistent with good tolerability
## Key Features of New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Apixaban and Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral direct thrombin inhibitor</td>
<td>Oral direct Factor Xa inhibitors</td>
</tr>
<tr>
<td>Prodrug (rapid biotransformation to active drug)</td>
<td>Directly acting compound – no biotransformation</td>
</tr>
<tr>
<td>Inhibits free and fibrin-bound FIIa activity</td>
<td>Inhibit free and fibrin-bound FXa activity, and prothrombinase</td>
</tr>
<tr>
<td>Fixed dosing – no coagulation monitoring required</td>
<td>Fixed dosing – no coagulation monitoring required</td>
</tr>
<tr>
<td>Max inhibition of FIIa after 1–4 h</td>
<td>Max inhibition of FXa after 1–4 h</td>
</tr>
<tr>
<td>$T_{1/2}$: dabigatran, 12–17 h</td>
<td>$T_{1/2}$: apixaban 12 h; rivaroxaban 6–9 h</td>
</tr>
<tr>
<td>Few food/drug interactions</td>
<td>Few food/drug interactions</td>
</tr>
<tr>
<td>Renal excretion: 80%</td>
<td>Renal excretion: 66%, 25% resp.</td>
</tr>
</tbody>
</table>

### Phase III AF Trials:

- **Dabigatran:** RE-LY
- **Apixaban:** ARISTOTLE
- **Rivaroxaban:** ROCKET AF
QUESTIONS