Inadequacies in current therapies for atrial fibrillation have made new drug development crucial. Conventional antiarrhythmic drugs increase the risk of ventricular proarrhythmia. In drug development, the focus has been on favourable multichannel-blocking profiles, atrial-specific ion-channels, and novel non-channel targets (upstream therapy). Molecular modification of the highly effective multichannel blocker, amiodarone, to improve safety and tolerability has produced promising analogues such as dronedarone, although this drug seems less effective than does amiodarone. Vernakalant, an atrial-selective drug with reduced proarrhythmic risk, might be useful for cardioversion in atrial fibrillation. Ranolazine, another atrial-selective agent initially developed as an antianginal, has efficacy for atrial fibrillation and is being tested in prospective clinical trials. So-called upstream therapy with angiotensin-converting enzyme and angiotensin-receptor inhibitors, statins, or omega-3 fatty acids and fish oil that target atrial remodelling could be effective, but need further clinical validation. We focus on the basic and clinical pharmacology of newly emerging antiarrhythmic drugs and non-traditional approaches such as upstream therapy for atrial fibrillation.

Pathogenesis

Atrial fibrillation can be maintained by sustained rapid ectopic activity or by re-entry (figure 1).4,5 Re-entry needs a susceptible substrate and a trigger, usually provided by an ectopic beat. Ectopic activity is caused by abnormal local spontaneous discharges from overactive ectopic pacemakers. Normal atrial tissue is unlikely to have enhanced ectopy or re-entry resulting from remodelling that is induced by cardiac diseases.6 Figure 2 shows the main mechanistic determinants of atrial fibrillation. Ectopic activity can be attributable to delayed or early afterdepolarisations (figure 2). Delayed afterdepolarisations result from spontaneous release of diastolic Ca2+ from the sarcoplasmic reticulum, typically caused by either overload of sarcoplasmic reticulum or dysfunction of sarcoplasmic reticulum Ca2+ release channels.9–12 Early afterdepolarisations result when excessive prolongation of action potential duration generates afterdepolarisations by mechanisms that are dependent on Ca2+. In response to sympathovagal discharge, action potential of short duration (parasympathetic effect) can combine with prolonged Ca2+ transients (sympathetic effect), also causing early afterdepolarisations.13

Re-entry is thought of in two different ways (figure 2). According to the leading circle idea, it depends on a balance between cellular refractoriness and conduction speed.14,15 When refractoriness is short or conduction is slow, the likelihood of continuous conduction in a potential re-entry zone is increased. Re-entry terminates if refractoriness is prolonged (eg, by prolongation of action potential duration) or conduction is accelerated, because the advancing wavefront encounters tissue that is still refractory, and dies out. According to the spiral wave notion,15,16 re-entry is maintained by a rapidly circulating rotor with a wavefront rotating around a central core. The size of the spiral wave is established by tissue excitability and refractoriness—high excitability and short refractoriness allow the spiral...
wave to rotate quickly around a small core, stabilising rotor maintenance. Additionally, cores tend to drift. The faster the rotor rotates, the less its core drifts (like a top rotating rapidly, which stays more steadily in position than it does when it is slow). Manoeuvres that reduce excitability or prolong refractoriness enlarge and slow rotors, increasing core wandering and the chance that rotors will extinguish against anatomical boundaries or refractory tissue.

Remodelling increases the likelihood of ectopic firing or re-entry (figure 1). It promotes ectopic firing by altering cardiomyocyte handling of Ca\(^{2+}\) to promote development of delayed or early afterdepolarisations.\(^{13,14}\) Electrical remodelling due to rapid atrial rates (like those during atrial fibrillation) shortens atrial refractoriness by reduction of action potential duration.\(^{15-17}\) Decreased L-type Ca\(^{2+}\) current, along with increased inward rectifier K\(^{-}\) current (I\(_{\text{K,IR}}\)) and constitutively active acetylcholine-dependent K\(^{-}\) current (I\(_{\text{K,ACH}}\)) are major contributors to shortening of action potential duration, and thus to functional re-entry.\(^{18-25}\) Atrial electrical remodelling explains why paroxysmal (short-term) atrial fibrillation tends to become persistent,\(^{26}\) why persistent atrial fibrillation is resistant to treatment\(^{27}\) and why recurrence of atrial fibrillation is especially likely in the first days after cardioversion.\(^{28}\)

Long-term atrial fibrillation causes cellular structural remodelling (cardiomyocyte hypertrophy and glycogen accumulation).\(^{29,30}\) Additionally, sustained rapid atrial activation might promote atrial fibrosis, which could interfere with atrial conduction and create an irreversible substrate for atrial fibrillation.\(^{31,32}\) Atrial fibrosis is a common feature of many pathologies associated with atrial fibrillation\(^{33,34}\) and seems to have a central role in pathogenesis of atrial fibrillation.\(^{32,35}\) Furthermore, atrial stretch and enlargement, features of many associated disorders, are important contributors to development of atrial fibrillation.\(^{34,35}\) The ability of an antiarrhythmic intervention to suppress atrial fibrillation depends on its capacity to suppress underlying mechanisms. Some antiarrhythmic interventions suppress this disorder by beneficially altering the atrial substrate, but they promote potential ventricular arrhythmia mechanisms, causing serious ventricular proarrhythmia—the main factor restricting the value of presently available antiarrhythmic drugs.

Rhythm versus rate control
There are two potential approaches to atrial fibrillation management—restoration and maintenance of sinus rhythm (rhythm control), and leaving patients in atrial fibrillation but controlling the ventricular response (rate control).\(^{36}\) The relative merits of these approaches have been extensively debated.\(^{37}\) Theoretically, sinus-rhythm maintenance is preferable, but several studies, most recently the AF-CHF trial,\(^{38}\) have failed to show that this method of rhythm control is better than is rate

**Figure 1. Key mechanisms in atrial fibrillation**
Atrial fibrillation can be maintained by either re-entrant or rapid and sustained ectopic activity. Development of re-entrant depends on action of a trigger (usually from an ectopic beat) acting on vulnerable substrate. In normal hearts, atrial ectopy is rare and atrial electrical properties are unsuitable for maintenance of atrial fibrillation. Atrial remodelling creates a substrate for re-entrant atrial fibrillation, by altering ion-channel function or inducing tissue fibrosis. Remodelling can also make ectopic activity more likely by producing changes in cell Ca\(^{2+}\) handling that cause triggered activity. EADs=early afterdepolarisations. DADs=delayed afterdepolarisations.

**Figure 2. Basic mechanisms underlying ectopic (A) or re-entrant (B) activity**
Yellow box=expected effects of class I antiarrhythmic drugs. Green box=expected effects of class III antiarrhythmic drugs. (A) Delayed afterdepolarisations (DADs) are caused by spontaneous diastolic Ca\(^{2+}\)-release events. Excess intracellular Ca\(^{2+}\) is exchanged across the membrane for Na\(^{+}\), producing inward movement of positive ions that depolarises cell. If depolarisation is large enough, it can reach threshold and cause ectopic firing (left). Early afterdepolarisations (EADs) result when the action potential is excessively long, allowing Ca\(^{2+}\) currents to reactivate and depolarise the cell (right). (B) Continuous activity in a leading-circle re-entry circuit depends on an appropriate balance between conduction velocity and refractory period (RP), and is favoured by small values of each (left). Maintenance of spiral-wave activity depends on tissue excitability and refractoriness, which govern rate and size of primary spiral-wave rotor and positional stability of core around which it rotates (right). APD=action potential duration.
control. The failure of rhythm-control therapy to benefit hard endpoints, such as mortality and stroke rates, might be related to inadequacy of therapeutic approaches, especially the risk of proarrhythmia. Data from the ATHENA trial\(^3\) suggest that the antiarrhythmic agent dronedarone might reduce cardiovascular mortality, admissions, and stroke rates in patients with atrial fibrillation.

Traditional antiarrhythmic drugs inhibit K\(^+\) currents (class III agents) or Na\(^+\) currents (class I agents). Effects of traditional antiarrhythmic agents on the main arrhythmia mechanisms are shown in figure 2. Class III drugs suppress re-entry by increasing refractory periods, but can produce torsade de pointes arrhythmias that are related to early afterdepolarisations. They can also worsen mechanisms associated with delayed afterdepolarisations. Pure class I agents suppress ectopic activity associated with early and delayed afterdepolarisation, although most clinically used class I agents also have K\(^+\) channel-blocking (class III) activity.

Classical leading circle re-entry theory predicts that Na\(^+\) channel blockade should facilitate re-entry by slowing conduction; however, class I drugs terminate atrial fibrillation and prevent its recurrence, probably because of their action to destabilise spiral-wave generators (rotors).\(^5\) Potent class I drugs have a strong effect on slowing conduction in ischaemic ventricular tissue, increasing the risk of ventricular tachyarrhythmias and sudden death in patients with coronary artery disease.\(^5\) Presently available class I and class III antiarrhythmic drugs have a modest and similar efficacy in the prevention of atrial fibrillation.\(^7\) More restricting than their insufficient efficacy is the risk of adverse events, especially life-threatening ventricular proarrhythmia. New antiarrhythmic drug development for atrial fibrillation aims to avoid proarrhythmia while maintaining or improving therapeutic effectiveness.

**New antiarrhythmic drugs**

**Amiodarone analogues**

Amiodarone is the most effective drug for treatment of atrial fibrillation, and has restricted proarrhythmic potential.\(^3\) It blocks Na\(^+\), Ca\(^{2+}\), and K\(^+\) channels (displaying actions of all antiarrhythmic classes),\(^9\) and inhibits the consequences of α-adrenoceptor and β-adrenoceptor stimulation.\(^9\) Furthermore, it causes venodilation,\(^6\) and suppresses electrical remodelling.\(^9\) Despite these advantages, this drug is limited by its very long half-life and potentially severe extracardiac side-effects.\(^6\)

**Dronedarone**

Dronedarone was designed on the basis of the amiodarone structure to keep pharmacokinetic complexity and toxicity to a minimum by reduction of lipophilicity and elimination of iodine moieties that cause thyroid dysfunction (figure 3). Other amiodarone homologues are celivarone (SR149744)\(^4\) and budiodarone (ATT-2042).\(^4\) Similar to amiodarone, dronedarone is a multichannel blocker with antiadrenergic properties; it prolongs action potential duration and reduces heart rate, with low risk of torsade de pointes arrhythmias.\(^6\)

Maximum dronedarone plasma concentrations are reached within 1–4 h. Plasma protein binding exceeds 98%. Oral bioavailability is only about 15%, but increases up to three-fold if taken with food.\(^4\) Steady-state concentrations are achieved within 7 days of 400 mg twice daily,\(^4\) with trough plasma concentrations at steady state between 60 and 150 ng/mL. Dronedarone is extensively biotransformed by cytochrome P450 (CYP3A4) enzymes, with little excretion of unchanged drug in bile and urine. The major metabolite, N-debutyldronedarone, has ten times lower plasma concentrations than does the parent compound, and is much less potent. The elimination half-life (about 24 h) is much shorter than that for amiodarone, which is very slow (up to many weeks) because of delayed removal from adipose tissue stores. Potent CYP3A4 inhibitors (eg, ketoconazole or erythromycin) can raise dronedarone plasma concentrations. Dronedarone increases serum digoxin levels by inhibition of P-glycoprotein intestinal and renal excretion, and can raise serum creatinine concentrations by inhibition of renal organic-cation transport.\(^5\)

Table 1 shows double-blind, randomised placebo-controlled trials of dronedarone. In the DAFNE study,\(^1\) dronedarone 400 mg twice daily, but not 600 mg or 800 mg doses, significantly delayed recurrence of atrial fibrillation. The absence of a dose-response relation
was unexplained. In the EURIDIS and ADONIS trials, the median times to recurrence of atrial fibrillation were significantly longer and ventricular rates during recurrence lower for dronedarone than for placebo. Post-hoc analyses of pooled EURIDIS and ADONIS data showed that dronedarone greatly decreased the combined endpoint of admission or death. The efficacy of dronedarone for rate control in patients with permanent atrial fibrillation was tested in the ERATO trial. When added to standard therapy, dronedarone reduced resting ventricular rate by 12·3 beats per min, with the effect increasing during exercise.

ANDROMEDA was a survival study in patients with systolic left ventricular dysfunction. The trial was prematurely discontinued because of increased mortality attributable to worsening of heart failure in the dronedarone group. 6 months later, mortality rates were similar (13·5% for dronedarone vs 12·3% for placebo; hazard ratio [HR] 1·13, 95% CI 0·73–1·74, p=0·60), but dronedarone is nevertheless contraindicated in class III and IV heart failure.

In the ATHENA trial, dronedarone substantially reduced the primary endpoint (all-cause mortality and cardiovascular admissions) by 24% and total admissions by 28%. Dronedarone also reduced risk of death from cardiac arrhythmia, a secondary endpoint (HR 0·55, 0·34–0·88, p<0·001). The median time to first atrial fibrillation or recurrence of atrial flutter was increased by dronedarone, and the likelihood of permanent atrial fibrillation or atrial flutter was greatly reduced. Median heart rate during these disorders was also lower in the dronedarone group (75 beats per minute vs 84 beats per minute, p<0·001).

A meta-analysis of the pooled data from five randomised placebo-controlled trials (ERATO, DAFNE, EURIDIS, ADONIS, and ATHENA) in 6157 patients with atrial fibrillation or atrial flutter showed reduced time to first cardiovascular admission or death (HR 0·76, 0·69–0·84, p<0·001), and decreased incidence of cardiovascular (0·71, 0·52–0·96, p=0·017) or sudden death (0·49, 0·28–0·86, p<0·011). Thus dronedarone controls both rhythm and rate in atrial fibrillation and atrial flutter, and seems to reduce cardiovascular admissions and death.

In a non-prespecified post-hoc analysis, dronedarone decreased risk of stroke versus placebo. An analysis of numbers in brackets are 95% CIs. AF=atrial fibrillation. NYHA=New York Heart Association. CHF=congestive heart failure. LVEF=left ventricular ejection fraction. DM=diabetes mellitus. BP=blood pressure. TIA=transient ischaemic attack. LA=left atrium. MI=myocardial infarction. P=placebo group. D=dronedarone group. HR=hazard ratio. bpm=beats per minute. SB=sinus rhythm.
New Drug Class

Because dronedarone reduces heart rate and presence of atrial fibrillation increased risk of stroke by result from underuse of anticoagulants. Notably, mechanisms of benefit is needed to clarify this observation and identify recurs might also be of benefit. Further investigation resulted in rates similar to those reported in community risk of stroke by 36%. Although blood pressure reductions were slightly greater with dronedarone and with placebo, history of hypertension or measured blood pressure had no predictive value. These results suggest the possibility that dronedarone itself reduces risk of stroke in atrial fibrillation, an effect that has not previously been observed with antiarrhythmic drugs.

One major limitation of this ATHENA subanalysis was that stroke was not a prespecified endpoint. Thus strokes might have been under-reported. Additionally, no potential mechanism of action was shown. Suppression of thromboembolism related to atrial fibrillation and attributable to reduction in atrial fibrillation burden is possible. However, restoration of sinus rhythm and atrial contraction did not reduce stroke risk in AFFIRM, although this outcome might result from underuse of anticoagulants. Notably, presence of atrial fibrillation increased risk of stroke by 60%. Because dronedarone reduces heart rate and dilates blood vessels, potential anti-ischaemic properties of dronedarone might have contributed. Although the decrease of blood pressure was small, even such reductions could decrease risk of stroke. Rate-slowng properties when atrial fibrillation recurs might also be of benefit. Further investigation is needed to clarify this observation and identify mechanisms of benefit.

In ATHENA, use of oral anticoagulant therapy resulted in rates similar to those reported in community practice. None of the completed dronedarone trials enrolled patients with highly symptomatic atrial fibrillation, although relief of symptoms is the main indication for maintenance of sinus rhythm in patients with this disorder. Additionally, quality of life was not assessed. These issues limit relevance of this therapy for community practice.

The DIONYSOS trial tested dronedarone versus amiodarone in patients with persistent atrial fibrillation. Preliminary results show that recurrence of atrial fibrillation during follow-up at 7 months after electrical cardioversion was higher with dronedarone (63.5%) than with amiodarone (42.0%), but drug discontinuation was more frequent with amiodarone (13.3%) than with dronedarone (10.4%). These data suggest higher tolerability but less efficacy for dronedarone than for amiodarone. A meta-analysis confirmed that patients treated with amiodarone were more likely to maintain sinus rhythm than were those treated with dronedarone (HR 0.49, 95% CI 0.37–0.63; p<0.001). However, amiodarone was associated with a trend toward greater all-cause mortality (1.61, 0.97–2.68, p=0.07) and more adverse events needing drug discontinuation (1.81, 1.33–2.46, p<0.001). These results and those of ANDROMEDA underscore the need for head-to-head mortality trials and stroke prevention studies to better define the role of dronedarone in therapy for atrial fibrillation.

The reason for the lowered efficacy of dronedarone compared with amiodarone is unclear. A contributing factor might be that cardiac accumulation of amiodarone is greater than that of dronedarone, and efficacy of N-desethylamiodarone (the major amiodarone metabolite) is better than is that of N-debutylidronedarone. Concentrations of N-desethylamiodarone in human hearts are higher than are those of amiodarone, whereas N-debutylidronedarone does not accumulate. Heightened local hypothyroidism is an unlikely explanation, because inhibition of T3 binding to thyroid hormone α1 receptors is similar for N-desethylamiodarone and N-debutylidronedarone. Possibly, amiodarone interacts with thyroid hormone, dependent on the iodide moieties that are absent in dronedarone, which are important for its antiarrhythmic efficacy. Other actions of amiodarone that are not shared by dronedarone might also contribute to its better efficacy. For example, the electrical remodelling-induced I_{Ca,L} decrease in α1c subunit expression is prevented by amiodarone, and whether dronedarone possesses similar effects is unknown.

Although short follow-up periods preclude definitive conclusions about long-term safety, trials so far have provided no evidence for thyroid dysfunction induced by dronedarone or pulmonary toxic effects. The most frequently reported adverse events for dronedarone versus placebo in ATHENA were gastrointestinal (26.2% vs 22.0%), skin disorders (10.3% vs 7.6%), and
increased serum creatinine (4.7% vs 1.3%), due to inhibited renal-tubular secretion. Patients with class III or class IV heart failure were excluded from all clinical trials apart from ANDROMEDA,8,18 in which the increased rate of admission for worsening congestive heart failure or death in the dronedarone group (HR 2.13, 95% CI 1.07–4.25, p=0.03) raised safety concerns for patients with moderate-to-severe congestive heart failure.55 In DIONYSOS, the dronedarone group had increased rate of admission for worsening congestive heart failure or death in the dronedarone group (HR 3.57, 95% CI 2.0–6.2, p<0.0005). Inclusion criteria were reversible cause of AF; CHF; NYHA IV CHF; Reversible cause of AF, class NYHA IV CHF. Exclusion criteria were atrial fibrillation or lowering of ventricular rate. The European Medicines Agency (EMEA) approved dronedarone to prevent recurrence of AF more than 35%. The American Food and Drug Administration (FDA) on March 18, 2009, for sinus-rhythm maintenance in patients with a history of atrial fibrillation. Dronedarone has been recommended for approval by the European Medicines Agency (EMA) and approved by the American Food and Drug Administration (FDA) on March 18, 2009, for sinus-rhythm maintenance in patients with a history of atrial fibrillation. Dronedarone is of little use for atrial flutter. Vernakalant affects cardiac Na⁺ and several K⁺ channels, including the atrial-selective currents Iₐur and IₐK,ACh. Na⁺ channel-blocking potency (especially during atrial fibrillation) is probably underestimated in preclinical voltage-clamp studies because of the experimental setting needed to record Iₐur and the very rapid rates of the fibrillating atrium. Thus vernakalant’s atrial antifibrillatory activity is probably attributable to rapidly unbinding Na⁺ channel blockade.71 The drug has mainly been used for termination of recent onset atrial fibrillation, but a longer-acting oral preparation is in development.

Intravenous vernakalant is generally given at an initial dose of 3 mg/kg, and then an additional 2 mg/kg if atrial fibrillation conversion fails after 15 min. Vernakalant is metabolised by CYP2D6, but plasma concentrations of intravenous vernakalant are similar in poor and extensive metabolisers.72 The elimination half-life is about 2 h. Oral administration of the pure salt is impractical because of a short plasma half-life, but a slow-release preparation is undergoing clinical trials.73

Findings from one phase 2 and three phase 3 randomised, double-blind, placebo-controlled studies,74–76 showed substantial efficacy for stopping atrial fibrillation—about 50% (versus 0–10% for placebo), with very few side-effects (table 2). Efficacy was high for recent-onset atrial fibrillation (3 h to 7 days), whereas longstanding atrial fibrillation rarely responded favourably. Median time to conversion in ACT III was 8 min, and the 24 h recurrence rate was very low. Vernakalant is of little use for atrial flutter. Vernakalant has been recommended for approval by

### Table 2: Efficacy of vernakalant in randomised clinical trials of patients with atrial fibrillation

<table>
<thead>
<tr>
<th>CRAFT 74</th>
<th>ACT I 75</th>
<th>ACT II 76</th>
<th>ACT III 77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>Sustained AF for 3 h to 3 days</td>
<td>Sustained AF for 3 h to 45 days</td>
<td>Postoperative AF or atrial flutter for 3 h to 3 days</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Reversible cause of AF, CHF</td>
<td>Class NYHA IV CHF</td>
<td>Reversible cause of AF, class NYHA IV CHF</td>
</tr>
<tr>
<td>Treatment</td>
<td>3 mg/kg IV, then 2 mg/kg if no conversion</td>
<td>3 mg/kg IV, followed by 2 mg/kg if no conversion</td>
<td>3 mg/kg IV, followed by 2 mg/kg if no conversion</td>
</tr>
<tr>
<td>Follow-up</td>
<td>24 h</td>
<td>24 h</td>
<td>6 days</td>
</tr>
<tr>
<td>Patients</td>
<td>56</td>
<td>336</td>
<td>161</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td>Termination of AF: 61% (V) vs 5% (P) (p=0.0005)</td>
<td>Conversion of short duration AF (3 h to 7 days) to SR: 62.2% (V) vs 4.9% (P) for AF lasting 3–48 h (difference of success 57.2%; 95% CI 46.4–68.0); 23.8% (V) vs 0% (P) for AF lasting 3–7 days (difference of success 23.8%; 95% CI 10.9–36.7)</td>
<td>Conversion of AF or atrial flutter to SR: 45% (V) vs 15% (P) (p=0.0002); conversion of AF to SR: 47% (V) vs 14% (P) (p=0.0003); no significant conversion of atrial flutter to SR</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>Patients in SR at 1 h: 53% (V) vs 5% (P) (p=0.0014); patients in SR at 24 h: 79% (V) vs 45% (P) (p=0.005); median time to SR conversion: 14 min (V) vs 162 (P) (p=0.016)</td>
<td>Conversion of long-duration AF (8–45 days) to SR: 79% (V) vs 0% (P) for AF lasting 8–45 days (p=0.09); no significant conversion of atrial flutter to SR</td>
<td>Median time to SR conversion with V: 12.3 min (range 0.5–57.1 min)</td>
</tr>
</tbody>
</table>

the FDA for intravenous conversion of recent-onset atrial fibrillation.

Vernakalant’s efficacy compares favourably with that reported for other available compounds for atrial fibrillation termination, although no comparative trials are available. Because of its slow onset of action, amiodarone is less suitable for acute atrial fibrillation cardioversion than are other drugs. Ibutilide has lower efficacy than does vernakalant and substantial proarrhythmic potential attributable to inhibitory effects on \( I_{\text{Na}} \) effects that are not shared by vernakalant. A phase 3 superiority study of intravenous vernakalant versus amiodarone in recent-onset atrial fibrillation (AVRO trial) is ongoing.

Vernakalant could also prove useful for prevention of recurrence of atrial fibrillation. Preliminary results from a double-blind, placebo-controlled, randomised dose-ranging phase 2 study showed that high-dose oral vernakalant prevents recurrence of atrial fibrillation without proarrhythmia; however, patients with decompensated heart failure were excluded. No phase 3 trial data are available. The most common side-effects of intravenous vernakalant are nausea, sneezing, and dysgeusia, probably related to central nervous system Na+ channel blockade. Adverse haemodynamic effects can arise, especially in the setting of pre-existing ventricular dysfunction, but are rare.

Other atrial-selective drugs

Ranolazine has antianginal properties of unknown mechanism and is approved for use in chronic angina. It prevents recurrent myocardial ischaemia in patients with acute coronary syndrome, without affecting the primary endpoint (major cardiovascular events). Researchers in the MERLIN-TIMI 36 trial investigated ranolazine in acute coronary syndrome in 6500 patients. Ranolazine therapy was associated with reduced non-sustained ventricular tachycardia in patients without ischaemia (5·0% in the ranolazine group vs 8·3% in the placebo group; HR 0·60, 95% CI 0·48–0·74, p=0·001). Less frequent atrial fibrillation was reported in the ranolazine group (1·7% vs 2·4%) than in the placebo group (0·74, 0·52–1·05, p=0·08). Ranolazine has atrial-selective Na+ channel blocking and late \( I_{\text{Na}} \)-inhibiting properties, and an ability to suppress atrial fibrillation in the presence of acetylcholine or ischaemia reperfusion, or isoproterenol in vitro.

Ranolazine has variable bioavailability after oral administration, probably because of extensive first-pass metabolism by CYP3A4 and to a lesser extent CYP2D6. The terminal elimination half-time is about 7 h. Findings of two small non-randomised studies showed that oral ranolazine safely converts new onset or paroxysmal atrial fibrillation and promotes sinus-rhythm maintenance. Large prospective studies of ranolazine in suppression of atrial fibrillation are in progress.

Several agents have been developed during the search for atrial-selective compounds for atrial fibrillation therapy. AZD7009 has atrial-selective effects in vivo. The compound is a mixed-channel blocker and effectively converts persistent atrial fibrillation in man. Research on AZD7009 was stopped because it had non-cardiovascular toxicity (reasons not specified), but congeners are being developed. AVE0118 inhibits several atrial-selective K+ channel targets, including \( I_{\text{Kur}} \) and \( I_{\text{LACC}} \) and unlike traditional class III drugs it maintains efficacy in the remodeled atrium. Clinical development was stopped for undisclosed reasons, but related compounds are in development. AVE1231 is one derivative with improved pharmacokinetics and atrial-selective \( I_{\text{Kur}}/\text{Kv1.5} \)-blocking actions. A wide range of other atrial-selective K-channel blockers are in active development.

Adjuvant therapy for sinus rhythm maintenance (upstream therapy)

Basic research into substrates that maintain atrial fibrillation has pointed to molecular targets upstream of the electrical aspects of atrial fibrillation as a novel potential therapeutic strategy. Atrial fibrillation is a common motif in pathological changes related to atrial fibrillation, and constitutes an interesting target for novel approaches in atrial fibrillation prevention. Candidates for upstream therapy include drugs suppressing the renin-angiotensin-aldosterone system, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins), and omega-3 fatty acids. None of these drugs have specific approval for atrial fibrillation treatment, but they are available and their present indications (hypertension, coronary artery disease, and heart failure) are some of the most frequent causes of atrial fibrillation.

Inhibitors of the renin-angiotensin-aldosterone system

Atrial angiotensin II concentrations increase in atrial fibrillation and stimulation of its receptors activate nicotinamide adenine dinucleotide-phosphate (NADPH) oxidase to produce oxidative stress or inflammation. Atrial angiotensin II also initiates intracellular signalling cascades that activate mitogen-activated protein kinases, causing myocyte hypertrophy, apoptosis, and fibroblast proliferation. Atrial angiotensin II also modifies atrial electrophysiology by indirect actions on ion channels. Interventions that inhibit the renin-angiotensin system prevent promotion of atrial fibrillation in animal models independently of haemodynamic actions. Several analyses of retrospective clinical trials suggest benefit of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 (AT1)-blockers in prevention of atrial fibrillation, especially in patients with left
ventricular hypertrophy or dysfunction. In a meta-analysis, researchers identified the greatest benefit was in patients after electrical cardioversion and with congestive heart failure. However, the large placebo-controlled GISSI-AF trial showed that valsartan did not reduce recurrence rates of atrial fibrillation, raising questions about the value of AT, blockers in secondary prevention. More than half of the patients in each group were taking ACE inhibitors, potentially confounding the results; however, valsartan inefficacy was independent of ACE-inhibitor use. Additionally, follow-up was 1 year only. The negative result might also have been attributable to intervention after atrial remodelling was established or slow ongoing remodelling rates during the trial.

Preliminary results of the ACTIVE I trial, including 9016 atrial fibrillation patients during a follow-up of 4-1 years, showed that irbesartan did not prevent cardiovascular events and had no effect on atrial fibrillation burden (report presented at European Society of Cardiology 2009 meeting in Barcelona). Irbesartan reduced admissions for heart failure (secondary endpoint) from 3.2% to 2.7% (HR 0.86, 95% CI 0.76–0.98, p=0.018), suggesting that AT, blockers could prevent deterioration of heart failure in hypertensive patients with atrial fibrillation. Further prospective studies are needed to establish the potential therapeutic value of ACE inhibitors and AT, blockers in prevention of atrial fibrillation and to define the populations of patients that benefit.

Aldosterone is generated in the heart and exerts many cardiac effects. In small animals, aldosterone causes atrial fibrosis and spironolactone prevents fibrosis. Selective aldosterone receptor blockade also suppresses atrial fibrillation in animal models of heart failure. Plasma aldosterone concentrations increase in patients with atrial fibrillation and atrial expression of the aldosterone receptor is higher in these patients than in those without the disorder. Patients with primary hyperaldosteronism have a 12-fold greater risk of atrial fibrillation than do controls matched for blood pressure. Hence blockade of aldosterone receptors could be a therapeutic option for patients with atrial fibrillation, but data from trials are not available.

**Anti-inflammatory agents**

Atrial tissue inflammation contributes to atrial arrhythmogenic remodelling and might be a target for therapies that suppress atrial fibrillation. Glucocorticoids have powerful anti-inflammatory properties and have efficacy against atrial fibrillation in animal and clinical studies, although their potential toxicity restricts their value in this disorder. Both statins and omega-3 fatty acids have anti-inflammatory and antioxidant actions. Statins are effective against several substrates that maintain atrial fibrillation. Statins are of benefit in prevention of atrial fibrillation, especially for postoperative atrial fibrillation. Epidemiological data about the effects of omega-3 fatty-acids on occurrence of atrial fibrillation are conflicting. Animal studies show model-dependent atrial-fibrillation-preventing effects, suggesting that omega-3 fatty acids prevent atrial fibrillation, especially in patients at risk of fibrotic structural remodelling. Peroxisome proliferator-activated receptor γ activators, such as pioglitazone, might suppress adverse cardiac remodelling and susceptibility to atrial fibrillation, but can also cause salt retention and might predispose to development of congestive heart failure.

**Alternative approaches and future developments**

Atrial fibrillation results from a range of pathophysiological processes; therefore different populations with this disorder might need specific therapeutic approaches. How to profile phenotypes for this disorder to deliver individualised therapy is a challenge for the future. Developments in pharmacogenetics, non-invasive imaging, and biomarkers might help. Atrial fibrillation ablation has evolved rapidly during the past decade. Pulmonary vein isolation is an effective therapeutic option for patient with paroxysmal atrial fibrillation, but success of this ablation is lessened in persistent disease. Despite extensive investigation, the precise mechanism of the pulmonary vein contribution to atrial fibrillation remains poorly understood. Nevertheless, prevention of recurrence of atrial fibrillation is more effective with ablation than with antiarrhythmic drugs. Antiarrhythmic drugs plus ablation are also better than is drug therapy alone. However, despite some advantages compared with drug therapy, the very large size of the population with this disorder, and the risks, cost, and specialised facilities and skills needed for ablation, are such that drug approaches will probably remain a mainstay for therapy. Biological approaches, such as cell-based and gene-based therapies, are in their infancy, but could eventually offer unique advantages in management of atrial fibrillation.

**Conclusions**

Atrial fibrillation is common problem that is difficult to treat. New pharmacological approaches are in active development and two new drugs, dronedarone and vernakalant, are likely to be widely available in the future. Novel therapeutic approaches will probably have a substantial effect on future management of this disorder. The complexity of underlying mechanisms and large variability in pathophysiology make it likely that distinct and often several therapeutic options will be needed for individual patients. The challenge will be to identify precisely the best treatment approach and timing for every patient.
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Contributors
DD drafted the summary of the planned seminar, drafted the major part of the manuscript text, including figures and tables, and critically revised the whole manuscript; SN drafted some parts of the manuscript, including figures and tables, and critically revised the whole manuscript. Both authors have seen and approved the final version.

Conflicts of interest
DD has received consultancy fees from AstraZeneca and speaker’s honoraria from Sanofi-Aventis. SN is a consultant for AstraZeneca, Devgen, Johnson&Johnson, Milestonics, Misprou, Otsuka, Relialt, Sequel, Wyeth Pharmaceuticals, Pierre-Fabre, and Xention Discovery.

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