The Role of Ranolazine as an Antiarrhythmic Drug

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Ranolazine: Background

- Currently approved as an antianginal agent in patients with chronic angina (class IIA).
- Exhibits antiarrhythmic effects related to its multichannel blocking effect, predominantly inhibition of late sodium (late INa) current and the rapid potassium rectifier current (IKr), as well as ICa, late ICa, and INa-Ca.
  - It also suppresses the early and delayed afterdepolarizations.
- Effective in the suppression of atrial and ventricular arrhythmias (off-label use) without significant proarrhythmic effect.

Shenasa M et al.
Card Electrophysiol Clin
2016; 8: 467–479

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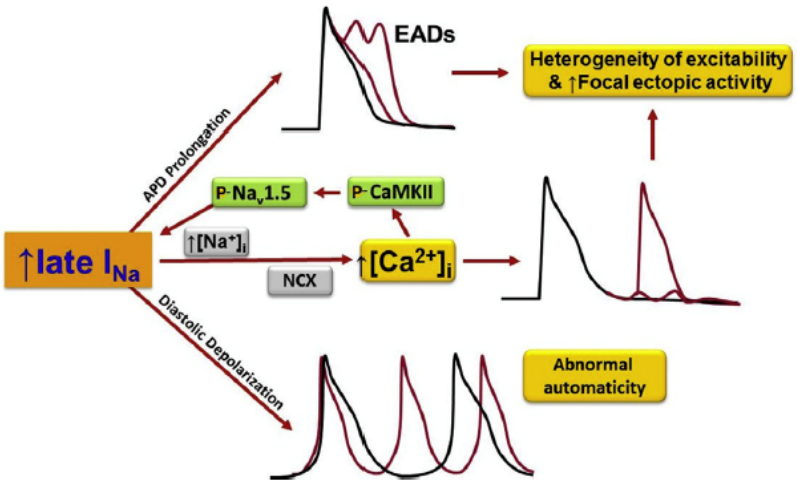
Ranolazine: Antiarrhythmic Drug Effect



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MERLIN-TIMI 36

- Evaluated the safety of ranolazine in patients with non–ST-elevation acute coronary syndromes.
- Double-blind, randomized (1:1), placebo-controlled, multinational trial that included 6560 patients within 48 hours of onset of acute coronary symptoms.
- Patients received intravenous (IV) ranolazine followed by either oral extended release of ranolazine (1000 mg twice a day in 3279 patients) or placebo (3281 patients).
- ***Patients administered ranolazine had significantly reduced episodes of VT ≥8 beats as well as SVTs and specifically new onset AF.***

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Circulation 2007

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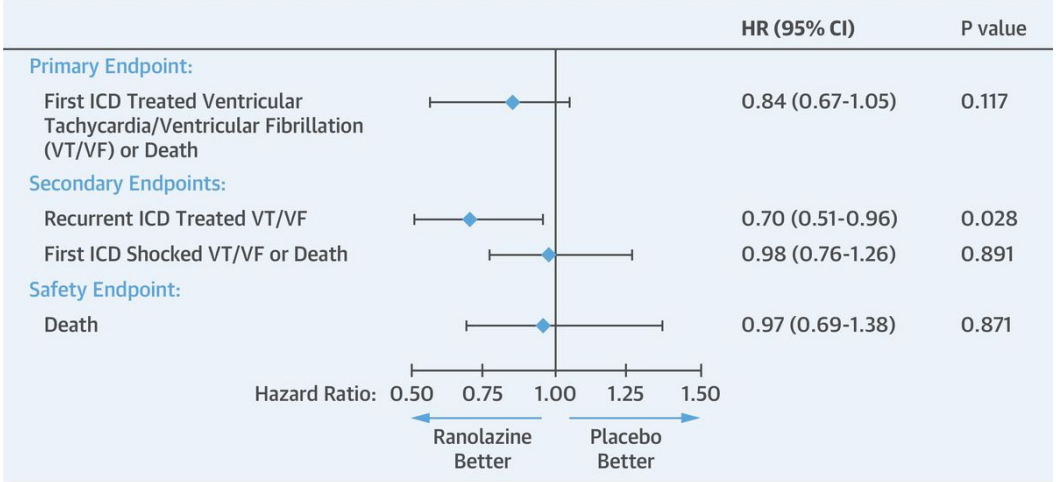
The RAID Trial



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Ranolazine: Safety

- Acute and long-term treatment with ranolazine has been shown to be safe even in patients with cardiac structural abnormalities, including
  - Acute coronary syndrome,
  - History of myocardial infarction,
  - Congestive heart failure.

- Ranolazine at the recommendation dosage does not pose a risk of TdP or pro-arrhythmia.
- Other noncardiac adverse effects include ***abdominal pain, asthenia, constipation, dizziness, headache, and nausea***.
  - The overall incidence of noncardiac side effects is less than 7%.

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Patients to Avoid

- Pre-existing QTc prolongation > 550 msec
- Patients on agents known to prolong the QT interval
  - Use only 500 mg bid when adding to a class III antiarrhythmic drug
  - Never add during loading phase of amiodarone
- Avoid CYP3A inhibitors or inducers
  - Diltiazem, ketoconazole, verapamil, macrolide antibiotics, HIV protease inhibitors, grapefruit juice
- Patients with creatinine > 2.5 mg/dl
  - Levels increase in patients with renal insufficiency
- End stage liver disease

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Our Experience

- Weak as a solo "AAD" but effective when added to amiodarone, dronedarone, and amiodarone
  - Minimal or no QT prolongation when added to dronedarone or sotalol
- Particularly effective in atrial arrhythmias associated with lung disease, including premature atrial contractions and multifocal AT
- Effective for scar based/ischemic PVCs (less so for idiopathic PVCs)
- Potentiates the efficacy of amiodarone so even patients with long-standing persistent AF patients can be maintained in sinus rhythm to allow for reverse remodeling pre-ablation
  - Have been able to lower dose of amiodarone to as low as 50 mg daily
  - Do NOT use during amiodarone loading or if dose > 200 mg a day

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Case Presentation 1

- 60-year old male with long-standing, persistent atrial fibrillation associated with rapid ventricular rates
- Presented with decompensated CHF and massive volume overload
  - No coronary disease; EF 20%
- Difficult to rate control despite triple AV nodal blocker therapy
- Failed to maintain sinus rhythm despite initiation of amiodarone

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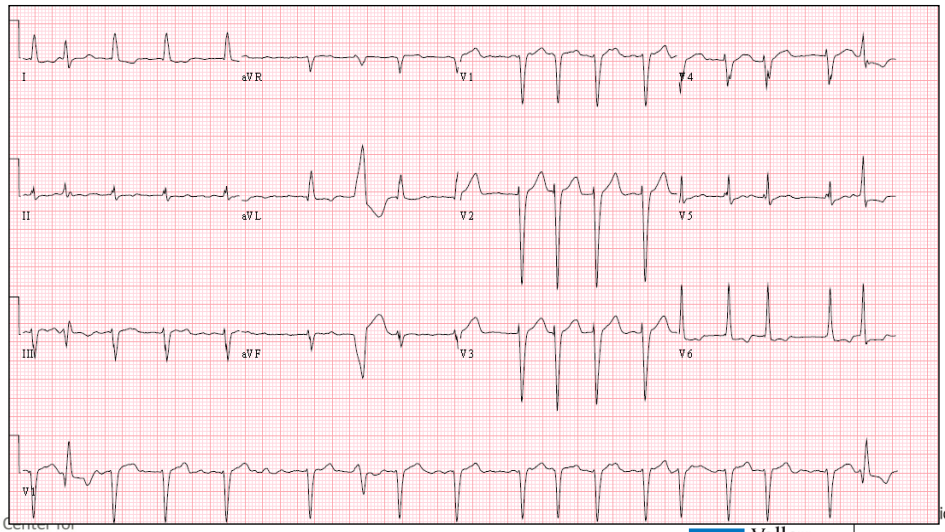
Case Presentation 1



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Case Presentation 1

- Ranolazine 500 mg bid added to amiodarone 200 mg daily
- Repeat cardioversion performed 2 weeks later restored sinus rhythm
  - A loop recorder was implanted for objective long-term ECG monitoring
- The patient maintained sinus rhythm on this combination of amiodarone and ranolazine
- Six weeks later, an echocardiogram showed an ejection fraction of 40%
- Cather ablation was performed 2 weeks later
- The patient has maintained sinus rhythm, is now off both ranolazine and amiodarone, and the ejection fraction has completely normalized

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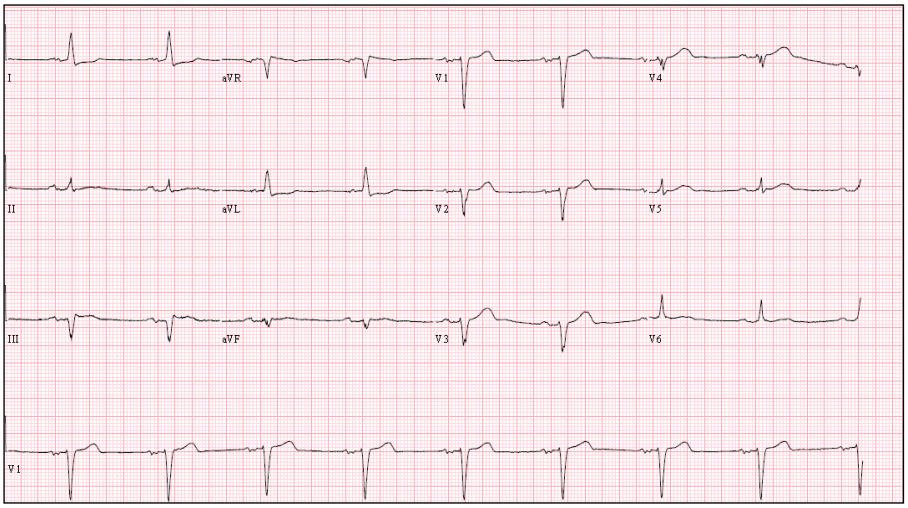
Case Presentation 1



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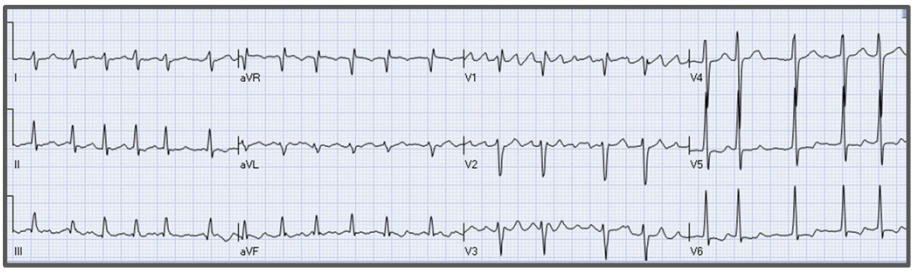
Case Presentation 2

- 62-year female with prior mechanical mitral valve replacement
- She developed highly symptomatic persistent associated with rapid ventricular rates
  - Intolerant to dofetilide



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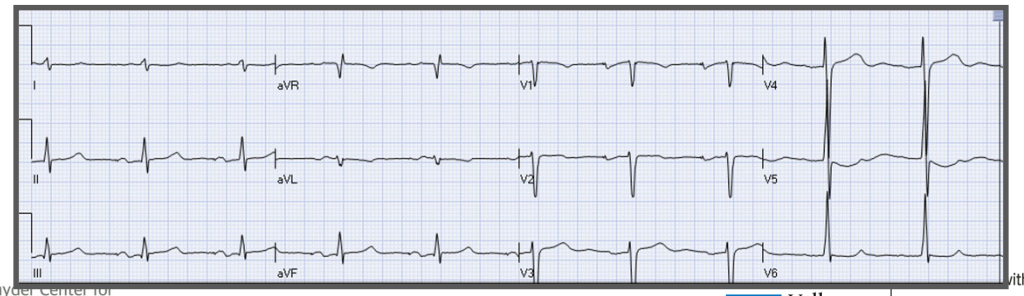
Case Presentation 2

- Following cardioversion, started on dronedarone 400 mg bid but continued to have paroxysmal atrial fibrillation
- Ranolazine 500 mg bid added
- Has maintained sinus rhythm for the past 3 years



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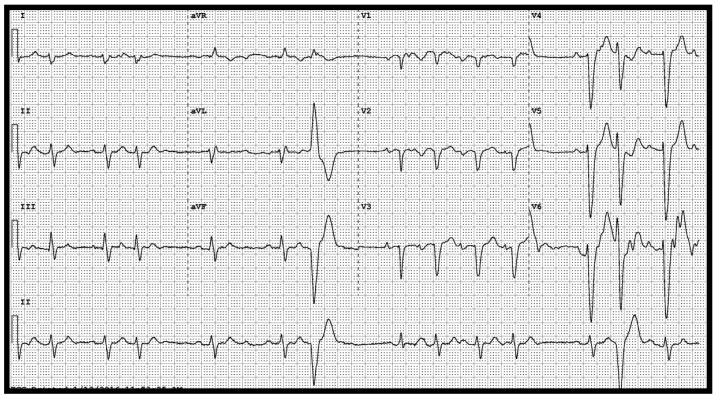
Case Presentation 3

- 87-year old male with oxygen dependent, end stage lung disease/emphysema
- Developed palpitations due to incessant APCs/MAT as well as PVCs
- Ejection fraction, which was previously normal, dropped to 20%



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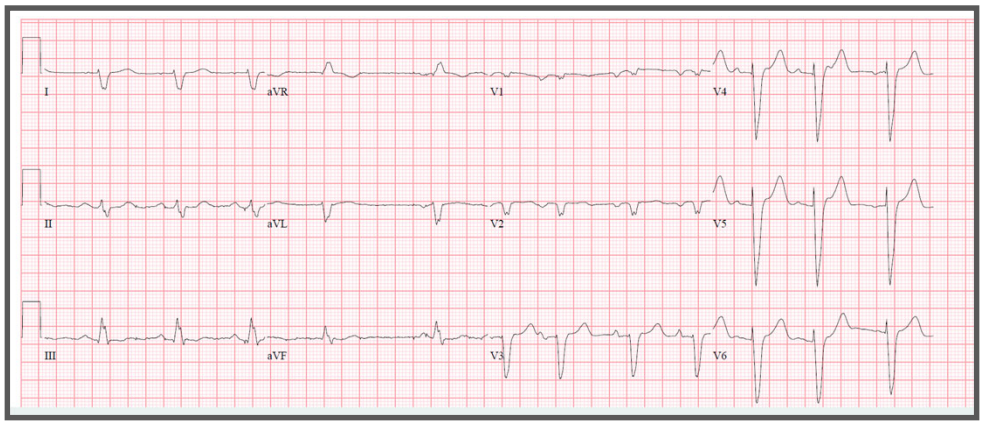
Case Presentation 3

- Post-ranolazine



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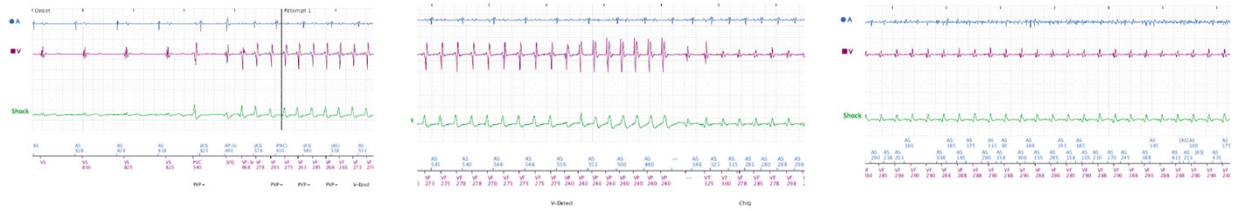
Case Presentation 4

- 67-year old male with Parkinson's disease and an ischemic cardiomyopathy (s/p ICD)
- Developed PVCs, non-sustained and sustained ventricular tachycardia for which he received both anti-tachycardia pacing and shocks from the ICD



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Case Presentation 4

- Patient reluctant to undergo ablation given his underlying Parkinson's disease
- Amiodarone started, successfully suppressed ventricular tachycardia, but was associated with multiple extra-cardiac side effects
- Ranolazine 500 mg bid added and amiodarone lowered first to 100 mg daily and then 50 mg daily
- No further episodes of sustained ventricular tachycardia or ICD shocks on this combination
- No noticeable side effects

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Conclusions

- Adding ranolazine to class III AADs potentiates their antiarrhythmic effect, without increasing toxicity.
- Increases the ability to restore and maintain sinus rhythm in difficult to treat patients with atrial fibrillation
  - Can be used to lower the daily dose of amiodarone
- May have a role in patients with an ICD
- Most common side effect: dizziness

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