New Drugs for PCP: What You Need to Know

Learning Objectives

1. List the recently approved drugs will have the largest impact on primary care practice
2. Discuss the efficacy, side effects, and cost of important novel drugs in primary care practice
3. Review the role of recently approved medications and their place among existing therapies

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New Drugs for the Primary Care Provider: What You Need to Know

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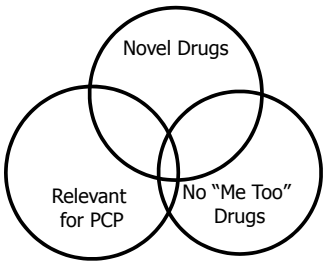
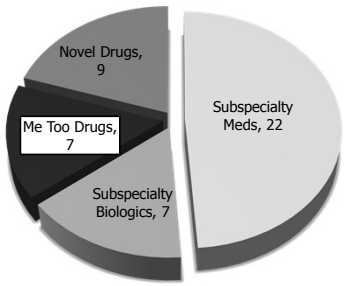
Important New Drugs for 2016: What We Need to Know



2015: More Potentially Novel Drugs than Recent Years

FDA New Drug Approvals in 2015: More Potentially Novel Drugs for Primary Care



Three Novel Drugs for Primary Care Practice

- Ivabradine to reduce admissions in CHF with reduced ejection fraction
- Alirocumab to reduce LDL cholesterol
- Idarucizumab to reverse anticoagulant effects of dabigatran

Historical Perspective

"Man has an inborn craving for medicine… The desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures… Even in minor ailments, which would yield to dieting or to simple home remedies, the doctor's visit is not thought to be complete without the prescription."

William Osler 1895

Mr. Saul Teeman

- 72 year old man
- NYHA class III CHF
- LVEF 30%
- On lisinopril and metoprolol
- Life limited by dyspnea
- Should I add ivabradine?

Ivabradine is an I_f Channel Blocker

- Cyclic nucleotide-gated channel blocker
- Binds to F channels in SA node
- Inhibits I_f current
- Slows diastolic depolarization in SA node
- Pure heart rate lowering agent

Physiologic Effects of Ivabradine

Increase	Decrease	No Change
Stroke volume	Heart rate	Blood pressure
Oxygen supply and demand	Preload	Ventricular repolarization
	Afterload	Myocardial contractility

BEAUTIFUL: Ivabradine vs. Placebo in Patients with CAD and Reduced LVEF

- N=10,917
- Stable CAD
- LVEF < 40%
- Ivabradine (target dose 7.5 mg bid) vs. placebo
- Median follow up 19 months
- Primary outcome = CV death + acute MI + admission for CHF

Lancet 2008;372:807

SHIFT: Ivabradine vs. Placebo for HFrEF

- N=6558
- Symptomatic CHF
- LVEF < 35%
- NSR with resting HR ≥ 70
- Admit for CHF in past year
- Stable on beta blocker if tolerated
- Ivabradine 7.5 mg bid vs. placebo
- Median f/u 23 months

Lancet 2010;376:875

Adverse Events More Common than Placebo in SHIFT

Event	Ivabradine %	Placebo %
Symptomatic bradycardia	5%	1%
Asymptomatic bradycardia	6%	1%
Atrial fibrillation	9%	8%
Phosphenes*	3%	1%

Phosphenes due to inhibition of electrical current in retina = Bright areas in visual field, kaleidoscopic effects, colored bright lights, multiple images

Reason for Caution: Increased Harm for Subset of Patients without CHF

- SIGNIFY trial
- Patients with stable CAD and no CHF
- LVEF > 40%
- No difference in composite outcome of CV death or nonfatal MI
- Among patients with activity-limiting angina: Increased incidence of composite outcome

NEJM 2014;371:1091

Other Considerations

Contraindications

- Decompensated CHF
- Sick sinus
- Severe liver disease
- Strong CYP3A4 inhibitors

Pregnancy

- Teratogenic
- Absolutely contraindicated during pregnancy

Cost of Drugs Used to Treat HFrEF

Drug	Cost for 30 days Rx (USD)
Lisinopril 40 mg qd	$3
Enalapril 40 mg qd	$40
Valsartan 160 mg bid	$52
Metoprolol XL 100 mg qd	$45
Carvedilol 25 mg bid	$15
Sacubitril 97 mg /valsartan 103 mg bid	$375
Ivabradine 5 mg bid	$375

Medical Letter August 2015

FDA Approved Indications

1. Stable symptomatic CHF
2. LVEF ≤ 35%
3. Sinus rhythm
4. Resting HR ≥ 70
5. Maximally tolerated beta blocker dose or contraindicated

Key Points

- Reduces CHF admits, CHF deaths among patients with HR ≥ 70
- No effect on all-cause or CV mortality
- Less benefit than for ACEi or beta blockers
- Harmful for activity limiting CAD and no CHF
- Ivabradine is well tolerated
- Unusual retinal side effects
- Appropriate to use as 3rd line drug as per FDA indications

Advice for Saul Teeman?

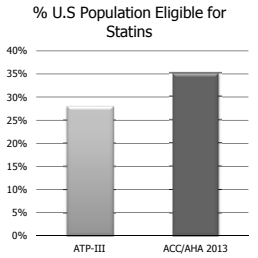
- Continue lisinopril and metoprolol
- Furosemide if volume overload
- Low Na^+ diet
- Reasonable to add ivabradine if HR ≥ 70

Ms. Elle Dièlle

- 60 year old woman with PAD and type 2 diabetes
- LDL 140 mg/dl on atorvastatin 80 mg qd
- No CAD to date
- Should I begin a biologic Rx to lower LDL and reduce risk of MI?

Prevalence of Hypercholesterolemia in the U.S.

- 32% of U.S adults have LDL levels > 130 mg/dl
- < One half are on treatment
- Fewer than 1/3 achieve target LDL
- ACC/AHA 2013 increases statin eligible patients by 25%



http://www.cdc.gov/cholesterol/facts.htm
Am Health Drug Ben 2014;7:430

Not All Patients with High LDL are Able to Tolerate Statins

- 10-15% of statin treated patients develop myalgia
- 1-5% incidence of myopathy (weakness or significant CK elevation)
- In the "treat to goal LDL" approach (no longer recommended by ACC/AHA), not all patients achieve LDL target with statins

PCSK9 Regulates LDL Metabolism

- Mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) are a genetic cause of familial hypercholesterolemia
- PCSK9 is a negative regulator of LDL receptors (LDLR) and causes degradation of LDLR
- LDLR removes LDL from circulation
- PCSK9 reduces ability of liver to remove circulating LDL cholesterol

Alirocumab

- Human recombinant Ig1 monoclonal antibody
- Binds and inhibits PCSK9
- Internalizes PCSK9/LDL complex
- Reduces serum PCSK9 levels
- Increases hepatic LDL receptors
- Results in increased LDL degradation
- Lowers serum LDL levels

ODYSSEY Trial of Alirocumab plus Statin vs. Statin Alone

- Phase 3 study (n=2341) at 320 sites
- CHD risk equivalent or
- Heterozygous hypercholesterolemia
  - Genotyping or
  - Clinical Criteria
- Maximum tolerated statin therapy
- Alirocumab 150 mg SC vs. placebo q 2 weeks for 78 weeks
- Primary endpoint change LDL at 24 weeks

NEJM 2015;372:1489

Entry Criteria into Study

Simon Broome Clinical Criteria (adults)

- Total chol > 290
- LDL > 190
- Tendon xanthomas in patient or relative

CHD Equivalent

- PAD
- Stroke
- CKD moderate: GFR 30-60 ml/min
- Diabetes + 2 additional risk factors

Meta-Analysis: All Outcomes

Outcome	OR for Rx vs. Placebo	95% CI
Mortality*	0.45	0.23-0.86
CV Mortality	0.50	0.23-1.10
Myocardial infarction*	0.49	0.36-0.93
Unstable angina*	0.61	0.06-6.14
Serious adverse events	1.01	0.87-1.18
% LDL reduction	59%	

Safety Outcomes in ODYSSEY

Event	Placebo %	Alirocumab %
Any adverse event	82.5	81.0
Serious adverse event	19.5	18.7
Study d/c	5.8	7.2
Major CV events	5.1	4.6
Nonfatal MI	2.3	0.9
Allergic reactions	9.5	10.1
Myalgia*	2.9	5.4
Neurocognitive events*	0.5	1.2
Ophthalmologic events*	1.9	2.9

* P < 0.05. Only myalgia significant in pooled safety data

Pooled Safety Data from 9 Trials: Significant Differences in Placebo Controlled Pools

Adverse Event	Placebo %	Alirocumab %
D/c due to adverse event	5.1	5.3
Myalgia	< 0.1	0.2
Worsened glucose tolerance	26.6	31.2
Injection site reactions	4.1	6.1
Serious allergic reactions	0.4	0.4
Serious neurologic events	< 0.1	0.2
Serious neurocognitive effects	0.2	0.1
Abnormal LFTs	1.8	2.5

FDA Prescribing Information

- Indications: heterozygous familial hypercholesterolemia or CVD who require additional LDL reduction
- 75 mg SC q 2 weeks (prefilled pens or syringes)
- Measure LDL 4-8 weeks after starting Rx
- If LDL response inadequate, increase to 150 mg SC q 2 weeks
- Injections safe at home, rotate injection site
- No data on pregnancy or breast feeding

Key Points

- Alirocumab reduces LDL to a greater extent than all current drugs
- Reduces LDL by additional 50-60% beyond that on maximum dose statins
- Reduces mortality and possibly CV mortality in up to 2 years in post-hoc analyses
- Only minor safety issues to date
- No safety data beyond 2 years
- Studies of clinical outcomes over more prolonged Rx underway

Recommendations

- Recommend alirocumab for patients with CAD or CAD equivalent if LDL above goal despite maximal tolerated statin therapy
- Consider for primary prevention if baseline LDL > 190 and total cholesterol > 290 and remain above target on maximal statin therapy
- Await longer term outcome and safety studies and post marketing surveillance
- Expected cost: $560 per injection (q 2 weeks) = $14,600 per year
- Manufacturer intends to offer cost assistance to selected patients

Advice for Ms. Elle Dièlle?

- Continue high dose atorvastatin
- Aspirin
- Submit prior authorization request or win the lottery
- Begin alirocumab 75 mg SC q 2 weeks

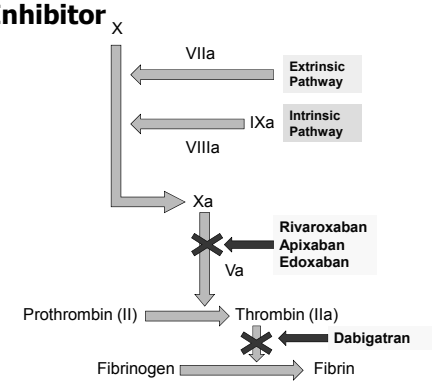
Ms. Bledsoe

- 74 year old woman
- On dabigatran for AF
- Upper GI bleed due to peptic ulcer
- Hct 22
- Bp 96/60
- How can I reverse the dabigatran effect?

The Novel Oral Anticoagulants (NOACs) are a Major Advance

- No monitoring required
- Similar or fewer bleeding complications than warfarin
- Equal or superior efficacy to prevent stroke in AF, prevent VTE after orthopedic procedures, and Rx of DVT and PE

Dabigatran is a Direct Thrombin Inhibitor



Summary of RECORD Trials: Rivaroxaban vs. Enoxaparin Prophylaxis After Surgery

	Surgery	*N*	*Composite Events %*	*RRR*
RECORD 1	THA	4541	3.7 vs 1.1	70%
RECORD 2	THA	2509	9.3 vs 2.0	79%
RECORD 3	TKA	2531	18.9 vs 9.6	49%
RECORD 4	TKA	3148	10.1 vs 6.9	31%

Lancet 2008;372:6

NOAC: Indirect Comparisons for Stroke Prevention in AF Apixaban Marginally Favored

Event %/year	Rivaroxaban Rocket AF	Dabigatran RELY	Apixaban ARISTOTLE
Stroke plus major emboli	1.7/2.2	1.1/1.7	1.3/1.60
Stroke	2.6/3.1	1.0/1.6	1.2/1.5
Mortality	1.9/2.2	3.6/4.1	3.5/3.9
Major bleeding	3.6/3.4	3.1/3.4	2.1/3.1
CNS bleeding	0.5/0.7	0.1/0.4	0.3/0.5

Indirect Comparisons of NOACs for Rx of DVT/PE

	Rivaroxaban	Dabigatran	Apixaban
Study	EINSTEIN-DVT	RE-COVER	AMPLIFY
# subjects	3449	2564	5395
Primary outcome	Recurrent VTE	Recurrent VTE or VTE death	Recurrent VTE or VTE death
Outcome vs. standard Rx	2.1% vs. 3.0%	2.4% vs. 2.1%	2.3% vs. 2.7%
Major bleeding	0.8% vs. 1.2%	1.6% vs. 1.9%	0.6% vs. 1.8%*

Outcomes comparable. Apixaban has marginally less bleeding

Curr Cardiol Rep 2014;16:463

Achilles Heel for NOACs: No Antidote for Rapid Reversal

- What to do if major bleeding or need for emergent surgery?
- Wait 2-3 days before full reversal of effect of NOACs
- Discontinue antiplatelet agents
- Prothrombin complex concentrates
- Tranexamic acid (anti-fibrinolytic)
- PRBC transfusions if major bleeding
- Hemodialysis (dabigatran)

Idarucizumab is a Novel Fab Fragment

- Monoclonal Antibody Fragment (Fab)
- Binds dabigatran in plasma
- 350-fold higher affinity than binding of thrombin by dabigatran
- Displaces thrombin from dabigatran
- Reverses anticoagulation
- Given as IV infusion

Phase I Trial of Efficacy of Reversal and Safety

- 47 healthy adult male volunteers
- Pretreated with dabigatran for 4 days
- Randomly assigned to addition of placebo or one of 4 doses of idarucizumab
- Primary endpoint = adverse effects
- Secondary endpoints for reversal of anticoagulation
- Outcome: no difference in adverse events between Rx and placebo groups

Lancet 2015;386:680

RE-VERSE AD: A RCT of Idarucizumab for Emergent Reversal

- 90 patients on dabigatran
- 51 with serious bleeding
- 39 requiring urgent surgery
- Primary endpoint is reversal of anticoagulant activity
- Secondary endpoint is restoration of hemostasis clinically
- Rx idarucizumab 2.5 mg IV x 2
- No placebo group
- Interim analysis in NEJM

NEJM 2015;373:511

Restoration of Hemostasis in Most Patients

- Group A: Serious bleeding
  - Cessation of bleeding in median of 11.4 hours
- Group B: Urgent surgery needed
  - 33/36 patients with normal hemostasis
  - 3 of 36 patients with excessive perioperative bleeding

Adverse Outcomes were Common Due to Trial Eligibility: Most thought not due to Idarucizumab

- 9 deaths in each group
- Thrombotic events in 5 patients
- Early deaths due to index event
- Late deaths due to comorbidities
- No placebo group
- No adverse outcomes clearly direct result of idarucizumab

FDA Approval

- Approved October 2015 as part of Accelerated Approval Program
- Based on interim analysis of RE-VERSE AD trial
- Post marketing surveillance
- Approved due to high mortality of eligible patients without Rx

Indications and Use

- Patients on dabigatran and either:
- Emergency/urgent surgery or procedure required or
- Life-threatening or uncontrolled bleeding
- 5mg IV dose x 1
- Cost = $3500 for one dose
- Only AE more common than placebo: headache
- No contraindications

In the Pipeline: A Reversal Agent for Factor Xa Inhibitors

- No current reversal agent for rivaroxaban, apixaban, edoxaban
- Andexanet alpha is modified Xa protein that binds factor Xa inhibitors
- Reverses anticoagulant effect
- Encouraging phase 3 trials
- Under consideration by FDA

Ms. Bledsoe

- Resuscitation
- All conservative measures
- Recommend idarucizumab to reverse dabigatran effect

Summary

- Ivabradine reduces CHF admits and mortality in HFrEF if resting HR ≥ 70
- Alirocumab reduces LDL by 50-60% beyond that achieved with statin and reduces mortality
- Idarucizumab fully reverses the anticoagulant effects of dabigatran, is safe, and expensive

A Final Thought…

"For some patients, though conscious that their condition is perilous, recover their health simply through contentment with the goodness of their physician."

Hippocrates

(460-375 BC)