Pharmacology Update – New on the Market and Does it Work?

James E. Tisdale, PharmD, FCCP, FAPhA, FAHA
Professor
Department of Pharmacy Practice
College of Pharmacy
Purdue University
&
Adjunct Professor
School of Medicine
Indiana University

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New on the Market

Recent Cardiovascular Drug Approvals by the FDA

Drug (Generic name)	Drug (Brand name)	Indication	Year approved
Apixaban	Eliquis®	• Nonvalvular atrial fibrillation • Prevention of VTE following hip or knee replacement • Treatment of DVT and PE	2012
Mipomersen sodium	Kynamro®	Homozygous familial hypercholesterolemia	2013
Omega-3-carboxylic acids	Epanova®	Hypertriglyceridemia	2014
Vorapaxar	Zontivity®	Reduction in thrombotic CV events in patients with a history of MI or PAD	2014

Apixaban

Eliquis

- Factor Xa inhibitor
- Half-life: 8-15 hours
- Metabolism: Hepatic (CYP 3A4)
- Elimination: Kidneys (27% of total clearance)
- Dose: 5 mg orally twice daily
  - Reduce to 2.5 mg twice daily if ≥ 2 of the following: age >80, weight < 60 Kg, serum Cr ≥ 1.5 mg/dL
- Drug interactions: Inhibitors & inducers of 3A4

Apixaban

ARISTOTLE Trial

- Prospective, randomized, double-blind
- Apixaban 5 mg twice daily vs warfarin (INR 2.0-3.0)
- n=18,201 patients with AF and ≥ 1 additional risk factor for stroke
- Primary outcome: Ischemic or hemorrhagic stroke or systemic embolism

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NEJM 2011;365:981-992.

Apixaban

ARISTOTLE Trial

Outcome	Apixaban (n=9120) event rate (%/yr)	Warfarin (n=9081) event rate (%/yr)	Hazard ratio (95% CI)	P value
1° Outcome: Stroke or systemic embolism	1.27	1.60	0.79 (0.66-0.95)	0.01
Stroke	1.19	1.51	0.79 (0.65-0.95)	0.01
Ischemic or uncertain type of stroke	0.97	1.05	0.92 (0.74-1.13)	0.42
Hemorrhagic stroke	0.24	0.47	0.51 (0.35-0.75)	<0.001
Systemic embolism	0.09	0.10	0.87 (0.44-1.75)	0.70

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NEJM 2011;365:981-992.

Apixaban

ARISTOTLE Trial

Outcome	Apixaban (n=9120) event rate (%/yr)	Warfarin (n=9081) event rate (%/yr)	Hazard ratio (95% CI)	P value
Key 2° Outcome: Death from any cause	3.52	3.94	0.89 (0.80-0.998)	0.047

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NEJM 2011;365:981-992.

Apixaban

ARISTOTLE Trial

Outcome	Apixaban (n=9120) event rate (%/yr)	Warfarin (n=9081) event rate (%/yr)	Hazard ratio (95% CI)	P value
Other 2° Outcomes:				
Stroke, systemic embolism, or death from any cause	4.49	5.04	0.89 (0.81-0.98)	0.02
Myocardial infarction (MI)	0.53	0.61	0.88 (0.66-1.17)	0.37
Stroke, systemic embolism, MI, or death from any cause	4.85	5.49	0.88 (0.80-0.97)	0.01
Pulmonary embolism or DVT	0.04	0.05	0.78 (0.29-2.10)	0.63

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NEJM 2011;365:981-992.

Apixaban

ARISTOTLE Trial

- **Conclusions:**
  - In patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, cause less bleeding, and resulted in lower mortality

NEJM 2011;365:981-992.

Apixaban

AF Guidelines 2014

- **Class I recommendations for apixaban:**
  - Patients with nonvalvular AF with prior stroke, TIA or a CHA_2DS_2-VASc score $\geq$ 2:
    - Warfarin (LOE A)
    - Dabigatran (LOE B)
    - Rivaroxaban (LOE B)
    - **Apixaban** (LOE B)
  - Patients with nonvalvular AF unable to maintain a therapeutic INR with warfarin:
    - Dabigatran (LOE C)
    - Rivaroxaban (LOE C)
    - **Apixaban** (LOE C)

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Circulation 2014;129:April 10 (epub ahead of print).

Mipomersen sodium

Kynamro

- Inhibitor of apolipoprotein B-100 synthesis
- Indications:
  - Homozygous familial hypercholesterolemia (HoHF)
  - Adjunct to lipid-lowering medications and diet to reduce LDL, apo B, total cholesterol, and non HDL
- No data on morbidity and mortality effects

Mipomersen sodium

Dosage & Administration

- 200 mg once weekly subcutaneous injection
- Available as:
  - Single use vial, 200 mg in 1mL
  - Single-use pre-filled syringe 200 mg in 1 mL
- Prior to treatment, measure:
  - ALT
  - AST
  - Alkaline phosphatase
  - Total bilirubin

Mipomersen sodium

Adverse effects

- Injection site reactions (84%)
  - Erythema
  - Pain
  - Tenderness
  - Pruritis
  - Local swelling
- Flu-like symptoms (30%)
  - Pyrexia
  - Chills
  - Myalgia
  - Arthralgia
  - Malaise
- Nausea
- Headache
- Elevations in serum transaminases

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Mipomersen sodium

Black Box Warning

- Risk of hepatotoxicity
  - Can cause elevations in transaminases (12%)
- Increases hepatic fat, with or without concomitant increases in transaminases
  - Mean absolute increase in hepatic fat 10%
  - Hepatic steatosis is a risk factor for advanced liver disease
- Due to risk of hepatotoxicity, mipomersen is available only through a restricted program under a REMS called Kynamro® REMS

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Kynamro package insert

Mipomersen sodium

Monitoring for Patients with Elevated Transaminases

AST or ALT	Treatment and Monitoring Recommendations
≥ 3x and <5x ULN	• Confirm elevation within 1 week • If confirmed, withhold dosing, obtain additional LFTs, and investigate to identify probable cause • If resuming mipomersen after transaminases resolve to < 3x ULN, monitor LFTs more frequently
≥ 5x ULN	• Withhold dosing, obtain additional LFTs, and investigate to identify probable cause • If resuming mipomersen after transaminases resolve to < 3x ULN, monitor LFTs more frequently

Kynamro package insert

Mipomersen sodium

Does it Work?

- Randomized, double-blind, placebo-controlled study
- n=51 patients with homozygous familial hypercholesterolemia
  - Already receiving maximum tolerated dose of a lipid-lowering drug
  - Mipomersen 200 mg sc weekly (n=34)
  - Placebo sc weekly (n=17)
- Duration: 26 weeks

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Lancet 2010;375:998-1006.

Mipomersen sodium

Does it Work?

- n=45 patients completed study (28 mipomersen, 17 placebo)

	Mipomersen	Placebo	p
Baseline LDL	441±139 mg/dL	402±143 mg/dL	NS
Mean % change in LDL (95% CI)	-24.7% (-31.6 to -17.7)	-3.3% (-12.1 to 5.5)	0.003
Injection site reactions	76%	24%	--
↑ ALT > 3xULN	12%	0	--

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Lancet 2010;375:998-1006.

Mipomersen sodium

Summary

- Effective for LDL reduction in HoFH
- Limited by adverse effects
- Not mentioned in 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
- Due to risk of hepatotoxicity, mipomersen is available only through a restricted program under a REMS called Kynamro® REMS

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Circulation 2014;129(suppl 2):S1-S45.

Omega-3 Carboxylic Acids

Epanova

- Fish oil-derived mixture of free fatty acids primarily composed of EPA and DHA
- Indication:
  - Adjunct to diet to reduce triglyceride concentrations in patients with severe (≥ 500 mgdL) hypertriglyceridemia
- No data on cardiovascular morbidity and mortality effects
- No data on risk for pancreatitis

Omega-3 Carboxylic Acids

Dosage & Administration

- 2 grams (2 capsules) or 4 grams (4 capsules) once daily
- Individualize according to response and tolerability
- Capsules should be swallowed whole and not broken open or crushed

Omega-3 Carboxylic Acids

Adverse effects (> 3%, > placebo)

- Diarrhea
- Nausea
- Abdominal pain
- Eructation

Omega-3 Carboxylic Acids

Does it Work?

- Randomized, placebo-controlled, double-blind study
- n=298 patients with serum TG 500-2,000 mg/dL
- Pre-study washout of lipid-altering medications *other than* statins or ezetimibe
- Randomized to:
  - Omega-3 carboxylic acids 2g daily
  - Omega-3 carboxylic acids 4g daily
  - Placebo (olive oil)
- n=12 weeks followup

Epanova® package insert

Omega-3 Carboxylic Acids

Does it Work?

Parameter (mg/dL)	Omega-3 – 2g (n=100)	Omega-3 – 4 g (n=99)	Placebo (n=99)	2g vs placebo	4g vs placebo
TG	BL 717 ↓ 25%	BL 655 ↓31%	BL 682 ↓10%	-16%*	-21%*
Non-HDL	BL 205 ↓8%	BL 225 ↓8%	BL 215 ↓1%	-7%*	-10%*
HDL	BL 27 ↑7%	BL 29 ↑5%	BL29 ↑2%	+6%	+4%
TC	BL 241 ↓6%	BL 254 ↓6%	BL 246 0	-6%	-9%
LDL	BL 77 ↑21%	BL 90 ↑26%	BL 78 ↑10%	+13%	+13%

BL = Baseline
*p<0.05

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Epanova® package insert

Omega-3 Carboxylic Acids

Summary

- Effective for TG reduction in patients with severe hypertriglyceridemia
- 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults:
  - If omega-3 fatty acids used for management of severe hypertriglyceridemia – evaluate patient for GI disturbances, skin changes, and bleeding (IIa, B)

Circulation 2014;129(suppl 2):S1-S45.

Vorapaxar

Zontivity

- Protease-activated receptor 1 (PAR-1) inhibitor
- Antiplatelet agent
- Indication:
  - Reduction in thrombotic CV events in patients with a history of MI or PAD

Vorapaxar

Properties

- Half-life: 8 days
- Metabolism: Hepatic (CYP 3A4)
- Elimination: Excreted in feces (58%) and urine (25%) – eliminated as metabolites, not parent drug
- Dose: 1 tablet (2.08 mg) orally once daily
- Drug interactions: Strong inhibitors & inducers of CYP3A4
- Can use in patients receiving aspirin or clopidogrel

Vorapaxar

Does it work?
Thrombin receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P)-Thrombolysis in Myocardial Infarction (TIMI 50)

- Randomized, double-blind, placebo-controlled, multinational study
- 1,032 sites in 32 countries
- n=26,449 patients with history of atherosclerosis:
  - MI or ischemic stroke within past 2 weeks to 12 months OR
  - PAD with intermittent claudication with ABI < 0.85 or prior limb revascularization

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N Engl J Med 2012;366:1404-13.

Vorapaxar

Does it work?
TRA 2P-TIMI 50

- Randomized to:
  - Vorapaxar 2.5 mg once daily
  - Matched placebo
- Median follow-up: 24 months

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N Engl J Med 2012;366:1404-13.

Vorapaxar

Does it work? TRA 2P-TIMI 50

Efficacy End Point	Vorapaxar (n=13,225)	Placebo (13,224)	Hazard Ratio (95% CI)	p
1° - CV death, MI, or stroke	9.3%	10.5%	0.87 (0.80-0.94)	<0.001
2° - CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization	11.2%	12.4%	0.88 (0.82-0.95)	0.001
CV death or MI	7.3%	8.2%	0.86 (0.78-0.94)	0.002
CV death	2.7%	3.0%	0.89 (0.76-1.04)	0.15
MI	5.2%	6.1%	0.83 (0.74-0.93)	0.001
Any stroke	2.8%	2.8%	0.97 (0.83-1.14)	0.73
Ischemic stroke	2.2%	2.6%	0.85 (0.72-1.01)	0.06

N Engl J Med 2012;366:1404-13.

Vorapaxar

Does it work? TRA 2P-TIMI 50

Toxicity End Point	Vorapaxar (n=13,225)	Placebo (13,224)	Hazard Ratio (95% CI)	p
GUSTO moderate or severe bleeding	4.2%	2.5%	1.66 (1.43-1.93)	<0.001
TIMI clinically significant bleeding	15.8%	11.1%	1.46 (1.36-1.57)	<0.001
TIMI non-CABG-related major bleeding	2.8%	1.8%	1.46 (1.22-1.75)	<0.001
TIMI CABG-related major bleeding	7.6%	6.1%	1.13 (0.48-2.66)	0.79
Fatal bleeding	0.3%	0.2%	1.46 (0.82-2.58)	0.19
Intracranial bleeding	1.0%	0.5%	1.94 (1.39-2.70)	<0.001

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N Engl J Med 2012;366:1404-13.

Vorapaxar

Does it work? TRA 2P-TIMI 50

Net Clinical Outcome	Vorapaxar (n=13,225)	Placebo (13,224)	Hazard Ratio (95% CI)	p
CV death, MI, stroke, or GUSTO moderate or severe bleeding	11.7%	12.1%	0.97 (0.90-1.04)	0.40
CV death, MI, stroke, urgent coronary revascularization, or GUSTO moderate or severe bleeding	13.4%	14.0%	0.96 (0.89-1.02)	0.20
Death from any cause, MI, stroke, or Gusto severe bleeding	11.9%	12.8%	0.92 (0.85-0.99)	0.02

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N Engl J Med 2012;366:1404-13.

Vorapaxar

Summary

- Inhibition of PAR-1 with vorapaxar reduces the risk of CV death or ischemic events in patients with stable atherosclerosis who were receiving standard therapy
- Inhibition of PAR-1 with vorapaxar increased the risk of moderate or severe bleeding, including intracranial hemorrhage

N Engl J Med 2012;366:1404-13.

Soon (?) on the Market

In the Pipeline

Drug	Class/Mechanism	Potential Indication(s)	Date NDA Submitted
Edoxaban (Savaysa)	Factor Xa inhibitor	Nonvalvular atrial fibrillation	January, 2014
Idarucizumab*	Humanized antibody fragment against dabigatran	Antidote to dabigatran	Designated Breakthrough Therapy by FDA, June 2014
Ivrabadine	I_f current inhibitor	Heart failure	Fast track designation granted by FDA, April 2014
LCZ696	Dual inhibitor of angiotensin II receptor and neprilysin	Heart failure	Final quarter 2014

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Questions?

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