With a Little Help From My Friends:

The role of non-statin therapy in the management of dyslipidemia

Welcome!

We will begin shortly

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CPhA is pleased to welcome the Association of Faculties of Pharmacy of Canada (AFPC) as our webinar co-host today

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Today's Speaker

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@ArdenBarry

Disclosure

- I have **no** current or past relationships with commercial entities
- I have **not** received a speaker's honourarium for this learning activity
- I am a member of the primary panel of the Canadian Cardiovascular Society (CCS) guidelines for the management of dyslipidemia for the prevention of CVD in the adult

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Learning Objectives

1. Gain an appreciation for recent evidence to support/refute the role of non-statin therapy in combination with statin therapy;
2. Understand the mechanism and role of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in the management of dyslipidemia;
3. Identify clinical scenarios where non-statin therapy may be considered as add-on to statin therapy in the management of dyslipidemia.

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LDL-C Hypothesis

- Cholesterol is a component of atherosclerotic plaques
- Atherosclerosis can be experimentally produced in herbivores
- Higher LDL-C is associated with a higher risk of CVD
- Patients with genetic LDL-C disorders have a high risk of premature CVD

However…

- ↓ LDL-C with Rx does not necessarily equal ↓ CV events

Am J Cardiol 2010;106:1364-6

Non-Statin Therapy

- Bile acid sequestrants
- Anacetrapib
- **Ezetimibe**
- **Fibrates**
- Lomitapide
- Mipomersen
- **Niacin**
- **PCSK9 inhibitors**

Non-Statin Therapy

Drug Class	LDL-C	HDL-C	TG
Ezetimibe	↓ 18%	↑ 1%	↓ 6%
Fibrates	↓ 5-20%	↑ 10-20%	↓ 20-50%
Niacin	↓ 5-25%	↑ 15-35%	↓ 20-35%
PCSK9 inhibitors	↓ 40-70%	–	–

RxFiles 11th edition 2017

Poll Question

- What do you typically recommend in addition to statin therapy?

1. Ezetimibe
2. Fibrate
3. Niacin
4. PCSK9 inhibitor
5. Nothing

Poll Question

- Have you ever recommended/had a patient on a PCSK9 inhibitor?

1. Yes
2. No

Ezetimibe

Ezetimibe

- SHARP:
  - 9270 patients with CKD
  - Ezetimibe 10 mg PO daily and simvastatin 20 mg PO daily vs placebo
  - Follow-up: 4.9 yr
  - Reduced major CV events by 2.1% (NNT=48)
  - No significant reduction in mortality

Lancet 2011;377:2181-92

Ezetimibe

- IMPROVE-IT:
  - 18,144 patients with a recent ACS
  - All patients on simvastatin 40 mg PO daily
  - Ezetimibe 10 mg PO daily vs placebo
  - Follow-up: 7 yr
  - Reduced major CV events by 2% (NNT=50)
  - No significant reduction in mortality

N Engl J Med 2015;372:2387-97

Fibrates

Fibrates

- ACCORD:
  - 5518 patients with T2DM
  - All patients on simvastatin 20 mg PO daily
  - Fenofibrate 160 mg PO daily vs placebo
  - Follow-up: 4.7 yr
  - No significant reduction in major CV events or mortality

N Engl J Med 2010;362:1563-74

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Niacin

Niacin

- AIM-HIGH:
  - 3414 patients with CVD
  - All patients on simvastatin ± ezetimibe
  - Niacin ER 1500-2000 mg PO daily vs placebo
  - Follow-up: 3 yr
  - No significant reduction in major CV events or mortality

N Engl J Med 2011;365:2255-67

Niacin

- HPS2-THRIVE:
  - 25,673 patients with CVD
  - All patients on simvastatin ± ezetimibe
  - Niacin ER/laropiprant 2000/40 mg PO daily vs placebo
  - Follow-up: 3.9 yr
  - No significant reduction in major CV events or mortality
  - Increase in serious adverse events with niacin/laropiprant

N Engl J Med 2014;371:203-12

Summary

	CV events	CV mortality	All-cause mortality
SHARP	↓	No difference	No difference
IMPROVE-IT	↓		
ACCORD	No difference		
AIM-HIGH			
HPS2-THRIVE			

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PCSK9 Inhibitors

PCSK9 Inhibitors

- Fully human mAb
- Two agents:
  - Alirocumab (Praluent®)
  - Evolocumab (Repatha™)
- SC injection q 2 weeks or monthly
- Adverse effects: nasopharyngitis, upper respiratory tract infections, nausea, diarrhea, injection site reactions

Nat Rev Cardiol 2014;11:563-75

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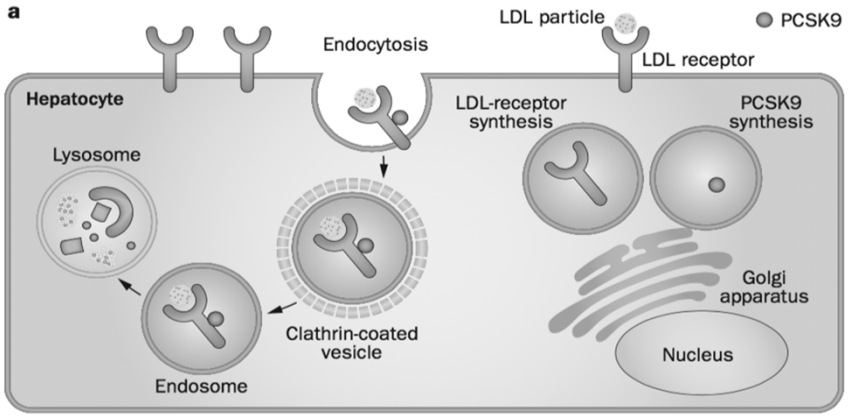
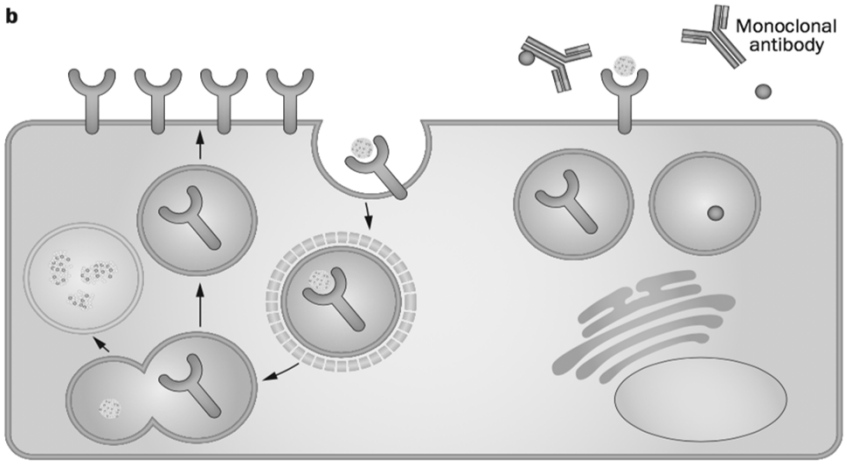
PCSK9 Inhibitors



Nat Rev Cardiol 2014;11:563-75

PCSK9 Inhibitors



Nat Rev Cardiol 2014;11:563-75

Alirocumab

- ODYSSEY LONG TERM:
  - 2341 patients with FH or CHD/CHD equivalent
  - All patients on statin therapy
  - Alirocumab 150 mg SC q 2 weeks vs placebo
  - Follow-up: 1.5 yr

N Engl J Med 2015;372:1489-99

Alirocumab

	Alirocumab	Placebo	p	NNH
Serious adverse event (%)	18.7	19.5	0.66	
Local injection site reaction (%)	5.9	4.2	0.10	
Myalgia (%)	**5.4**	**2.9**	**0.006**	**40**
Neurocognitive disorder (%)	1.2	0.5	0.17	
Ophthalmologic event (%)	2.9	1.9	0.65	

	Alirocumab	Placebo	p	NNT
All CV events (%)	4.6	5.1	0.68	
Major adverse CV events (%)	**1.7**	**3.3**	**0.02**	63

N Engl J Med 2015;372:1489-99

Evolocumab

- FOURIER:
  - 27,564 patients with CVD
  - All patients on statin therapy
  - Evolocumab 420 mg SC q monthly or 140 mg SC q 2 weeks vs placebo
  - Follow-up: 2.2 yr

N Engl J Med 2017;376:1713-22

Evolocumab

	Evolocumab	Placebo	p	NNT
Major CV events (%)	**5.9**	**7.4**	**<0.001**	**67**
All CV events (%)	**9.8**	**11.3**	**<0.001**	**67**
CV death (%)	1.8	1.7	0.62	
All-cause death (%)	3.2	3.1	0.54	

	Evolocumab	Placebo	p	NNH
Serious adverse events (%)	24.8	24.7	NS	
Injection site reactions (%)	2.1	1.6	**<0.001**	**200**

All other adverse events were not significantly different between groups

N Engl J Med 2017;376:1713-22

PCSK9 Inhibitors

- Cost:
  - Both agents ~$600 per month (~$7200 per year)
  - CDR recommended 50-80% price reduction for these agents to be considered cost-effective

CCS Dyslipidemia Guidelines

- Ezetimibe 2nd-line in patients with CVD if LDL-C target not achieved on maximally tolerated statin
- Do **not** recommend niacin + statin in patients who have achieved LDL-C target
- Do **not** recommend fibrates + statin in patients who have achieved LDL-C target
- Consider PCSK9 inhibitor if LDL-C target not achieved on maximally tolerated 1) statin ± ezetimibe in patients with CVD or 2) statin in patients with heterozygous FH

Can J Cardiol 2016;32:1263-82

Cases

Case 1

Mr. Kite
62 yo M

PMHx:
1. T2DM
2. HTN
3. Dyslipidemia
4. Obesity (BMI 45)
5. Smoker

Rx:
1. Atorvastatin 40 mg PO daily
2. Metformin 1000 mg PO bid
3. Liraglutide 1.2 mg SC daily
4. Insulin glargine 70 units SC daily
5. Ramipril 15 mg PO daily
6. Amlodipine 5 mg PO daily

LDL-C 2.1 mmol/L
BP 141/71 mmHg, HR 83 bpm

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Case 2

Billy Shears
55 yo M

PMHx:
1. Smoker
2. ?HTN
3. ?Dyslipidemia

Recent anterior STEMI
PCI (DES) to mLAD
Averse to Rx

Rx:
1. Atorvastatin 80 mg PO daily
2. Ramipril 5 mg PO daily
3. Metoprolol 25 mg PO bid
4. ASA 81 mg PO daily
5. Ticagrelor 90 mg PO bid

LDL-C 3.2 mmol/L (pre-STEMI)
BP 128/78 mmHg, HR 72 bpm

Case 3

Lovely Rita
45 yo F

PMHx:
1. FH
2. + FamHx premature CVD
3. Ex-smoker

Rx:
1. Atorvastatin 10 mg PO daily
2. Omega-3 fatty acids 1000 mg PO daily
3. ASA 81 mg PO daily

LDL-C 5.7 mmol/L
BP 122/66 mmHg, HR 64 bpm

Case 4

Lucy in the Sky
39 yo F

PMHx:
1. Schizophrenia
2. T2DM
3. Dyslipidemia
4. HTN
5. NASH

Rx:
1. Rosuvastatin 40 mg PO daily
2. Fenofibrate 160 mg PO daily
3. Perindopril 4 mg PO daily
4. Ziprasidone 80 mg PO bid
5. Metformin 1000 mg PO bid

Cannot calculate LDL-C
Non-HDL-C 3.3 mmol/L
TG 8.7 mmol/L
BP 128/75 mmHg, HR 76 bpm

Case 5

Vera
50 yo F

PMHx:
1. T2DM
2. Dyslipidemia
3. Hypothyroidism

Rx:
1. Simvastatin 40 mg PO daily
2. Fenofibrate 160 mg PO daily
3. Levothyroxine 112 mcg PO daily
4. Ramipril 5 mg PO daily

LDL-C 3.7 mmol/L
TG 1.9 mmol/L
BP 134/70 mmHg, HR 70 bpm

Case 6

Chuck and Dave
75 yo M

PMHx:
1. HTN
2. T2DM
3. CAD (CABG x 3)
4. AVR
5. OA
6. Ex-smoker

Rx:
1. Atorvastatin 40 mg PO daily
2. Ramipril 10 mg PO bid
3. Amlodipine 10 mg PO daily
4. Hydrochlorothiazide 25 mg PO daily
5. Metformin 1000 mg PO bid
6. Glyburide 5 mg PO bid

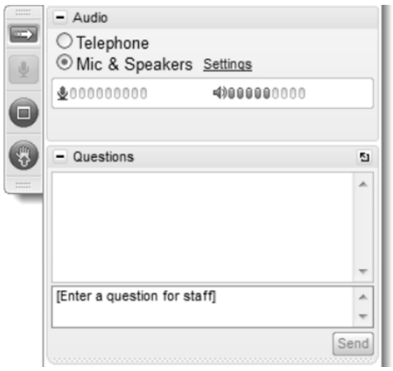
LDL-C 1.8 mmol/L
BP 156/77 mmHg, HR 72 bpm

Key Points

- Always titrate statin to maximally tolerated dose before considering addition of non-statin therapy
- Consider ezetimibe or PCSK9 inhibitor for certain patients based on the evidence
- Fibrates and niacin have questionable (if any) role as add-on therapy to reduce CV events

Questions

Please type your questions in the "Questions" window in the control panel and click **Send**



Thank you!

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