Preventing Broken Hearts:
The Science Behind Cardiovascular Disease

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What is cardiovascular disease?

• Number one cause of death globally
• 31% of deaths worldwide
• >75% are in low/middle-income countries
What is cardiovascular disease?

Tonight, we will focus on the vessels.
Atherosclerosis

- Hardening of the arteries
- Atheroma: lump of gruel
  - Plaques narrow arteries
  - Plaques can rupture, blocking blood flow
How do we clinically define CVD?

- Level of plaque (% occlusion)

How do we clinically define CVD?

Cardiovascular “events”

• Heart attack
• Stroke

Procedure to open arteries

• Stent
• Bypass
Atherosclerosis is not new!

Mummies from preindustrial populations
CVD risk factors

- Smoking
- High blood pressure
- Diabetes/obesity
- Increased age
CVD risk factors

Cholesterol abnormalities

– Low HDL ("good") cholesterol (>40 mg/dl)
– High LDL ("bad") cholesterol (<130 mg/dl)
– High Total: HDL ratio (>3.5:1)
Roadmap for the evening

1. Cholesterol metabolism and CVD
2. Standard therapy: statins
3. New therapies from human genetics
4. Dietary fat: friend or foe?
Cholesterol myths

Myth I: All cholesterol is bad.

Cholesterol

Estrogen

Testosterone

Boris TM - Public domain
Cholesterol myths

Myth 1: All cholesterol is bad.
Cholesterol myths

Myth 2: Cholesterol comes only from your diet.
The liver makes/packages cholesterol

Packages VLDL for release into the bloodstream

Science in the News, A potential new weapon against heart disease: PCSK9 inhibitors.
LDL is cleared by the liver

Problem: this process is not very efficient!

LDL stays in the blood
LDL can stick on blood vessels
LDL can move below the endothelium
Enter the immune system!
LDL activates the immune system
LDL activates the immune system

Macrophage
LDL is bad for macrophages
Atherosclerotic plaques are mixtures of cholesterol/cells.
Atherosclerosis is a progressive disease
Preventing plaque: HDL

HDL: Contains ApoA1 protein: cannot convert to LDL
Preventing plaque: HDL
Lifestyle affects HDL levels

Things that raise HDL

Exercise – National Park Service (public domain), Fruit – Agricultural Research Service (public domain); Olive Oil, Pixabay, Open source
Part I recap

• High LDL in blood promotes atherosclerosis.
• Plaques contain a mixture of cholesterol and immune cells.
• HDL can bring cholesterol back to the liver.
Questions?
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Framingham Heart Study

1st large study devoted to risk factors for CVD

- 1948 – 5,209 patients
- 1971 – 2nd generation
- 2002 – 3rd generation
- 1994 – Omni
- 2003 – Omni 2
FHS Data helps estimate CVD risk

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Risk score: 10% -> 10% of people with this profile will have a heart attack in 10 years
CVD risk factors

- High total cholesterol
  - Low HDL (“good”) cholesterol
  - High LDL (“bad”) cholesterol
- Smoking
- High blood pressure
- Diabetes/obesity
- Increased age
Strategy I: Lower LDL!

Statins: Zocor, Lipitor, Crestor (and many others + generics)

1996-2012: Lipitor/atorvastatin had $125 billion in sales, most-prescribed drug in history
Statins inhibit cholesterol synthesis

Liver is “cholesterol deprived”
Statins increase LDL receptor levels

Liver pulls more LDL out of the blood!
Statins also reduce inflammation
Two jobs for statins

• Primary prevention
  – Prevent CVD-associated event (heart attack, stroke)

• Secondary prevention
  – Prevent another event in someone who’s already had one
Are statins effective for everyone?

• Primary prevention
  – Prevent CVD-associated event (heart attack, stroke)

• Secondary prevention - yes
  – Prevent another event in someone who’s already had one
Are statins effective for everyone?

• Primary prevention – it depends on risk level
  – Prevent CVD-associated event (heart attack, stroke)

• Secondary prevention - yes
  – Prevent another event in someone who’s already had one
Problems with statins

Muscle pain – CDC (public domain), Confused Smiley (public domain)
Part 2 Recap

• We can estimate CVD risk based on certain factors.
• Statins decrease LDL by increasing liver LDL uptake.
• Statins work well for many, but not all patients.
Questions?
Intermission

Stand up and move around!!!
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What determines my CVD risk?

Complex disease: Genetics and environment play a role

Can we look to human genetics to better understand/treat CVD?
Rare cases: Single gene has a large effect

LDL receptor mutations (low LDL clearance)
Rare cases: Single gene has a large effect

ApoB
(LDL can’t bind LDL receptor)
Familial hypercholesterolemia (FH)

- From 1 parent: ~1 in every 300 - 500 people
  - Total cholesterol of 350 - 550 mg/dl
- From both parents: ~1 in a million
  - Total cholesterol of 650 - 1000 mg/dl

Remember, our goal is usually 200 mg/dl!
FH and PCSK9

- 2003: Scientists identified PCSK9 as a third gene for FH
- Overactive PCSK9 increases CVD risk
- Could PCSK9 be a good drug target?
PCSK9 inactivating mutations

• Inactive PCSK9: decreased CVD risk!

• Two people (so far) in the world have no PCSK9: LDL is less than 15 mg/dl!!!
LDL receptor recycling is important
PCSK9 inhibits LDL receptor recycling
PCSK9 may account for statin failure

When the liver increases LDL receptor levels…

PCSK9 levels also increase (variably)
The PCSK9 decade

- PCSK9 inactivating mutations found to lower cardiovascular disease risk
- extra PCSK9 linked to low LDL in mice
- mutations in PCSK9 shown to cause genetic high cholesterol (FH)
- PCSK9 crystal structure elucidated, facilitating the design of drugs that bind specifically to PCSK9
- low LDL linked to mutations in PCSK9
- low LDL in mice lacking PCSK9
- PCSK9 antibody inhibitor decreases LDL in mice and primates
- Amgen phase I trial results released
- Regeneron/Sanofi phase I trial results released
- Amgen phase III trial results released
- Regeneron/Sanofi phase III trial results released

Legend:
- human genetics
- basic science
- therapeutic research

Science in the News, A potential new weapon against heart disease: PCSK9 inhibitors.
PCSK9 Inhibitors

Liver pulls more LDL out of the blood!
Open questions on PCSK9i

- Do these drugs improve CVD?
- Are there negative side effects?
Only time will tell…

- Overall goal: to prevent CVD events/death
- What we end up doing: improving risk factors or “surrogate endpoints”
  - LDL
  - HDL
- Are we seeing the whole picture?
Cost/benefit ratio of PCSK9i

$14,000/year injectable drugs vs Generic statin pills

Who should take these drugs?
How much better must PCSK9 inhibitors be to justify their cost?
Part 3 summary

- PCSK9 is a success story for human genetics research.
- PCSK9 inhibitors appear to be powerful CVD drugs.
- Longer-term studies are needed to evaluate CVD impact/general health.
Questions?
Roadmap for the evening

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Types of fatty acids

Saturated fatty acid

Unsaturated fatty acid
Unsaturated vs saturated fats

**Saturated fats**
- Solid at room temperature
- Associated with CVD

**Unsaturated fats**
- Liquid at room temperature
- Healthy fats
Ancel Keys: Seven countries study

1960s

Percent calories from saturated fat

CVD events/death per 100 people

Keys et al., 1970
Margarine: a butter replacement?

Partial Hydrogenation

Vegetable Shortening/margarine

Unsaturated fatty acid

Trans fatty acid

Trans fats look like saturated fats!
Why trans fats?

- Cheap
- Easy to transport
- Long shelf life

- Are trans fats healthier than saturated fats?
The problem with trans fats

HDL  cholesterol  LDL
The problem with trans fats

HDL → cholesterol → LDL
Trans fats are a CVD nightmare

- Increase LDL
- Decrease HDL
- Increase inflammation
- Increase endothelial dysfunction
There is no trans fat debate

- 2015: FDA says trans fat is no longer “generally recognized as safe”
- Gives food manufacturers three years to remove them from food

- Labeling decreased US TF consumption ~78% from 2003-2012
Predicted effects of 0 TFs

2008 estimate: save 50,000 lives/year (8%)

Centers for Disease Control

• 7,000 fewer deaths per year (1%)

• 20,000 heart attacks (3%)
What about saturated fat?

• Saturated fat raises LDL cholesterol

• What happens when you replace saturated fat with other nutrients?
Nutrients are not created equal.

Saturated fat -> Trans fat

Saturated fat -> Carbohydrates

Saturated fat -> Unsaturated fat
A whole foods approach

Instead of emphasizing one nutrient, we need to move to food-based recommendations. What we eat should be whole, minimally processed, nutritious food—food that is in many cases as close to its natural form as possible. —Dariush Mozaffarian, dean of the Friedman School of Nutrition, Tufts University

http://www.hsph.harvard.edu/magazine-features/is-butter-really-back/
Food quality is important for our cardiovascular health.

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Summary

• CVD is a complex disease.
• The most successful CVD therapies increase liver LDL uptake.
• PCSK9 inhibitors represent an important new therapy for those with high CVD risk.
• Nutrition and public health can make a big difference for CVD prevention.
Thank you!

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