

Cardiovascular disease physiology

Linda Lowe-Krentz

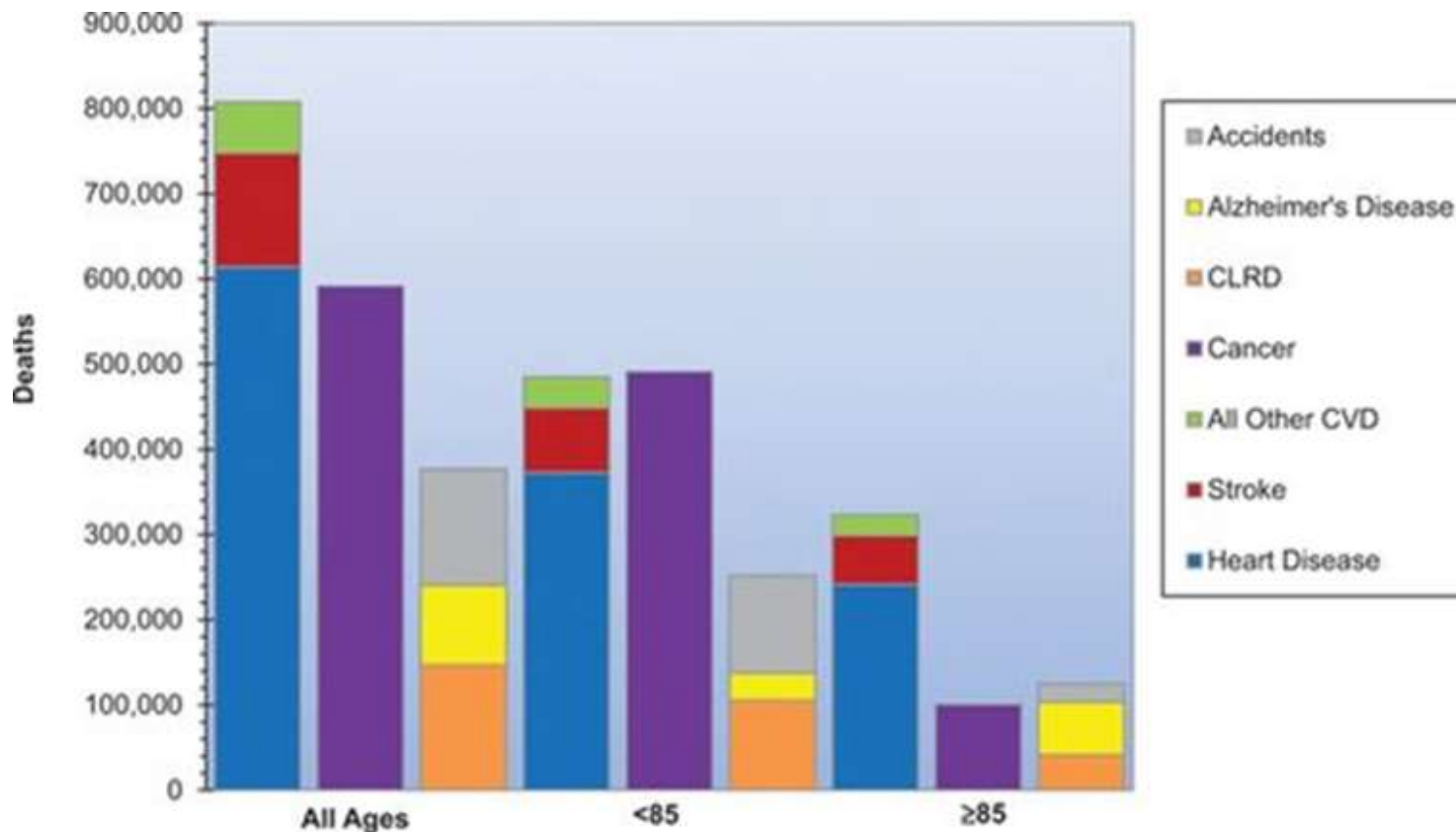
Bioscience in the 21st Century

November 8, 2019

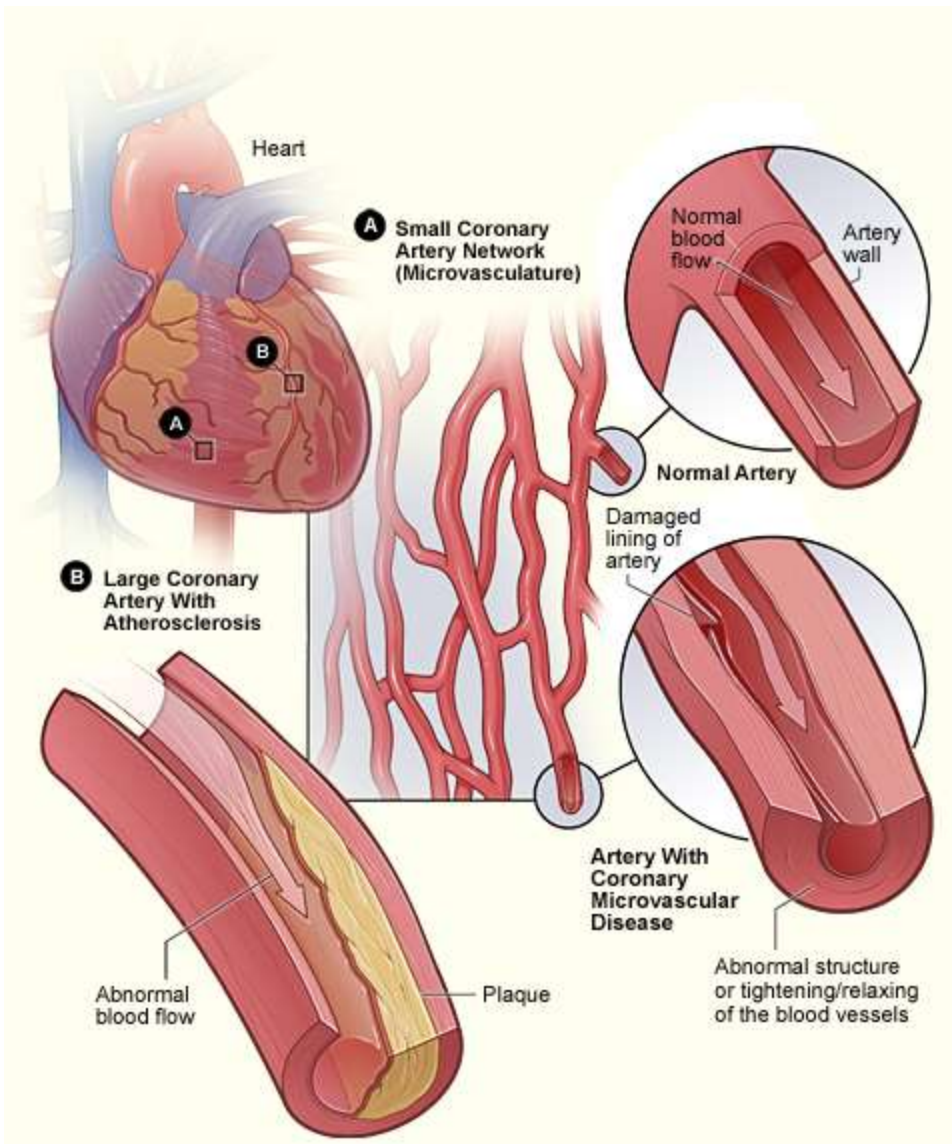
Content

- Introduction – The number 1 killer in America
 - Some statistics
 - Recommendations
- Cardiovascular diseases
 - Damage
 - Current treatments
- Control of vascular tone (hypertension)
- Some vascular research at Lehigh

Cardiovascular disease (CVD) and other major causes of death: total, <85 years of age, and ≥85 years of age.

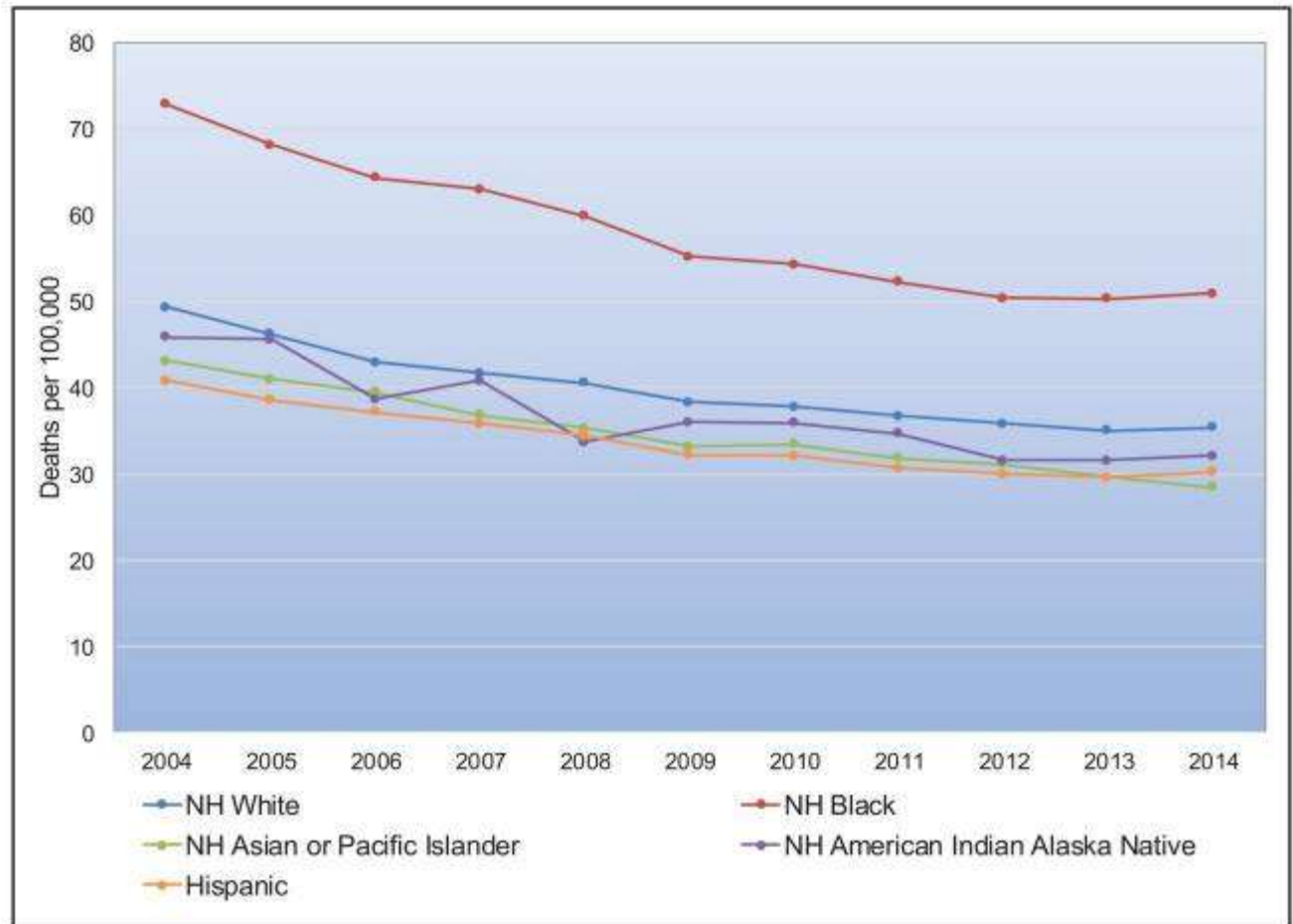


<https://www.nhlbi.nih.gov/health-topics/coronary-microvascular-disease>



Some Good news.

In many western developed countries, deaths from coronary heart disease have decreased steadily as treatment options have improved, and as people have made life-style changes.

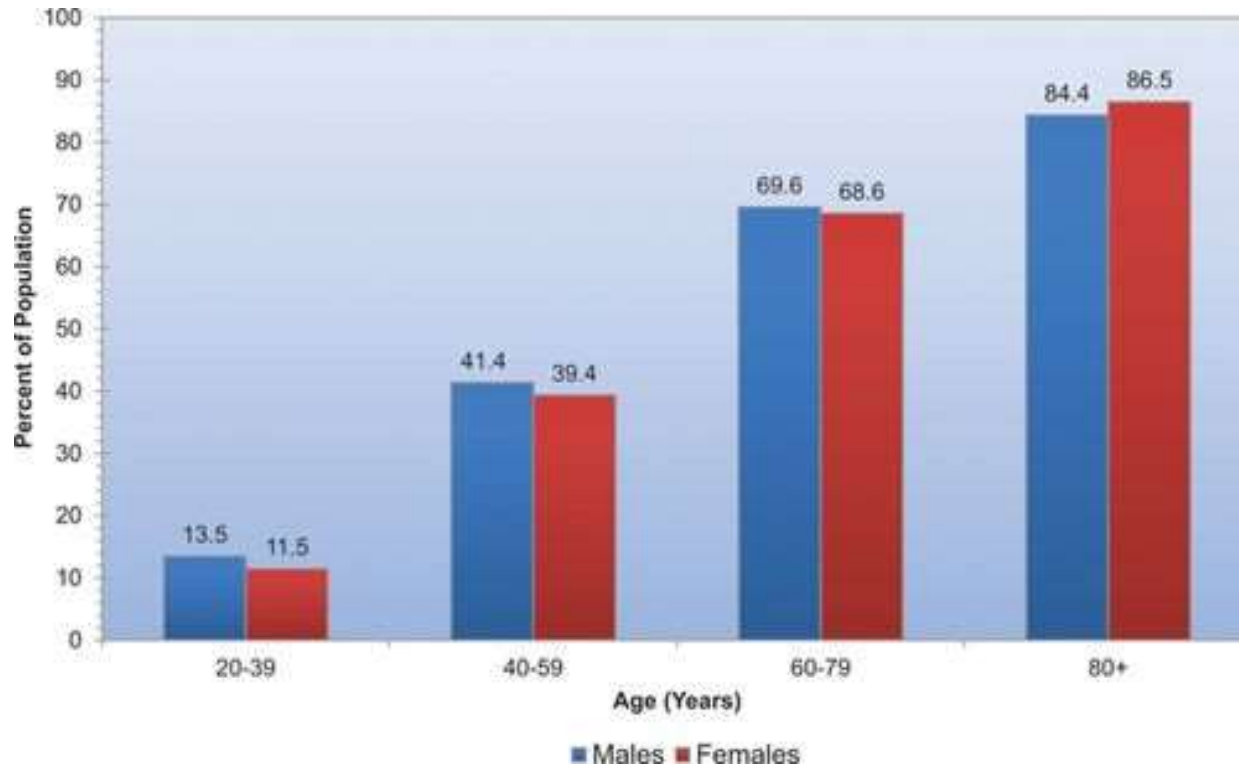


In the 1970s, the overall US rate was closer to 450 deaths per 100,000



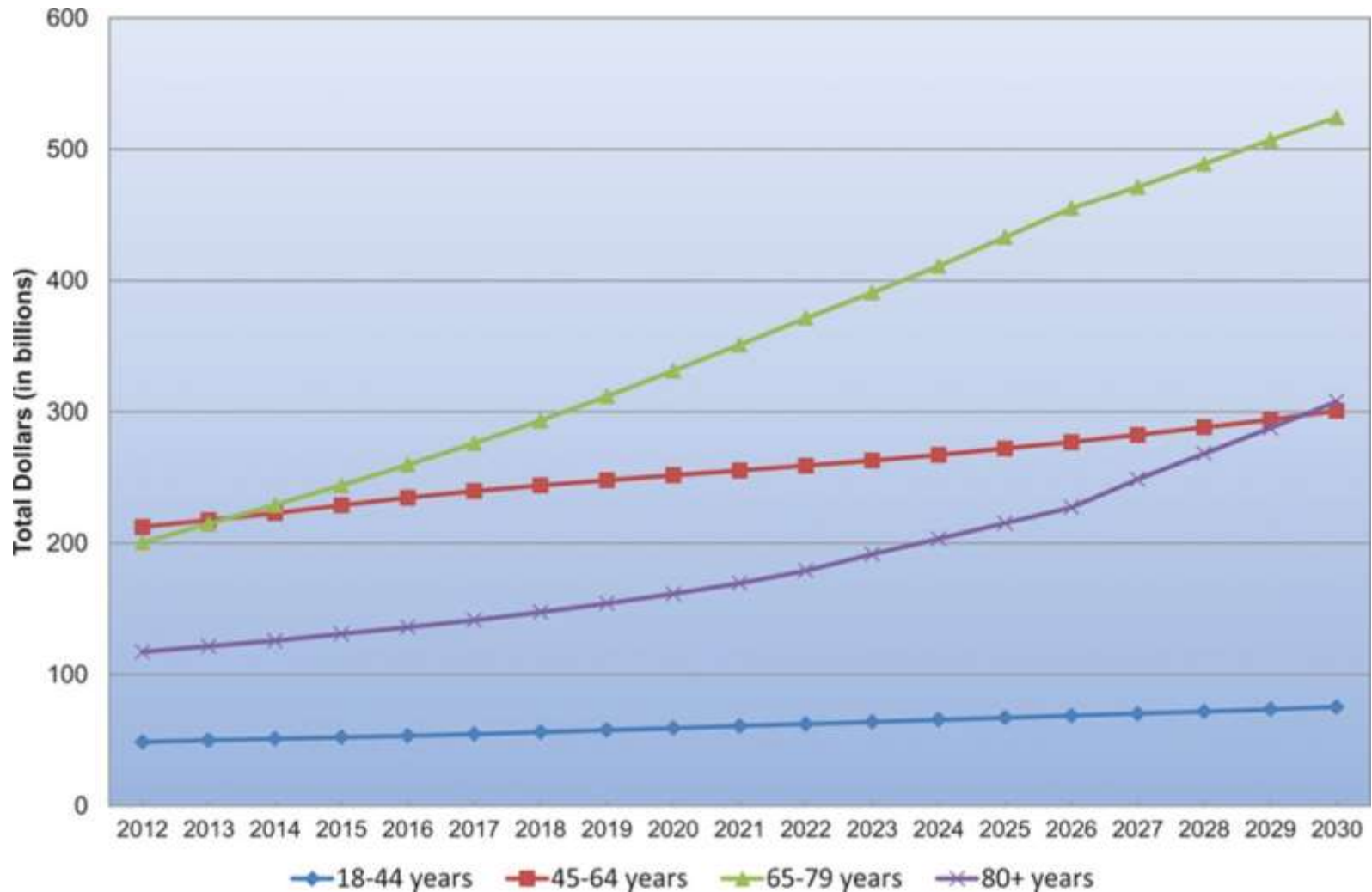
Emelia J. Benjamin. Circulation. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association, Volume: 135, Issue: 10, Pages: e146-e603, DOI: (10.1161/CIR.0000000000000485)

Cardiovascular disease prevalence



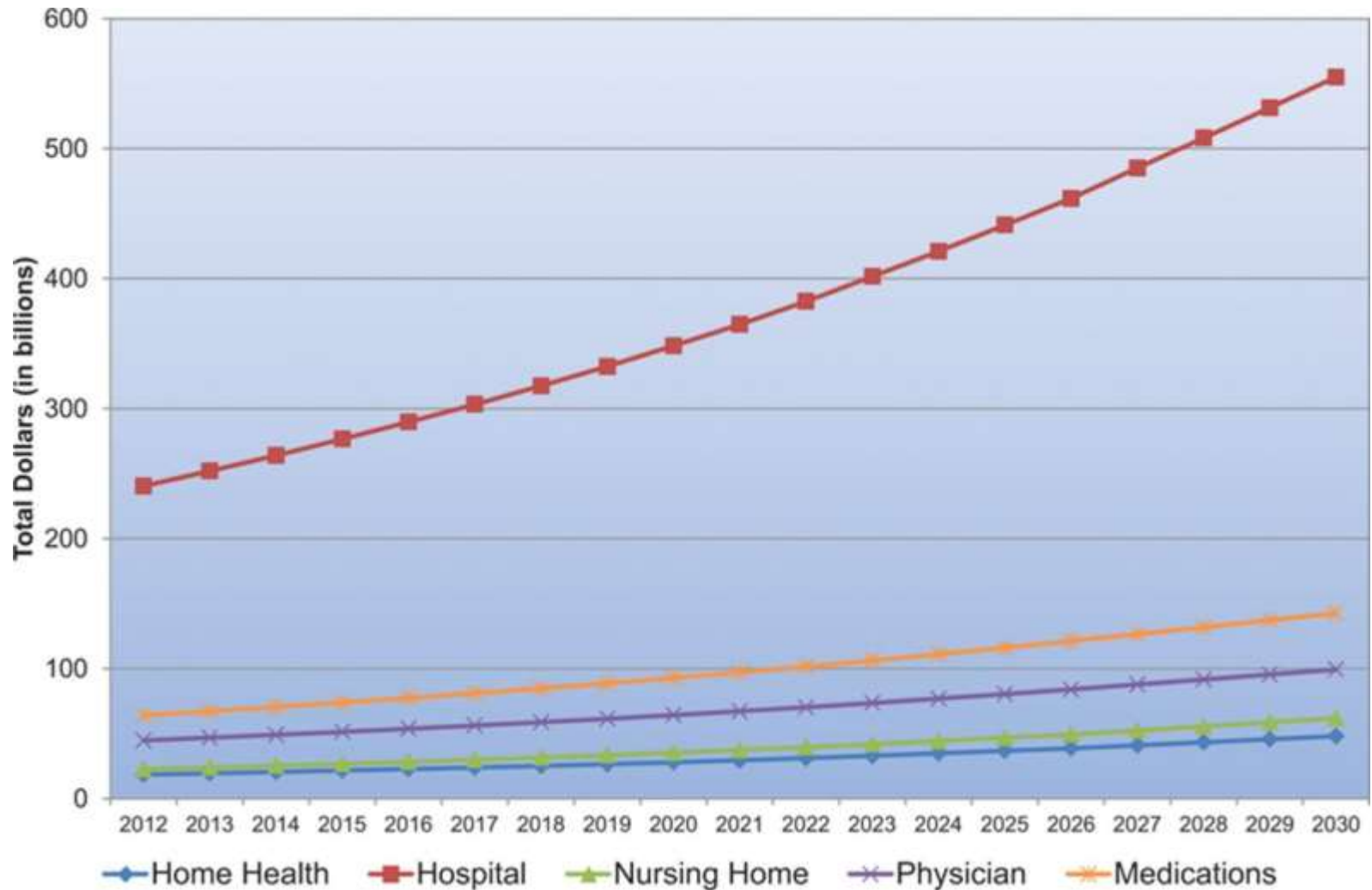
Emelia J. Benjamin. *Circulation*. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association, Volume: 135, Issue: 10, Pages: e146-e603, DOI: (10.1161/CIR.0000000000000485)

Projected total (direct and indirect) costs of total cardiovascular disease by age (2012 \$ in billions).



Go A S et al. *Circulation*. 2014;129:e28-e292

Projected direct costs of total cardiovascular disease by type of cost (2012 \$ in billions).

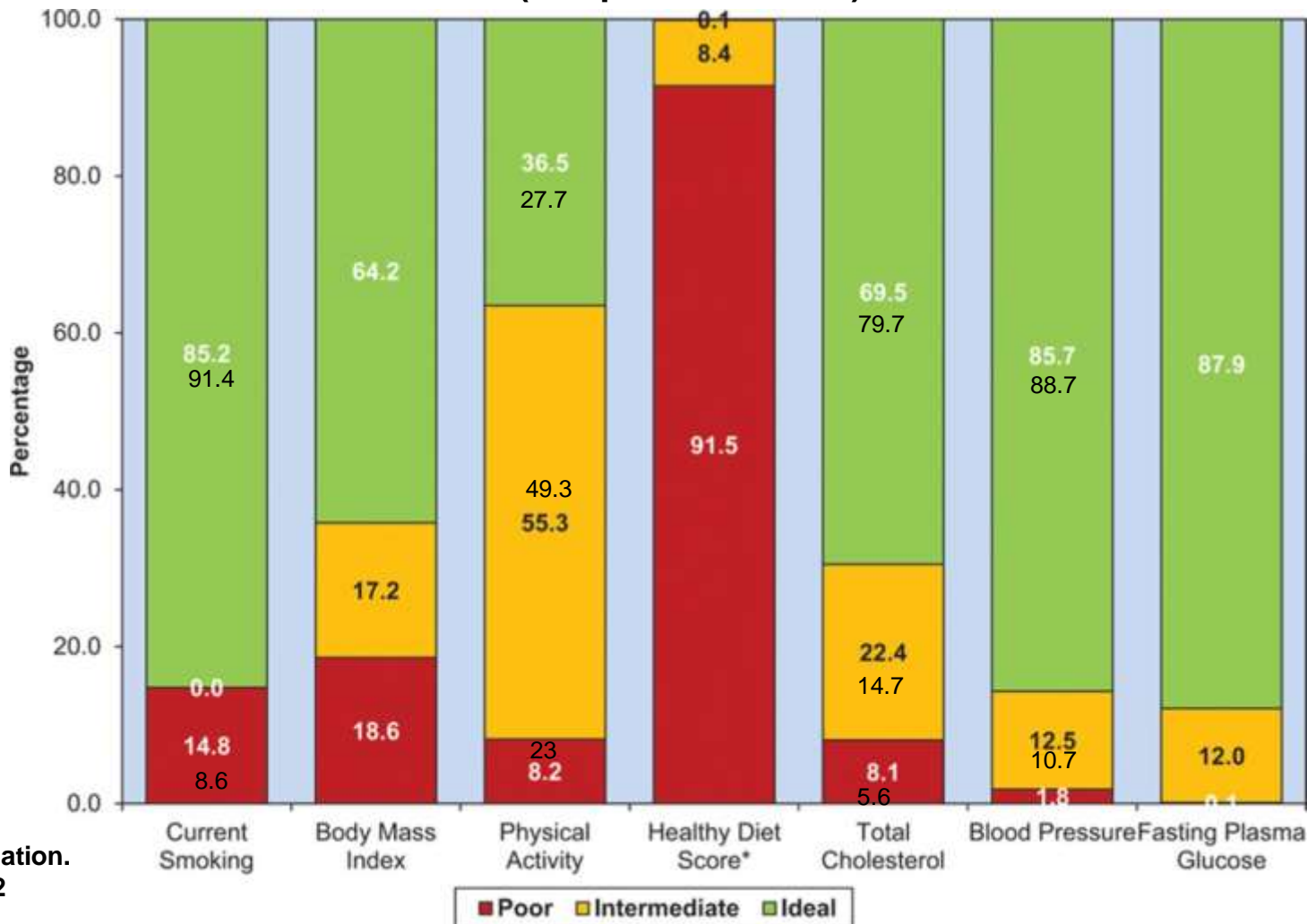


Go A S et al. Circulation. 2014;129:e28-e292

Risk Factors

- High blood pressure (above 120/80 mm Hg)
- Serum cholesterol [high LDL cholesterol and low HDL, or high total cholesterol]
- Body Mass Index (BMI) [above 30]
- High triglycerides
- Smoking
- Drinking
- Diabetes (high blood sugar)

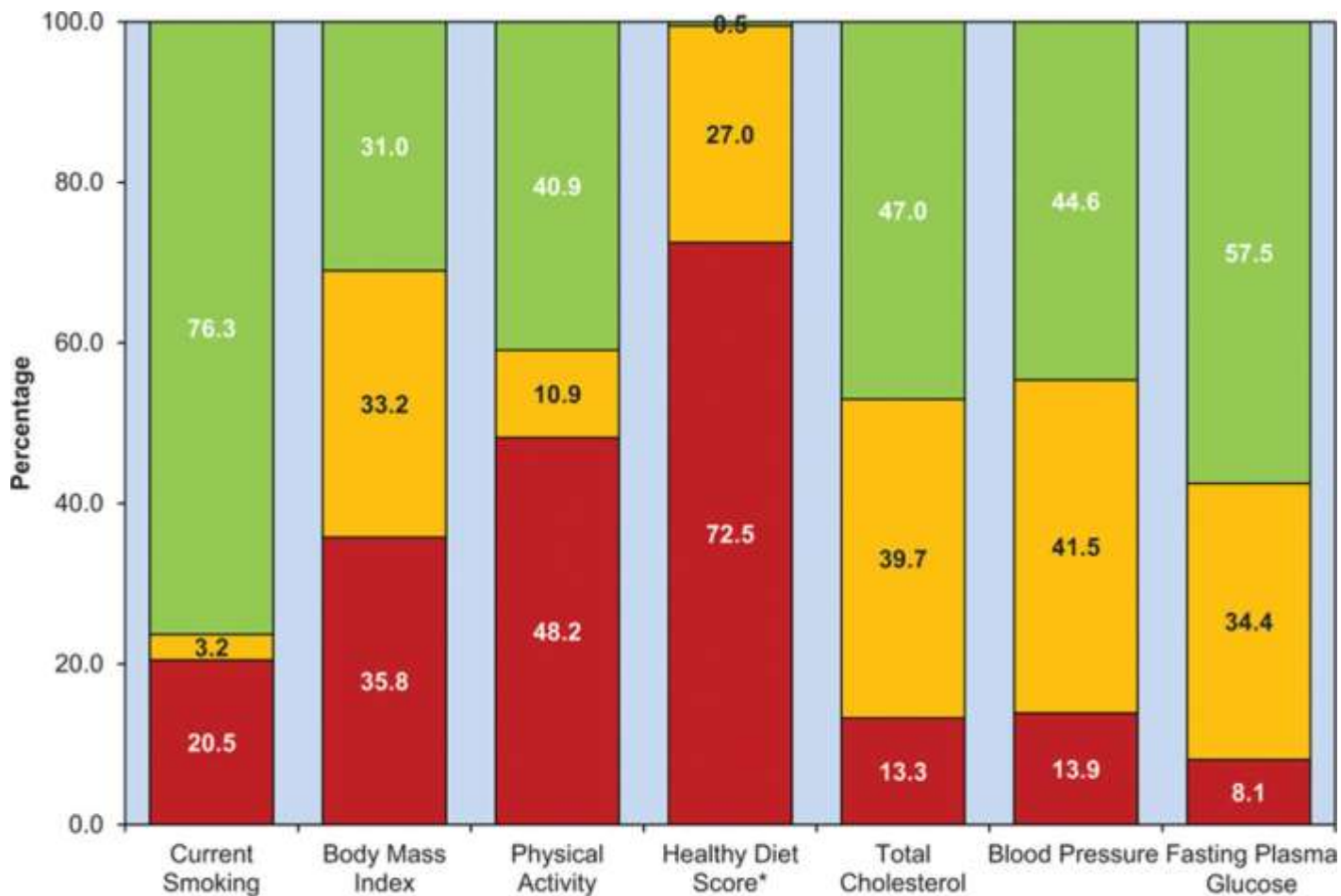
Prevalence (unadjusted) estimates for poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of cardiovascular health in the American Heart Association 2020 goals among US children aged 12 to 19 years, National Health and Nutrition Examination Survey 2009 to 2010 (#s updated to 2014).



Go A S et al. *Circulation*.
2014;129:e28-e292



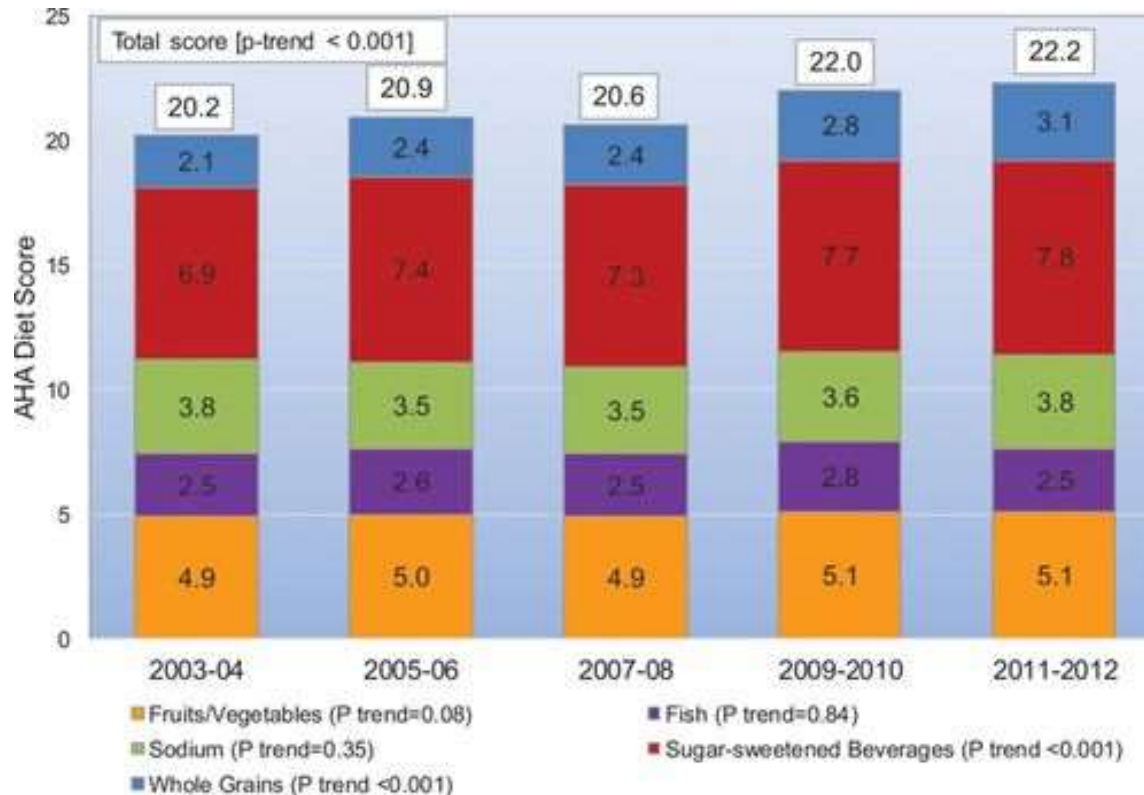
Age-standardized prevalence estimates for poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of cardiovascular health in the American Heart Association 2020 goals among US adults aged ≥ 20 years, National Health and Nutrition Examination Survey 2009 to 2010.



Go A S et al. *Circulation*. 2014;129:e28-e292



Dietary recommendations



Max score is 50

Fruits/Veg. aim for 4.5 c/day

Fish aim for 2+ servings/week

Sodium aim for less than 1500 mg/day

Sugar beverages less than 36 oz/week

Grains 3 or more 1 oz servings/day



Emelia J. Benjamin. Circulation. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association, Volume: 135, Issue: 10, Pages: e146-e603, DOI: (10.1161/CIR.0000000000000485)

Metabolic Syndrome

- **Central obesity** (excessive fat tissue in and around the abdomen)
- **Atherogenic dyslipidemia** (blood fat disorders — mainly high triglycerides and low HDL cholesterol)
- **Insulin resistance or glucose intolerance** (the body can't properly use insulin or blood sugar)
- **Prothrombotic state** (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- **Raised blood pressure** (130/85 mmHg or higher)
- **Proinflammatory state**

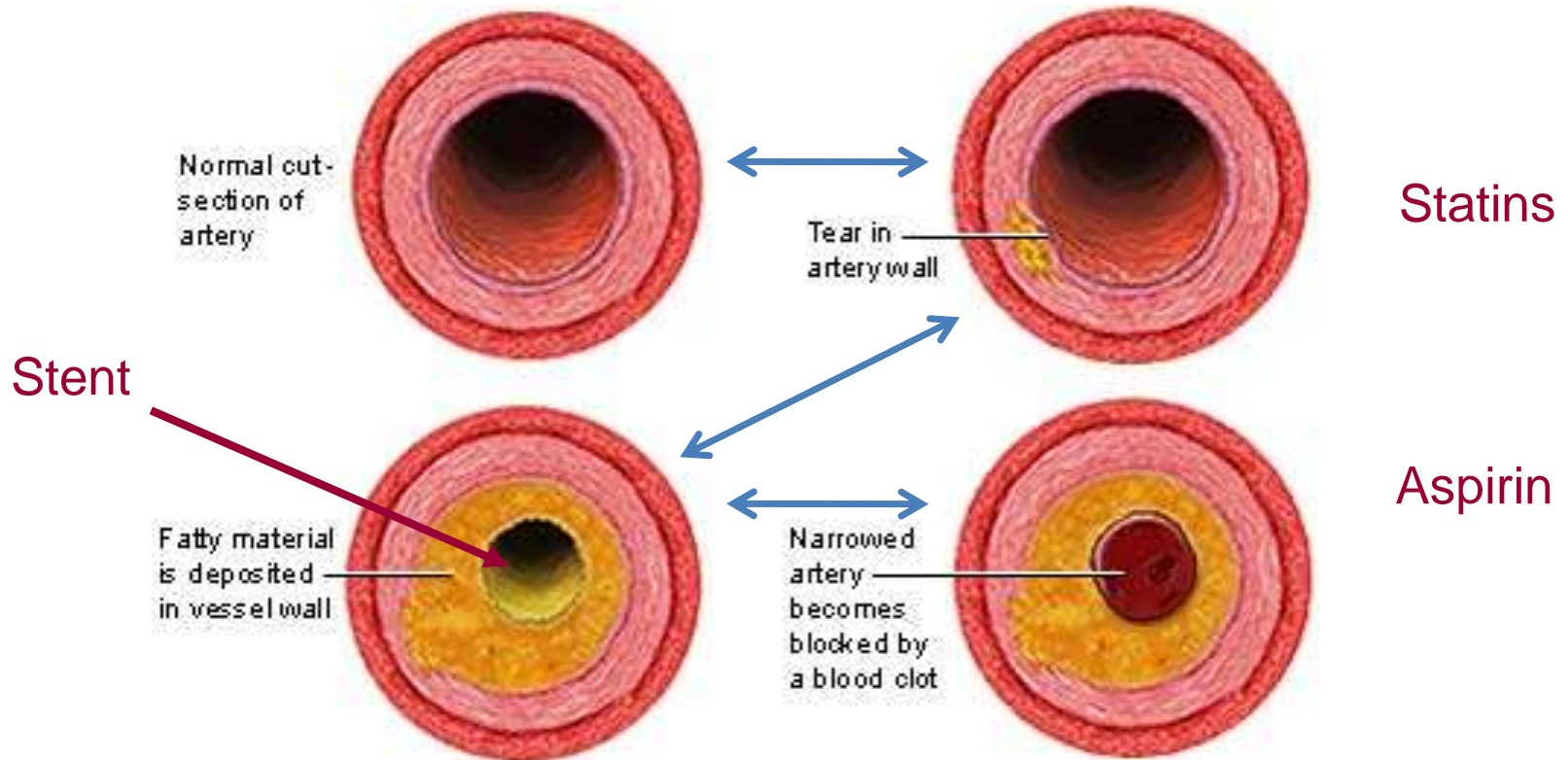
Obesity

- Diet
 - Portion size
 - Physical Activity
 - Genes
- Fat as an endocrine tissue
 - Makes leptin – lowered desire to eat, more use of stored fat
 - Makes inflammatory signaling molecules
 - Decreases synthesis of signals that in turn cause a decrease in blood pressure
 - with the result being increased blood pressure



Ob/ob mouse from “Nutritional Science”

Progression of Vascular Disease



Cut-section of artery



Tear in artery wall

Macrophage cell

Cholesterol deposits

Red blood cell

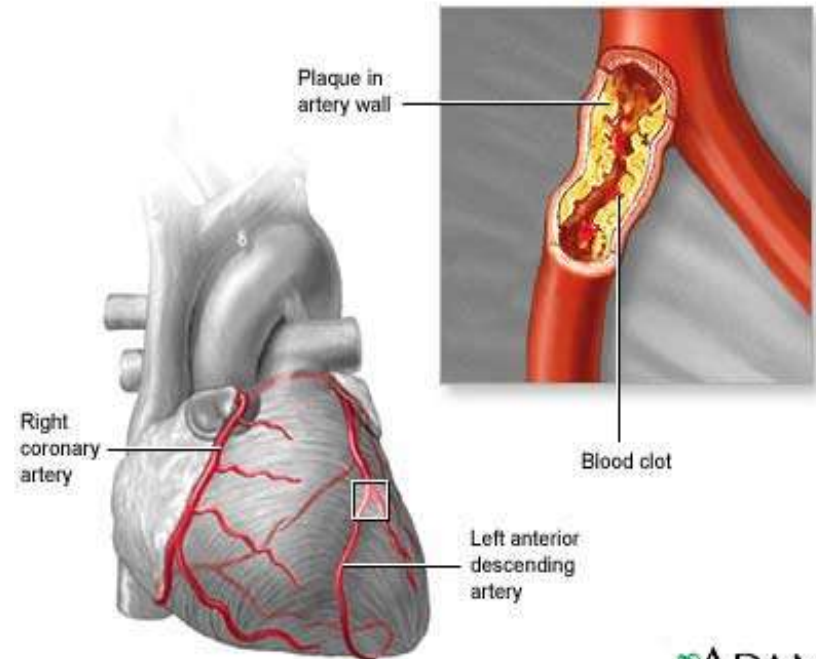
Macrophage foam cell

Fat deposits

 ADAM.

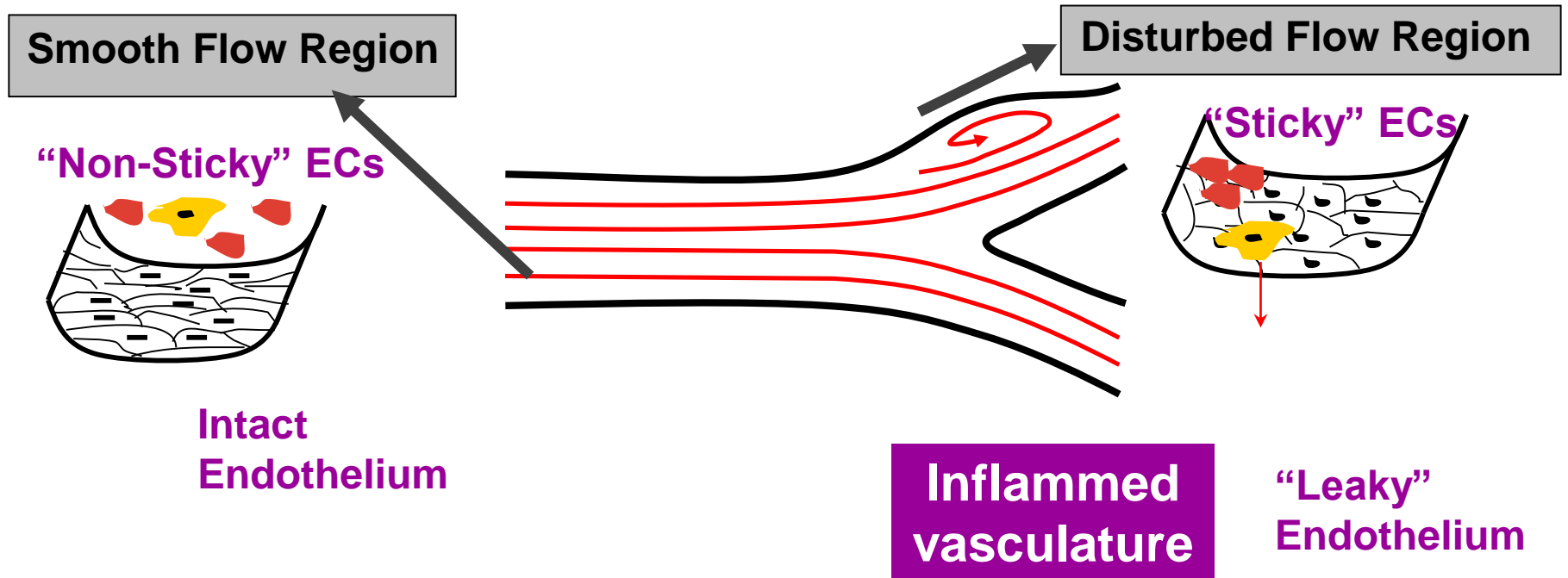
Atherosclerosis

- Leads to narrowing/
blocking of arteries
 - Blocked flow to the heart
 - Myocardial Infarction
(heart attack)
 - Blocked flow to the brain
 - Ischemic Stroke



Bypass

Atherosclerosis Locations

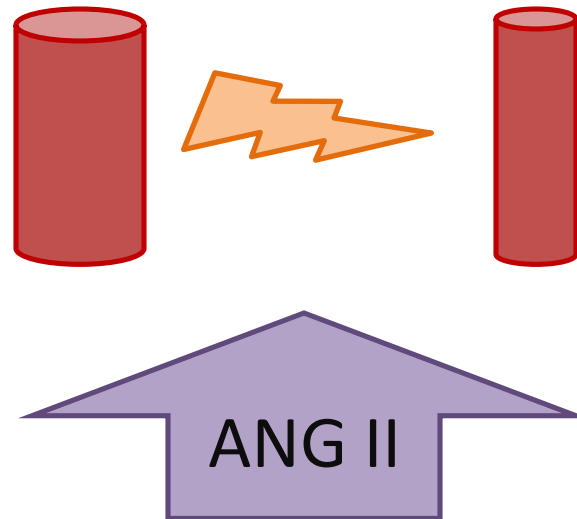


Meron Mengistu

Flow, along with other factors, contributes to risk.

Hypertension

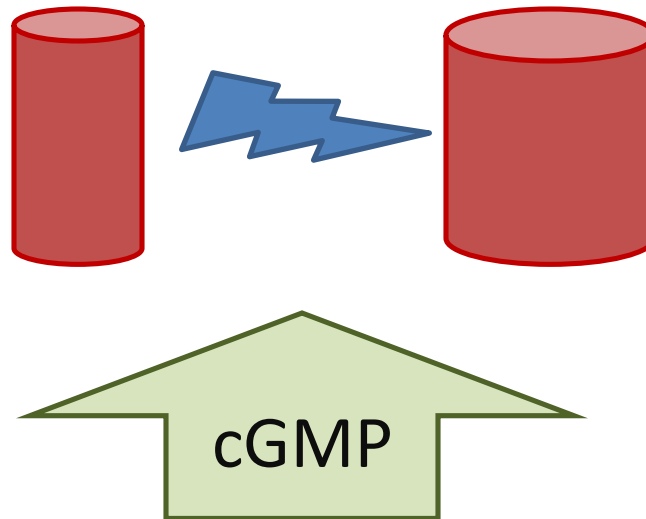
- Angiotensin is a major contraction signal that increases blood pressure transiently



Diuretics,
Ace inhibitors,
 β -blockers,
Calcium channel
blockers

Relaxation of blood vessels

- NO (nitric oxide) and atrial natriuretic factor both cause increases in cGMP



Nitroglycerin

- But cGMP is typically rapidly degraded by proteins called PDEs

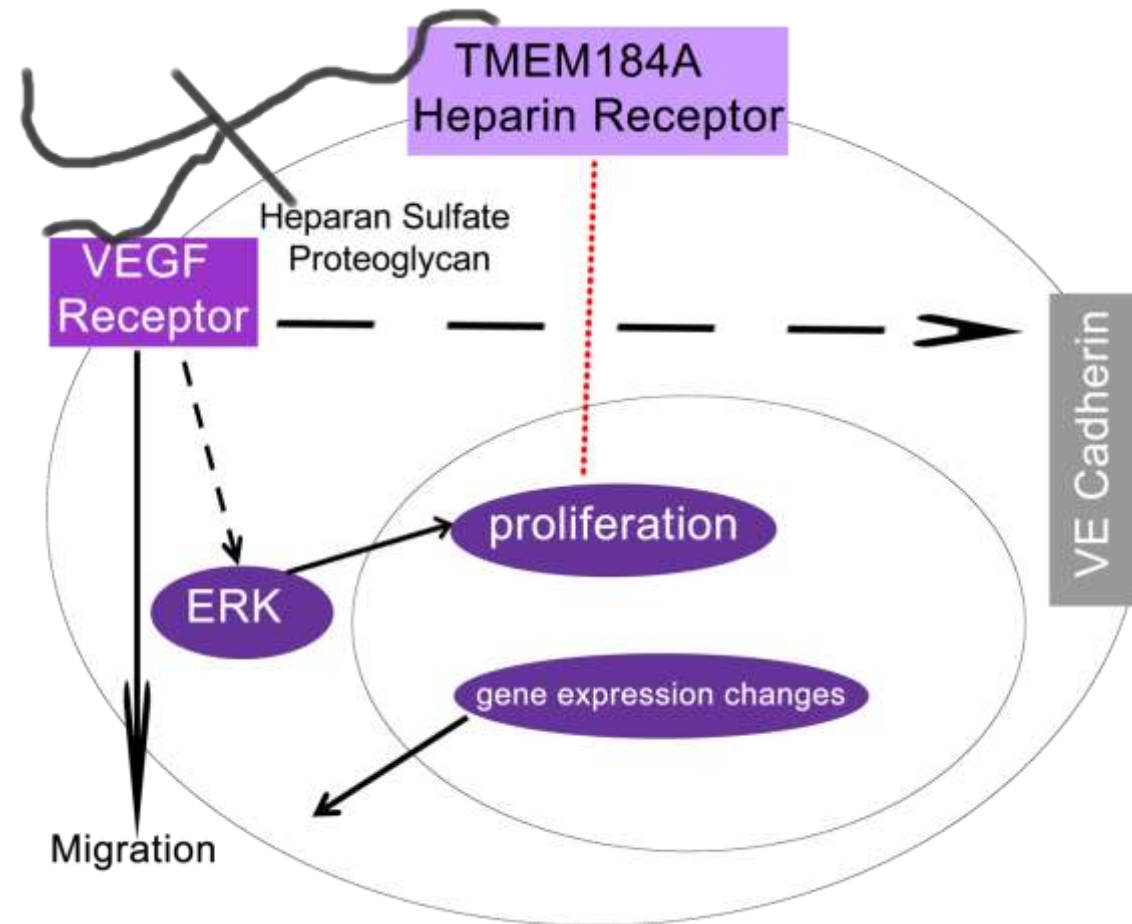


- PDE3 is primarily in cardiac muscle
- PDE6 is primarily in the retinas
- PDE5 is primarily in vascular smooth muscle

Sildenafil citrate

- Blocks PDE5 80 to 4000 times more effectively than it blocks other PDE isoforms (except PDE6)
- Therefore in vascular smooth muscle cells cGMP remains elevated longer.
- Viagra is a trade name for sildenafil citrate

Model of Heparin Receptor Mediated Anti-growth Effects in VSMCs and Anti-inflammatory Effects in Endothelial cells



Questions:

Identification of the Receptor

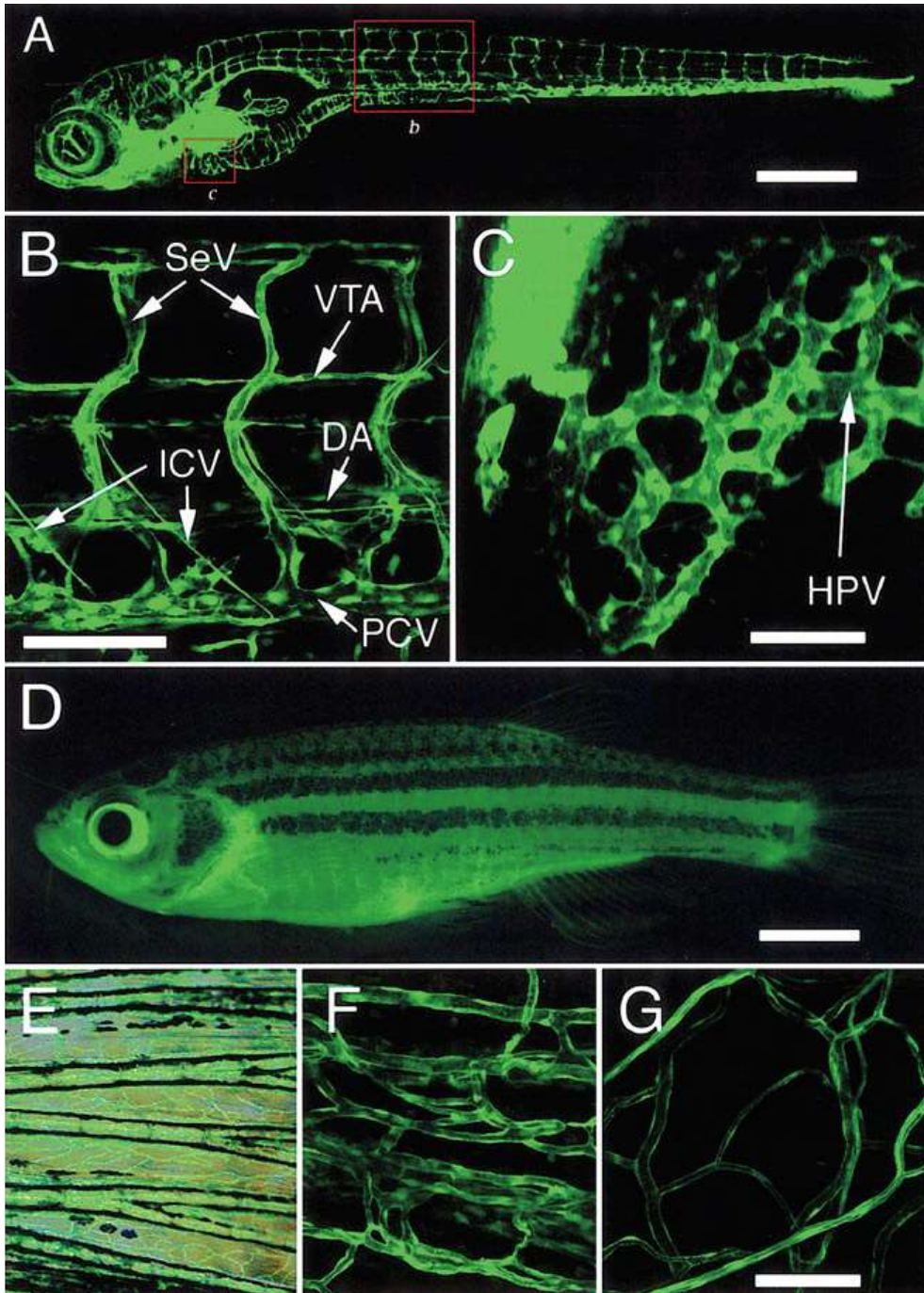
- Protein identity
- Validation
- Heparin binding ability

1. Does the signal go through eNOS? **Yes, and Ca^{2+}**

Channels are involved in both vascular smooth muscle and endothelial cells.

2. What are the inflammatory targets in endothelial cells?

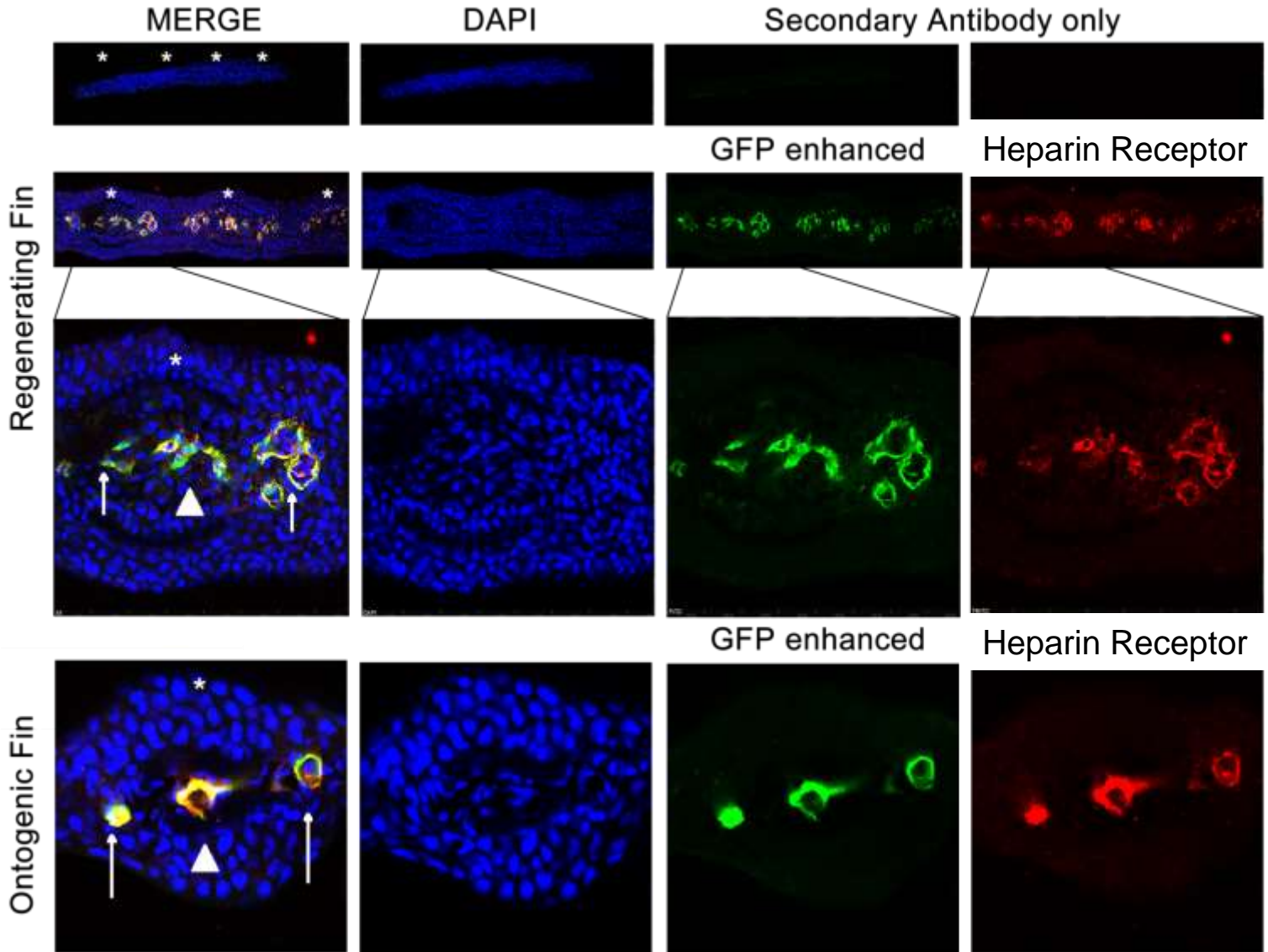
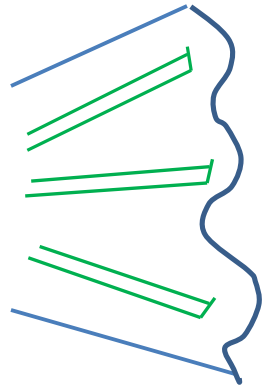
3. What are the functions in an animal? **See the next slides.**



- A. 7 day old larva
- B. Trunk vessels at 7 days
- C. Liver vasculature, 5 day larva
- D. Full length view of TG(fli1:EGFP) fish
- E. Tail fin with merged transmitted light
- F. Tail fin microvasculature in adult
- G. Blood vessels associated with surface scales

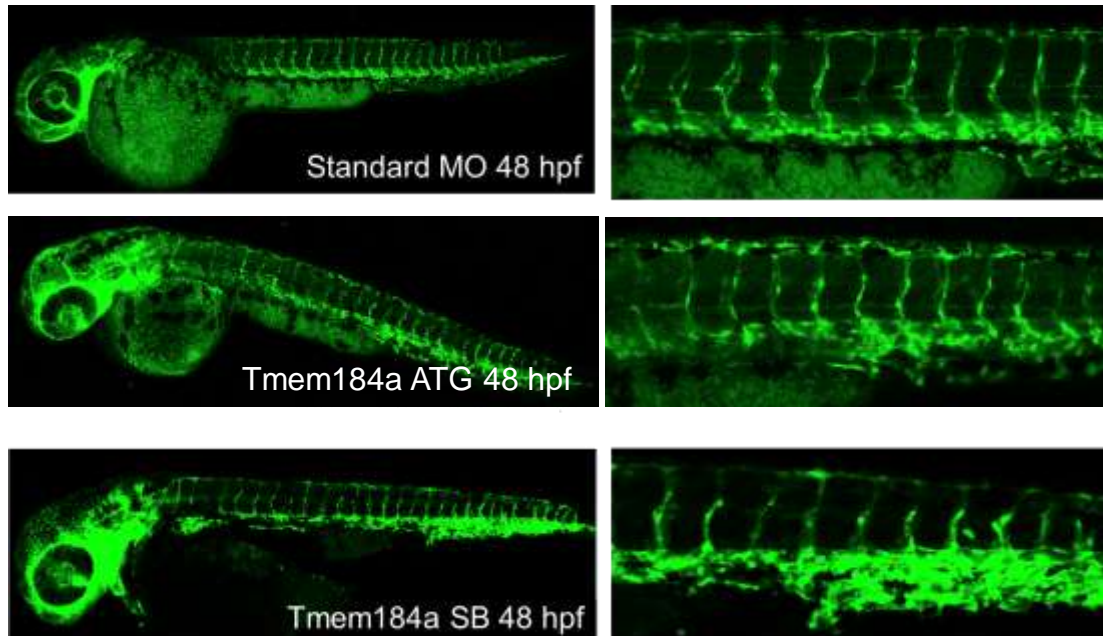
*Lawson and Weinstein, 2002
Developmental Biology 248:307*

And what about angiogenesis?



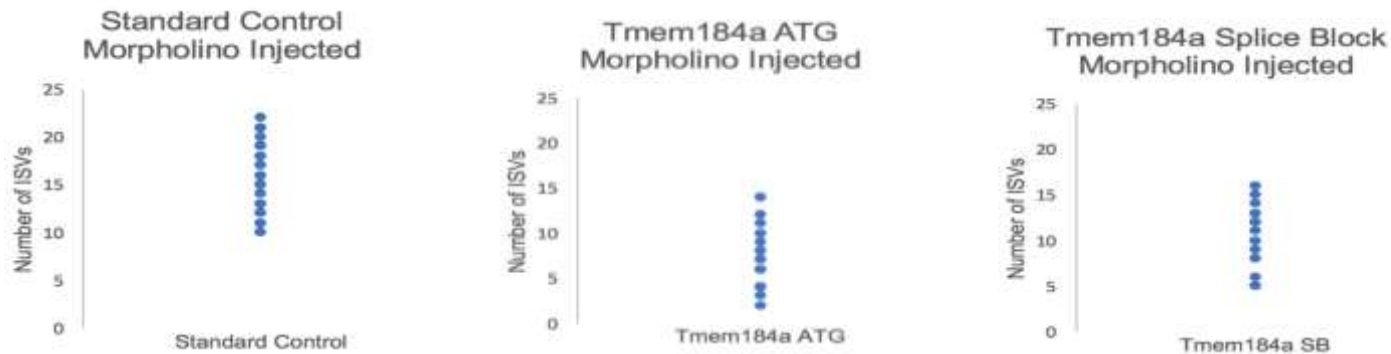
Farwell, et al.
Frontiers in
Physiology
2017

Developmental Angiogenesis



Also, cell proliferation is maintained.
Cell to cell adhesion is decreased.

Field, et al.,
submission 2019



Where do scientists go from here?

- Can research dissociate components of diet from their effects on heart disease?
- What types of communication/education can lead to improved activity levels, diet, etc?
- Current treatment of vascular diseases is increasing life-span, but at significant cost. Can we slow development of vascular disease and increase the time until expensive interventions are required?