WHAT IS CHOLESTEROL

A substance produced by the liver (and every other cell) that has vital functions in the body

Cholesterol that is produced in the liver circulates in the blood
TYPES OF CHOLESTEROL

LDL (“Lousy”): Linked to ↑ heart disease
HDL (“Helpful”): Linked to ↓ heart disease
Triglycerides (TG): Also linked to ↑ heart disease. High in diabetes and “insulin resistance”
Total cholesterol: LDL+HDL+TG/5
RATIO of TC:HDL contains all CAD (coronary artery disease) risk prediction*

*Criqui & Golomb 1998 Am J Med 105 48S-57S
Cholesterol has Functions*

- Membrane function, enzymes fcn
- Transmembrane exchange
- Cell barrier function
- Cell energy: Maintenance of voltage gradient
- 1° organic molecule in the brain?
- Essential to synapse formation
- Essential to myelin sheaths
- Protects vs toxins; α-oxidant transport
  - Paraoxonase; CoQ10; Fat soluble vitamins
- Regulates neurotransmitters: e.g. 5-HT
Cholesterol Has Products

Cholesterol

- 7a-hydroxy-4-cholesten-3-one
  - 7a-hydroxycholesterol
  - 7a,12a-dihydroxy-4-cholesten-3-one
  - 3a,7a,12a-trihydroxy-5beta-cholestanolic acid

| Cholic Acid | Chenodeoxycholic Acid |

27-hydroxylase

27-hydroxycholesterol

7a-hydroxycholesterol

12a-hydroxylase

7a-hydroxy-4-cholesten-3-one

11-oxo-3a,7a,12a-trihydroxy-5beta-cholestanolic acid

3a,7a,12a-trihydroxy-5beta-cholestanolic acid

27-hydroxylase

3a,7a,12a-trihydroxy-5beta-cholestanolic acid

3a,7a-oxo-4-cholestenolic acid

3a,7a-Dihydroxy-5-cholestanolic acid

3β-hydroxy-5-cholestanolic acid

3β,7a-Dihydroxy-5-cholestanolic acid

25-hydroxycholecalciferol

1,25-dihydroxycholecalciferol

7-dehydrocholesterol

Pregnenolone

20,22-Dihydroxycholesterol

Dihydroxycholesterol

Mixed function oxidase

Cholecalciferol (Vitamin D3)

Calcitriol

17α-hydroxylase

3β-hydroxysteroid dehydrogenase

17α-OH pregnenolone

17α-hydroxyprogrenolone

Progesterone

3β-hydroxysteroid dehydrogenase

11α-hydroxylase

21-hydroxylase

17α-OH progesterone

11-deoxycorticosterone

11-deoxy cortisol

11β-hydroxylase

Cortisol

11β-hydroxylase

Aldosterone (Mineralocorticoid)

5α-reductase

Estradiol (Estrogen)

Estrone

17β-dehydrogenase

Aromatase

Dihydrotestosterone

Testosterone (Androgen)

Androstenedione

Androstenediol

17β-dehydrogenase

3β-dehydrogenase

17α-hydroxylase

17,20-lyase

21-hydroxylase

11-deoxy cortisol

11β-hydroxylase

Cortisone (Glucocorticoid)
CHOLESTEROL: FOCUS ON THE HEART

- HIGH CHOL IS LINKED TO HEART DISEASE*
- EACH 1% ↓ CHOL IS ASSOCIATED WITH 2%↓ CAD* - IN MIDDLE AGED MEN
- ↓CHOL IN M.A.MEN AT HIGH CAD RISK NOT ONLY ↓S CAD* BUT LENGTHENS LIFE
- *CORONARY ARTERY DISEASE, OR CAD
THE GOAL:
A GOOD CHOL/HDL RATIO

THAT IS, HIGH AMOUNT OF HDL VS OTHERS
• RAISE HDL
• LOWER TG
• LOWER LDL

*The real goal: a healthier, longer life.*
### DIETARY FATS & CHOLESTEROL

<table>
<thead>
<tr>
<th>TYPE</th>
<th>EXAMPLE</th>
<th>HDL</th>
<th>LDL</th>
<th>NET</th>
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<tbody>
<tr>
<td>SATURATED</td>
<td>BUTTER</td>
<td>↑</td>
<td>↑</td>
<td>±</td>
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<tr>
<td>MONOUNSAT.</td>
<td>OLIVE OIL</td>
<td>↑</td>
<td>↓</td>
<td>+++</td>
</tr>
<tr>
<td>POLYUNSAT (N6).CORN OIL</td>
<td>↓</td>
<td>↓</td>
<td>±</td>
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<tr>
<td>TRANS</td>
<td>HYDROG’D</td>
<td>↓</td>
<td>↑</td>
<td>-</td>
</tr>
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</table>

OMEGA-3 (FISH OIL>FLAX): LITTLE EFFECT ON CHOLESTEROL BUT LOWERS HEART RISK (high dose actually ↑LDL – sort of)

TRANS: MARGARINE, SHORTENING
FOOD & FATS

• HIGH OMEGA-3 FISH: cold water
  – SALMON
  – MACKEREL (Jack not King)
  – TUNA
  – SARDINES
FOOD & FATS

• CHOCOLATE: stearic acid = saturated
  – BUT RAISES HDL ONLY
• GARLIC: each clove/d -> 9% decrease chol
• PSYLLIUM, GUAR GUM, ETC: lower chol
• SOY: Lowers chol BUT brain atrophy reported

# FOOD & CHOLESTEROL

<table>
<thead>
<tr>
<th>CHOL</th>
<th>HD</th>
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<tbody>
<tr>
<td>BENEFIT</td>
<td>BENEFIT*</td>
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<table>
<thead>
<tr>
<th>Fruits</th>
<th>CHOL</th>
<th>HD</th>
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<tbody>
<tr>
<td>Apples</td>
<td>↓ LDL</td>
<td></td>
</tr>
<tr>
<td>Oranges</td>
<td>↑ HDL</td>
<td></td>
</tr>
<tr>
<td>Avocados</td>
<td>↑ HDL</td>
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<table>
<thead>
<tr>
<th>Nuts</th>
<th>CHOL</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ LDL, ↑ HDL</td>
<td>BENEFIT*</td>
<td></td>
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<table>
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<tr>
<th>High Carbs</th>
<th>CHOL</th>
<th>HD</th>
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<tbody>
<tr>
<td>↑ TG, Dense LDL, IR</td>
<td>HARM</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Trans Fat</th>
<th>CHOL</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ HDL, ↑ LDL</td>
<td>HARM**</td>
<td></td>
</tr>
</tbody>
</table>

* Have antioxidant effects
** Have prooxidant effect
TRANS FATS: NURSES’ HEALTH STUDY

• 85,095 women followed for 8 years
• High (vs Low) margarine eating “quartiles”
  * 50% ↑ heart attack (*P = 0.001)
  * ~70% ↑ heart attack if compare those with stable consumption over >10 yrs (N=67,000) (*P = 0.002)
• True irrespective of age, CAD RF, sat fat intake

Willett 1993 Lancet 341: 581
BUTTER VS MARGARINE: Case-Control Study

• 239 men and women admitted with 1st heart attack (MI)
• 282 Control subjects without MI

Compare >2.5 pats/d vs <1 pats/d
Margarine: ↑ MI 2.4-fold  p < 0.001
Butter: No effect

*Adjusted for age, energy intake, sex; and many other factors

Ascherio 1994 Circulation 89: 94
Omega-3 Fats and Fish

- Short chain omega-3 require inefficient conversion
- Omega-3 produx (DHA) blocked by trans fats
- Grass fed cattle make omega-3s; grain fed don’t
- Omega-3s have antiinflammatory properties (vs trans have pro-inflammatory)
- Strong protection against arrhythmia
- Improve cardiac mortality > events (DART)
- Improve total mortality > cardiac mortality
ALCOHOL

 Raises HDL. At high doses, raises TG. Lowers LDL only when causes liver disease

 Insulin Resistance: Associated with ↓ HDL, ↑ TG, ↑ waist and weight, ↑ SBP, ↑ glucose

 LOW DOSE ALCOHOL WITH MEALS -> INSULIN SENSITIZER

 HIGH DOSE ALCOHOL, NOT MEAL ASSOCIATED -> INSULIN RESISTANCE

 Criqui & Golomb 1999 JAMA 282:279 Should patients with diabetes drink to their health?

 BEER CONSUMPTION CAUSES BEER BELLY*
*Ignobel Prize winning study?
ALCOHOL

LOWER CAD DEATH: modest use
  Fruit/ Grapes ~ part of benefit
  Alcohol = part of benefit, probably

↑ OTHER DEATHS: Suicide, trauma, liver disease (coffee protects*), some cancers

OVERALL DEATH:
  Men: max 2/week - 2/day
  Women: max 1/day (breast cancer)
  Nondrinkers: Not tested: can’t advocate use
    Some people should not drink

*observational data
DIETS THAT EXTEND LIFE in clinical trials

- LOW-FAT CHOL-LOWERING DIETS – NO (neutral)
- HIGH “FIBER” DIET – NO (sl ↑ death)
- FATTY-FISH (if CAD) – YES* (30% decr death)
- ‘MEDITERRANEAN’ DIET* (vs AHA diet) – YES (56% decr death)

*Diet and Reinfarction trial; Lyon Diet Heart Study. Neither lowered cholesterol.

Burr 1989 Lancet ii: 757 Diet and Reinfarction Trial
diLorgeril 1998 Arch Int Med 158: 1181
Do CALORIE RESTRICTED DIETS increase longevity?

• What are the kinds of calories restricted? Prooxidants?
• Pathogen-free environment
• “We had trouble keeping them alive”
• Cold exposure

• (Low calorie diets: tend to promote weight cycling, IR. Focus on nutrient dense foods)
Beyond foods, how are other factors linked to cholesterol?
EXERCISE

Improves Cholesterol

• ↑ HDL
• ↓ TG

Also improves other risk factors for CAD

• ↓ DIABETES & “IR”
• ↓ HYPERTENSION
• ↓ PAD

• ↓ TOTAL MORTALITY, CAD, STROKE, PAD, DM, HTN, OBESITY, OSTEOPOROSIS, DEPRESSION, ANXIETY, COGNITIVE DECLINE, SOME CANCERS; ↑ RESILIENCE TO ILLNESS/INJURY/SURGERY
SMOKING

EFFECT ON CHOL  EFFECT ON HD
↓ HDL  ↑ HEART DISEASE*

*Also increases peripheral arterial disease; emphysema; lung cancer; oropharyngeal cancer; skin aging; poor wound and bone healing; worse outcomes with surgery or illness

• Associated with protection against Parkinson’s
STRESS

• MENTAL STRESS: ↑↑ cholesterol
• PHYSICAL “STRESS”*: ↓↓ cholesterol

* SURGERY, HEART ATTACK, BYPASS, INJURY, SERIOUS INFECTION, CHILDBIRTH
SO YOU WANT TO IMPROVE YOUR CHOLESTEROL (RATIO)

- EXERCISE
- DON’T SMOKE
- EAT LOTS OF FRUITS, VEGETABLES, NUTS
- SPURN TRANS FATS

THESE ARE GOOD FOR CHOLESTEROL RATIO; HEART HEALTH; & OVERALL HEALTH.
BESIDES CHOLESTEROL: WHAT ELSE IS LINKED TO CAD?

Traditional major RFs
• DIABETES & INSULIN RESISTANCE
• HIGH BLOOD PRESSURE
• INCREASED AGE
• MALE GENDER
• SMOKING

Other
• Inflammation
• Oxidative stress
HOW CAN THESE BE HELPED

• MALE GENDER (No fix here!?)
• SMOKING: Stop
• HYPERTENSION:
  “DASH diet”: LOTS fruits and veg; 3/day servings of dairy (marked stroke risk ↓ with dairy in men); Exercise
• “AGING”: Protect against oxidative stress? Avoid chemicals, pesticides, heavy metals, EM fields, fake foods/trans fats; and get antioxidant-rich nutrients, sleep, and moderate exercise
REDUCE INSULIN RESISTANCE

- Sleep enough
- Don’t skip meals or go long between them
- Correct sleep apnea (snorers beware; sing!)
- Breath
- Include protein/fat when you eat (not just carbs)
- Avoid ultra low calorie diets
- Avoid TV
- Dairy, Adequate vitamin D
- Coffee?
REDUCE INSULIN RESISTANCE

• Avoid trans fats (fast foods; baked goods)
• Limit simple carbos (wheat products, e.g.)
• Temper carbos with fat and protein
  -- Fat blunts glycemic rise, insulin surge
• -- Protein leads to release of glucagon, counteracts insulin
HOW DOES CHOL RELATE TO HEALTH MORE GENERALLY?

• Middle aged men: higher chol is linked to more cad; cvd; total death.
  – Each 1% ↓ in chol -> 2% ↓ in cad

• Postmenopausal women: higher chol is linked to ~more cad; but ~no change in total cvd or total death

• Older elderly: higher chol is linked to more resilience; less atrial fibrillation; *lower* total death. Sole clinical trial.
High Cholesterol & Mortality by Age

Cardiovascular Mortality

Death

Cholesterol

Middle Age

Age >70

Age >80

Total Mortality

Death

Cholesterol

Middle Age

Age >70

Age >80
Older Elderly: Hi Chol live Longer

• Age > 85, 10 year follow-up
• Each 39 mg/dl ↑ in total cholesterol was associated with a 15% ↓ in mortality
• RR 0.85 [95% CI 0.79-0.91]
• Similar death from heart disease across cholesterol groups at this age
• Lower death from cancer and infection in the high cholesterol group.

RCT data also support incr cancer with statins in age > 70 (PROSPER trial)

Low chol has been linked to incr infection risk including HIV: vit A, vit D as possible factors
• Weverling-Rijnsburger 1997 Lancet 350:1119
CANCER

Observational: low chol linked to cancer selectively in low SES & smokers: poor oxidant:antioxidant ¹

Statin RCT Middle Age:
OR 1.02 cancer, 1.01 cancer death², 1.03 breast can ³

Elderly RCT: Age > 70
HR 1.25 (1.04-1.51) ⁴

Meta-regression: significant age*statin interaction ⁵

Melanoma benefit? Some evidence suggestive…⁶,⁷

¹ Law 1991 Cancer Causes Control 2:253
² Dale 2006Jama 2006;295:74
³ Bonovas 2005 J Clin Oncol 23:8606
⁴ Shepherd 2002 Lancet 360:1623
⁵ Bonovas 2007 Cmaj;176:649
⁶ Dellavalle 2003 Am J Ther10:203
⁷ Dellavalle 2005 Cochrane RevCD003697
STATINS: 1\textsuperscript{st} and 2\textsuperscript{nd} best selling px drug

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>TRADE NAME</th>
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<tbody>
<tr>
<td>ATORVASTATIN</td>
<td>LIPITOR</td>
</tr>
<tr>
<td>SIMVASTATIN</td>
<td>ZOCOR</td>
</tr>
<tr>
<td>PRAVASTATIN</td>
<td>PRAVACHOL</td>
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<tr>
<td>ROSUVASTATIN</td>
<td>CRESTOR</td>
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<tr>
<td>LOVASTATIN</td>
<td>MEVACOR</td>
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<tr>
<td>FLUVASTATIN</td>
<td>LESCOL</td>
</tr>
<tr>
<td>VYTORIN</td>
<td>COMBO + EZETIMIBI</td>
</tr>
<tr>
<td>CADUET</td>
<td>COMBO + AMLODIPIN</td>
</tr>
<tr>
<td>PRAVAGARD</td>
<td>COMBO + ASPIRIN</td>
</tr>
</tbody>
</table>
Mevalonate Has Products

\[
\begin{align*}
\text{Acetyl-CoA} & \xrightarrow{\text{Acetyl-CoA thiolase}} \text{Acetoacetyl-CoA} \\
\text{HMG-CoA} & \xrightarrow{\text{HMG-CoA reductase}} \text{Mevalonic Acid} \\
\text{Mevalonate-5-Phosphate} & \xrightarrow{\text{Mevalonate kinase}} \text{Mevalonate-5-PP} \\
\text{Phosphomevalonate kinase} & \\
\text{Mevalonate-5-PP decarboxylase} & \xrightarrow{\text{Isopentenyl PP isomerase}} \text{Dimethylallyl pyrophosphate} \\
\text{Farnesyl PP synthase bisphosphonate (-)} & \xrightarrow{\text{Prephytoene pyrophosphate}} \text{Phytoene} \\
\text{Farnesyl PP} & \xrightarrow{\text{Prephytoene pyrophosphate}} \text{Phytoene} \\
\text{Farnesyl PP synthase bisphosphonate (-)} & \xrightarrow{\text{Lycopene}} \text{β-carotene} \\
\text{β-carotene-C4-oxygenase} & \xrightarrow{\text{Ketocarotenoid}} \\
\text{Geranylgeranylated proteins} & \xrightarrow{\text{Retinoids}} \text{Cholesterol} \xrightarrow{\text{Heme A}} \text{Farnesylated proteins} \\
\text{Dolichol} & \xrightarrow{\text{Ubiquinone}} \\
\end{align*}
\]

\( \text{PP} = \text{Pyrophosphate} \)
EFFECTS OF STATIN TREATMENT (STATINS), MAJOR RCTS

<table>
<thead>
<tr>
<th>CAD</th>
<th>Overall DEATHS</th>
<th>Overall Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH RISK MAM</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>LOW RISK MAM</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>HIGH RISK WOMEN</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>HIGH RISK AGE ≥ 70*</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>HIGH DOSE STATIN</td>
<td>↓</td>
<td>0</td>
</tr>
</tbody>
</table>

MAM = middle aged men

* Significant increase in cancer (Prosper trial)
Patient reports have support in the literature

Frequency of Spontaneously Reported Symptoms

- **Muscle**
  - 124

- **Cognition**
  - 75

- **Fatigue**
  - 36

- **Neuropathy**
  - 32

Other symptoms (with frequencies):
- Mood: 30
- GI: 22
- Headache: 17
- ALS: 10
- Liver: 9
- Personality: 8
- Dizziness: 8
- Temp reg: 8
- Elev blood gluc.: 7
- Wt gain: 7
- Vision: 5
- Bladder: 5
- Irreg HB: 4
- Kidney: 4
- Parkinson: 3
- RingEar: 2
- Elev CK: 2
- Erectile dys: 1
- Skin: 1
## AEs Reported

<table>
<thead>
<tr>
<th>AE</th>
<th>Highest Quality Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle/CK</td>
<td>RCT (CK)</td>
</tr>
<tr>
<td></td>
<td>Rdmiz dblblind crossover bx</td>
</tr>
<tr>
<td>Cognitive</td>
<td>RCT</td>
</tr>
<tr>
<td>Fatigue</td>
<td>RCT (ours, unpublished)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Case-Control (Denmark)</td>
</tr>
<tr>
<td>Sleep</td>
<td>RCT</td>
</tr>
<tr>
<td>Glucose</td>
<td>RCT</td>
</tr>
<tr>
<td>Hepatic</td>
<td>RCT</td>
</tr>
</tbody>
</table>

RISK FACTORS FOR ADVERSE EFFECTS

ADVANCED AGE: > 65, 70, 75, 80
FEMALE GENDER? FRAIL ELDERLY
HYPERTENSION
DIABETES
HIGH TRIGLYCERIDES
THYROID DISORDERS – even if treated
ASIAN ETHNICITY
INTERACTING MEDICATIONS: antibiotics, concurrent cholesterol medications, diltiazem, amiodarone, other
Many Interactions relate to Dose

- Substrates (metabolized by CYP450 isozymes)
- Inhibitors of CYP450 isozymes

Liver CYP450 enzymes:
- 3A4
- 2C9
- 2D6
- 1A2
- Others

Increased concentrations of substrate → Potential for adverse drug reactions
Interactions & Grapefruit Juice

Statins metabolism:
- CYP3A4: Atorvastatin, Simvastatin, Lovastatin, (Ceriva)
  CYP3A4 is Involved in the metabolism of about half of all drugs prescribed*
- CYP2C9: Fluvastatin
- Neither: Pravastatin (liver/kidney clear drug + nonP450-metabolites made by chem degradation in the stomach)

CYP3A4 inhibitors (many):
-azole antifungals; erythromycin; cyclosporin

Grapefruit Juice: inhibits CYP3A4†
- 10 Ss got 200cc/d‡ grapefruit juice x3 days, then simva dose:
- Peak [simvastatin] increased 3.9-fold (range 2.3-9.3-fold; P < 0.01)

* Medical Letter 2003;45:46
‡230cc is one cup
## EFFECTS OF STATIN TREATMENT (STATINS), MAJOR RCTS

<table>
<thead>
<tr>
<th></th>
<th>CAD</th>
<th>Overall Morbidity</th>
<th>Overall DEATHS</th>
<th>Overall Morbidity</th>
</tr>
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<tbody>
<tr>
<td>High Risk MAM</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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</tr>
<tr>
<td>Low Risk MAM</td>
<td>↓</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High Risk Women</td>
<td>↓</td>
<td>0</td>
<td>?</td>
<td></td>
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<tr>
<td>High Risk Age $&gt;$ 70*</td>
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<tr>
<td>High Dose Statin</td>
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<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MAM = middle aged men

* Significant increase in cancer (Prosper trial)
WHAT SHOULD YOU DO?

• GET DAILY EXERCISE!!! BEST DRUG
• EAT LOTS FRESH FRUITS, NUTS, VEGETABLES
• IF YOU SMOKE, STOP
• TOTALLY AVOID HYDROGENATED FATS (MOST PACKAGED BAKED GOODS, FAST FOODS)
• AVOID NONFOODS (soda, etc.)
• GET ENOUGH SLEEP
• BREATHE
• IF YOU DRINK, DON’T DRINK IN EXCESS
• IF YOU HAVE HEART DISEASE, EAT FISH
• IF A HIGH RISK MIDDLE AGED MALE, CONSIDER DRUGS
Thank You!