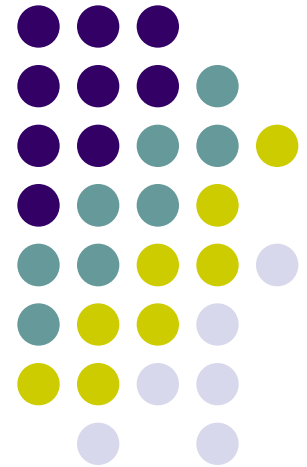


NLA Recommendations for the Diagnosis and Management of Familial Hypercholesterolemia in Children and Adults

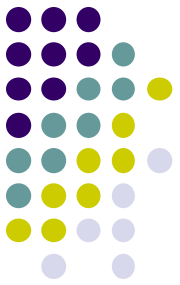
Anne Carol Goldberg, MD, FACP,
FAHA, FNLA

Associate Professor of Medicine
Washington University School of
Medicine

August 27, 2011

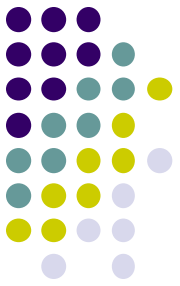


Anne Carol Goldberg, MD, FACP



- Financial disclosure:
 - Research contracts—Abbott, Merck, Genzyme/ISIS, Glaxo-Smith-Kline, Amarin, Aegerion, Novartis, Regeneron (to medical school)
 - Consulting—Genzyme/ISIS, Genentech/Roche, Merck

Why focus on FH?



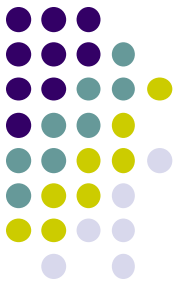
- An inherited genetic disorder causing high cholesterol concentrations and increased risk of premature coronary heart disease
- Untreated, FH leads to substantial CVD risk in men and women

FH Increases Risk of Premature CVD

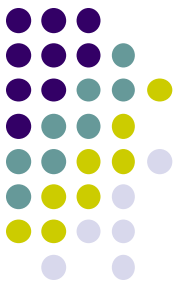


- Mean age of onset of cardiovascular events in men with FH is early 40s; women early 50s
- Although <5% of acute MIs occur in persons ≤ 40 yrs of age, presence of the familial hypercholesterolemia phenotype is associated with 20-fold increase in risk of MI by age 40

Why focus on FH?

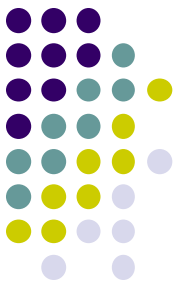


- FH is a treatable disease
- It is underdiagnosed and undertreated
- Earlier recognition and appropriate treatment can decrease the risk of developing CHD



Policy Statement

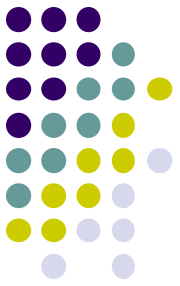
- Publication of policy statement in June 2011
Journal of Clinical Lipidology
 - > Developed from a meeting of FH experts in the field
 - > Focusing on five areas:
 - Public policy
 - Genetics, diagnosis and screening
 - Treatment options
 - Management in Adults
 - Management in pediatrics



NLA FH Expert Panel

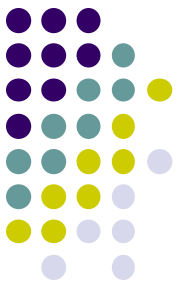
- Expertise in treatment of patients with FH
- Clinical and research backgrounds
- Pediatric and adult medicine practitioners
- Academic and private practice
- Physicians, nurse, pharmacist
- All 5 NLA regional chapters
- Expertise in: genetics, pharmacology, LDL apheresis, epidemiology, public health, clinical trials, pediatrics

NLA FH Expert Panel



- Anne C. Goldberg, MD, FNLA, Chair
- Paul N. Hopkins, MD, MSPH
- Peter P. Toth, MD, PhD, FNLA
- Christie M. Ballantyne, MD, FNLA
- Daniel J. Rader, MD, FNLA
- Jennifer G. Robinson, MD, MPH, FNLA
- Stephen R. Daniels, MD, PhD
- Samuel S. Gidding, MD
- Sarah D. de Ferranti, MD, MPH
- Matthew K. Ito, PharmD, FNLA
- Mary P. McGowan, MD, FNLA
- Patrick M. Moriarty, MD
- William C. Cromwell, MD, FNLA
- Joyce L. Ross, MSN, CRNP, FNLA
- Paul E. Ziajka, MD, PhD, FNLA

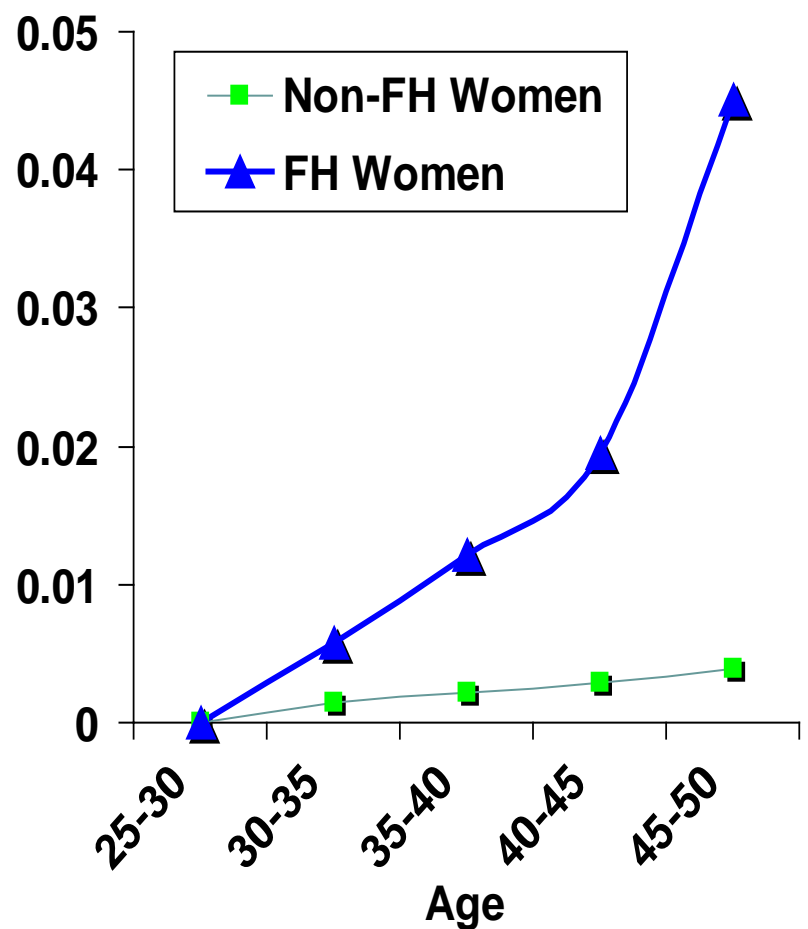
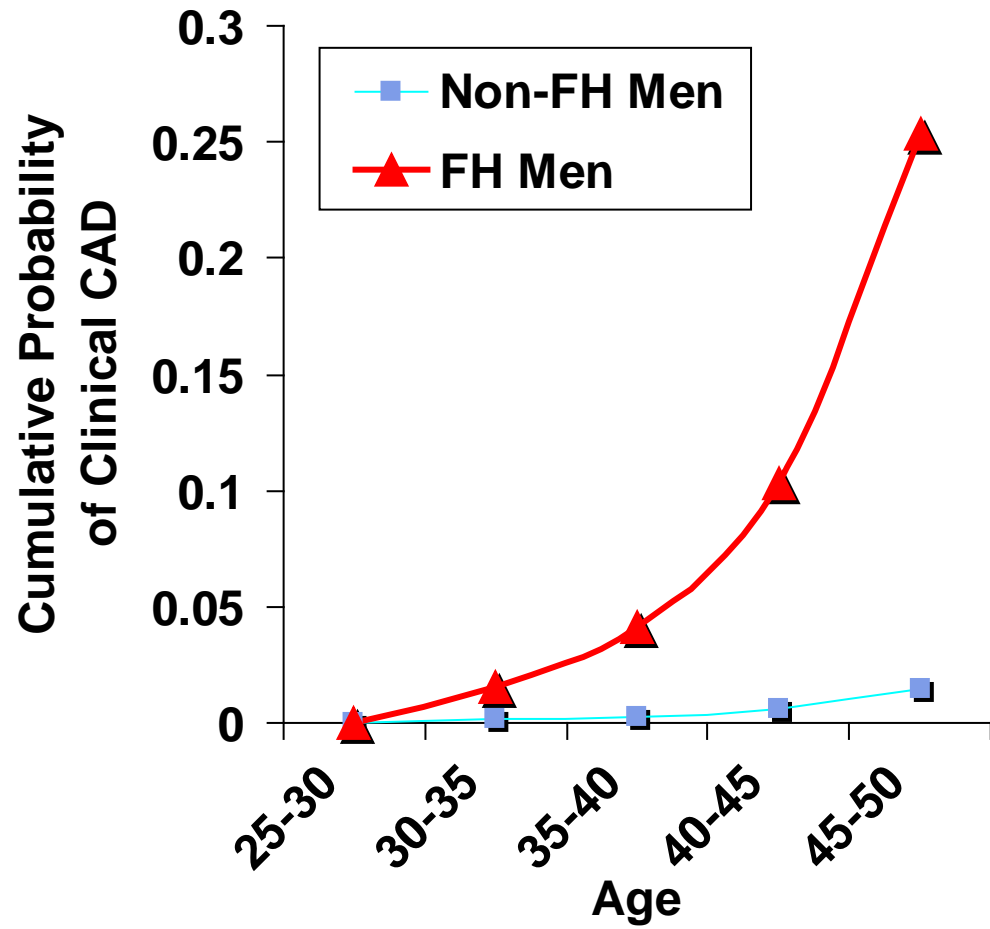
Definition of Familial Hypercholesterolemia (FH)



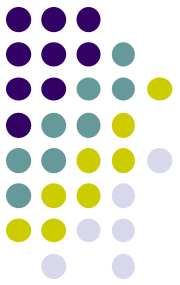
- Autosomal co-dominant high LDL-C
 - Most families have only heterozygotes
- Gene dosage effect
 - Homozygotes (or compound heterozygotes) have much higher LDL-C and much earlier CAD onset than heterozygotes
- FH refers to heterozygotes unless otherwise noted.



Non-Fatal CAD in FH (Utah) vs. General U.S. Population



Hopkins PN, et al. Am J Cardiol 2001; 87:547 and unpublished observations



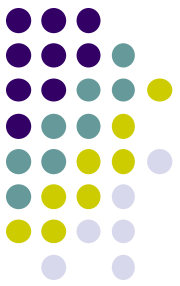
Prevalence of FH

- Most common “single gene” disease
- Heterozygous FH (TC \approx 300-550 mg/dL)
 - 1 in 500 people in many populations
- Homozygous FH (TC \approx 650-1000+ mg/dL)
 - 1 in 1 million people
- >12 million FH patients worldwide
- In the United States there are an estimated 620,000 people with FH

Populations with high prevalence of FH due to founder effect



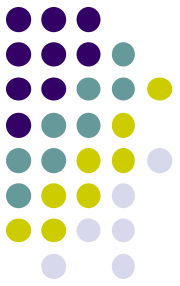
- French Canadian (1 in 100-270)
- Christian Lebanese (1 in 100)
- Several South African populations:
 - Dutch Afrikaner (1 in 100)
 - Ashkenazi Jewish (1 in 100)
 - South Asian Indian



Genetics of FH

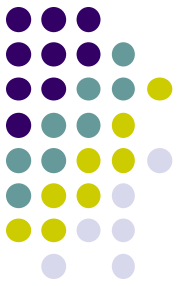
- All genetic causes lead to impaired LDL receptor function and decreased LDL removal
 - $\frac{1}{2}$ LDL catabolic rate \rightarrow 2x increase in LDL
- *LDLR* mutations (most common)
- *APOB* mutations (impair LDLR binding)
 - familial defective apo B (FDB)
 - only Arg3500Gln common
- *PCSK9* (proprotein convertase subtilisin-like / kexin type 9) gain of function mutations

LDLR Mutations



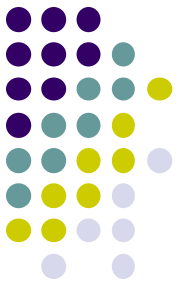
- Gene for *LDLR* resides on short arm of chromosome 19 (19p13.1-13.3).
- Missense, nonsense, insertions, deletions spread throughout *LDLR*.
- Over 1600 *LDLR* mutations are now documented.

Screening



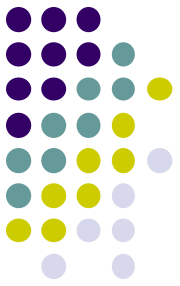
- Universal screening for elevated serum cholesterol is recommended.
- FH should be suspected when untreated fasting LDL-c or non-HDL-C levels are at or above the following:
 - Adults (≥ 20 years): LDL-C ≥ 190 mg/dL or non-HDL-C ≥ 220 mg/dL;
 - Children, adolescents and young adults (< 20 years): LDL-C ≥ 160 mg/dL or non-HDL-C ≥ 190 mg/dL.

Screening



- For all individuals with these levels, family history related to high cholesterol and heart disease in first-degree relatives should be collected.
- The likelihood of FH is higher in individuals with a positive family history of hypercholesterolemia or of premature CHD (onset in men before age 55 years and women before age 65 years).
- Cholesterol screening should be considered beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol. All individuals should be screened by age 20.

Diagnosis



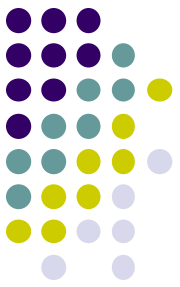
- These LDL cholesterol levels should prompt the clinician to strongly consider a diagnosis of FH and obtain further family information:
- LDL-C ≥ 250 mg/dL in a patient aged 30 or more;
- LDL-C ≥ 220 mg/dL for patients aged 20 to 29;
- LDL-C ≥ 190 mg/dL in patients under age 20.

Recognized FH Diagnostic Criteria



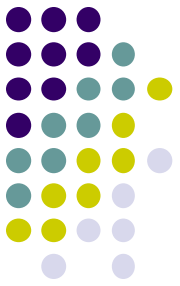
- Best characterized clinical diagnostic tools:
 - US MEDPED Program
 - Simon-Broome Registry Group (UK)
 - Dutch Lipid Clinic Network (Dutch MEDPED)
- DNA evidence:
 - Only the gold standard *in families with known mutation*
 - Lack of a known mutation does not rule out FH

Useful LDL-C cutpoints for FH diagnosis

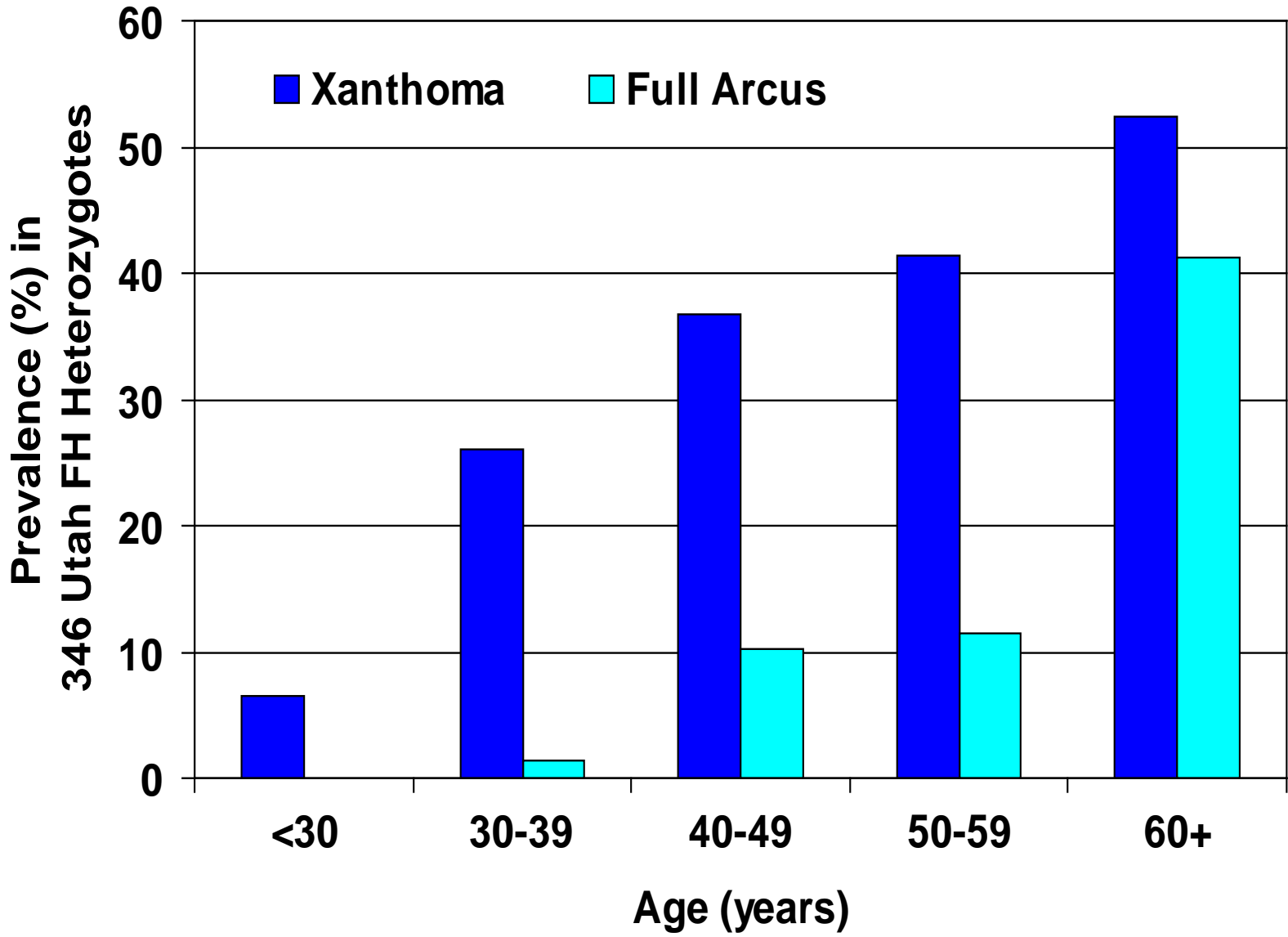


Category	Description	LDL-C (mg/dL) cutpoints		
		age <20	age 20-29	age 30+
1	General population 95 th percentile	130	160	190
2	80% have FH in first-degree relatives	150	170	200
3	80% have FH in general population	190	220	260
4	99% have FH in general population	220	240	280
5	99.9% have FH in general population	240	260	300

Diagnosis



- Absence of physical signs does not exclude possibility of FH
- Presence of tendon xanthoma – almost assures diagnosis but insensitive
- Arcus, xanthelasma, tuberous xanthomas not generally useful.



Heterozygous Familial Hypercholesterolemia:

Non-Specific Signs

Corneal arcus



Xanthelasma







Homozygous Familial Hypercholesterolemia:



5-year old



17-year old

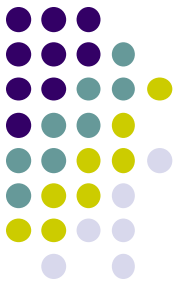


21-year old

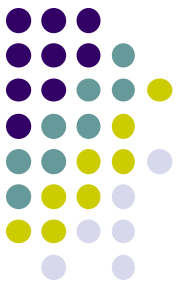
Cascade Screening



- Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients.
- As cascade screening proceeds, newly identified FH cases provide additional relatives who should be considered for screening.
- Cascade screening is the most cost-effective means of finding previously undiagnosed FH patients and is also cost-effective in terms of cost per year of life saved.



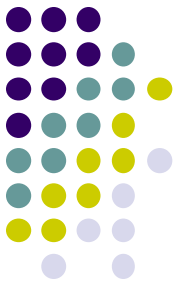
Pediatric Aspects of Familial Hypercholesterolemia



Measure Lipids

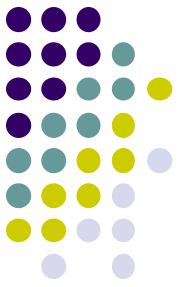
- Universally at ages 9-11 years and 17-21 years
- Can measure total cholesterol and HDL-cholesterol or fasting lipid profile
- Measure at > 2 years of age as part of CVD risk assessment
 - e.g. positive family history, other CVD risk factor, high risk condition, obesity

Screening Rationale



- This age identifies individuals at the potential onset of advanced atherosclerosis.
- This age has the best discrimination between those with and without inherited dyslipidemias and avoids confounding by pubertal related changes in lipid levels.
- Identifying dyslipidemia in those with other major CVD risk factors is critical for risk stratification.

Roles of Pediatricians and Lipid Specialists



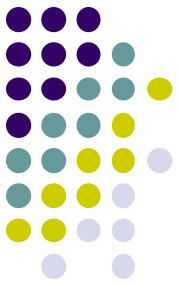
- Pediatricians responsible for screening
- Lipid Specialists generally will manage pharmacologic therapy

Pediatric Evaluation



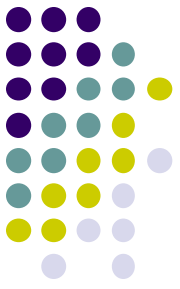
- LDL-C \geq 160 mg/dl consistent with FH
- Non HDL-C \geq 145 mg/dl in screening requires a full lipid panel
- History, PE and labs to exclude secondary hypercholesterolemia (hypothyroidism, nephrotic syndrome)
- Repeat lipid profile after diet intervention to confirm diagnosis
- Presence of additional risk factors intensifies risk

CVD Risk Management in FH



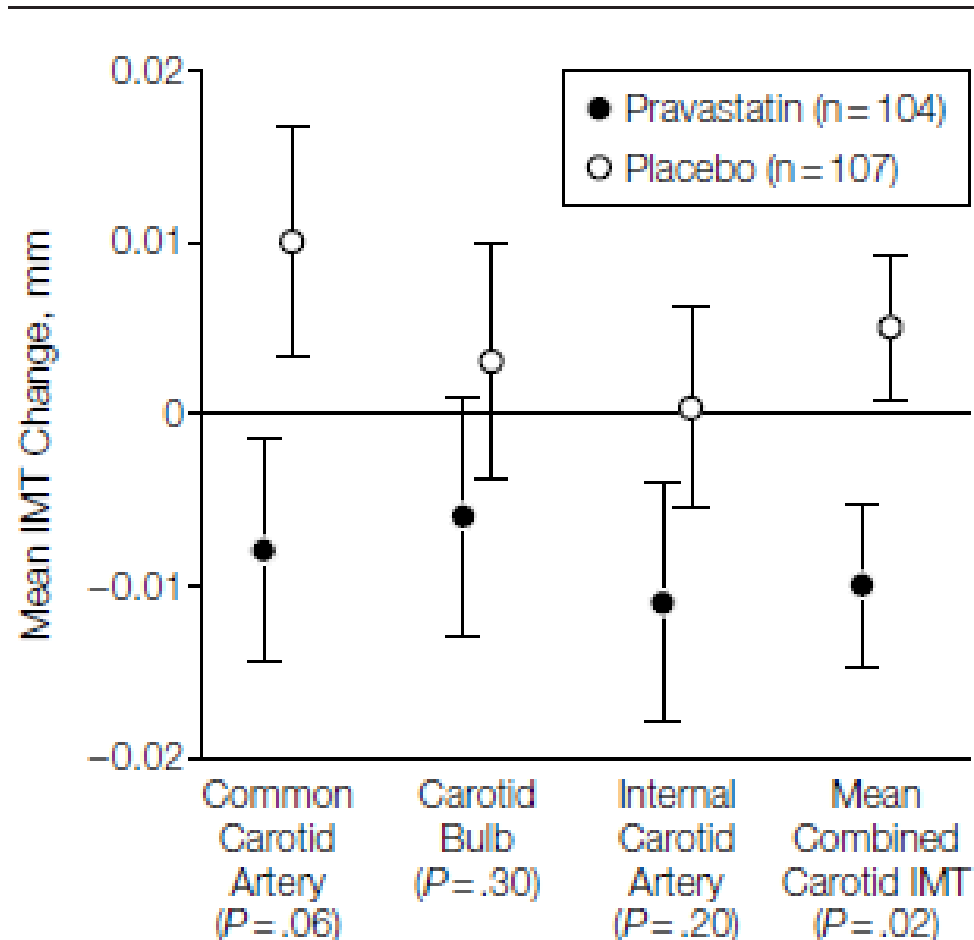
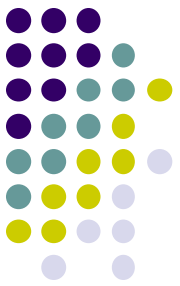
- Primordial prevention
 - Diet
 - Low sat fat/cholesterol
 - Appropriate energy intake
 - Exercise
 - Tobacco counseling
- Measure BP and BMI
- Measure lipoprotein (a) for risk stratification

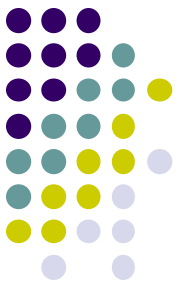
Age When Treatment is Considered



- Most statins approved above age 10, pravastatin for above age 8 years
- Pathologic/imaging data suggest age 10 or so is a critical period for advanced atherosclerosis development
- Higher risk subsets exist (higher LDL levels, multiple risk factors, family history)

Two years of pravastatin therapy induced significant regression of carotid atherosclerosis in children with familial hypercholesterolemia

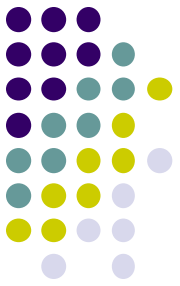




Treatment Rationale

- LDL \geq 190 mg/dl or \geq 160 mg/dl after diet or with multiple risk
- Clinical trials with medium term follow up suggest safety and efficacy of statins
- Goal: try to achieve 50% reduction or LDL < 130 mg/dl, need for balance between increased dosing and potential for side effects vs achieving goals
- Consider more aggressive LDL targets for those with additional CVD risk factors

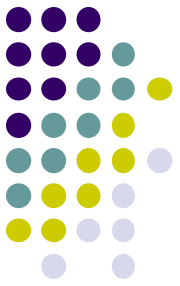
Medications for Children



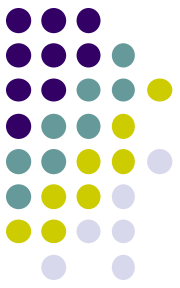
- Statins preferred
 - Randomized trials of up to 2 years duration for all important choices
- Bile acid sequestrants
 - Some trial data, poor compliance an issue
- Cholesterol absorption inhibitors (sitosterolemia)
 - No trial data, cancer risk?
- Niacin
 - Safety?, poorly tolerated

Following Children with FH

Probably by a specialist



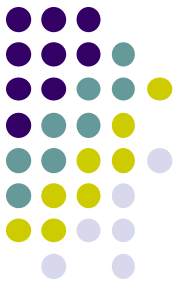
- Monitor lipids, LFTs, CK, muscle pain
- Assess for drug interactions
- Pregnancy advice for girls
- Lab checks at 1, 3, 6 months, then every 6 months
- Hold, then restart when symptoms resolve, for morbidity
- Reassess safety



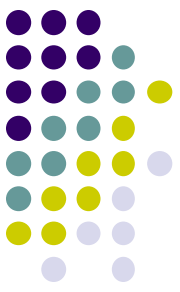
Homozygous FH

- Therapy begins at diagnosis regardless of age
- Statins, other agents may help but LDL apheresis usually necessary
- CVD monitoring critical
- Liver transplantation used in some centers
- ? Gene therapy

Pediatric Take Home Messages



- Universal screening for FH recommended at about age 10 years
- Treat FH with statins in childhood beginning at about age 10 years, younger if risk extreme
- Continue primordial prevention in FH patients
- Recognize homozygotes and refer to specialty centers



Treat All FH Patients

- Very high lifetime risk of coronary heart disease (CHD)
- Very high risk of premature onset CHD.
- Early treatment is highly beneficial.
 - Long term drug therapy of patients with FH removes the excess lifetime risk of CHD due to the genetic disorder, with a goal of reducing CHD risk to a level similar to that of the general population.
- FH requires lifelong treatment and regular follow-up.

Goldberg et al. *J Clinical Lipidology* 2011 5:133-140

Robinson JG, Goldberg A. *J Clinical Lipidol* 2011 5:S18-29

Evidence for Treating All FH Patients



- Untreated FH
 - Mean onset CVD
 - Men early 40's
 - Women in early 50's
 - 24 times higher risk of MI before age 40
- Long-term statin treatment largely ameliorates excess CVD risk due to FH
- Risk of long-term statin treated FH patients = Risk of general population

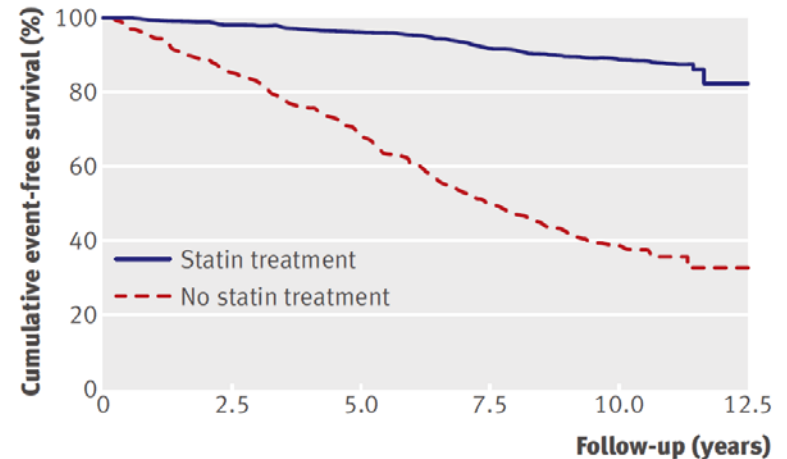
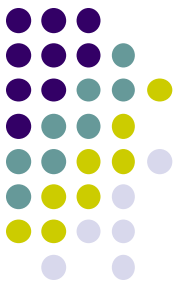


Fig 2 | Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment ($P < 0.001$ for difference)

Versmissen J, et al BMJ 2008; 337: a2423

Drug therapy required for almost all* FH patients



- Drug therapy required for children and adults if (after lifestyle changes)
 - **LDL-C ≥ 190 mg/dL OR**
 - **Non-HDL-C ≥ 220 mg/dL**
- For adult FH patients (≥ 20 years of age), drug treatment to **lower LDL-C $\geq 50\%$**
- **Statins** should be the initial treatment for all adults with FH.

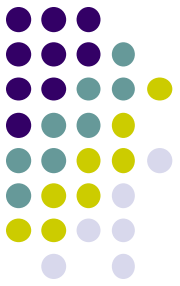
* Special considerations in women in child-bearing years: No statins, ezetimibe, or niacin during conception, pregnancy, or lactation

Highest Risk FH Patients = Intensify Drug Treatment

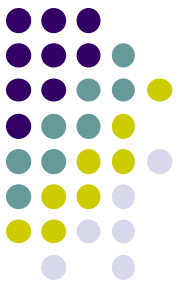


- Consider more aggressive treatment goals for highest risk FH patients
 - LDL cholesterol <100 mg/dL
 - Non-HDL cholesterol <130 mg/dL
- FH patients at highest risk
 - (very high risk compared to patients without FH)
 - Clinically evident CHD or other atherosclerotic CVD
 - Diabetes
 - Family history of very early CHD
 - Men <45 years of age or women <55 years of age
 - Current smoking
 - ≥ 2 CVD risk factors

Risk stratification algorithms should NEVER be used in FH patients



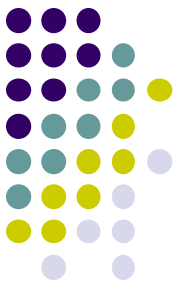
- Individuals with FH are at high short and long-term CHD risk.
 - **10-year CHD risk in the FH patient is not adequately predicted by any conventional risk assessment tools**
- 10-year assessment of risk is NOT recommended.
- All FH patients require treatment regardless of 10-year CHD risk
 - Lifestyle management
 - Very few will not require lipid-lowering drug therapy.



Lifestyle Modifications

- Diet
 - Reduce intakes of saturated fats and cholesterol: total fat 25-35% of total energy intake, saturated fatty acids $\leq 7\%$ of total energy intake, dietary cholesterol < 200 mg/d
 - Plant stanol or sterol esters (2 g daily)
 - Soluble fiber (10-20 g daily)
- Physical activity and caloric intake to achieve and maintain a healthy body weight
- Limit alcohol consumption
- Smoking cessation

Drug Treatment of FH



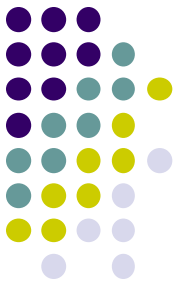
- Initial treatment with moderate to high doses of high-potency statins (simvastatin, atorvastatin, rosuvastatin, pitavastatin)
- Low-potency statins are generally inadequate
- Increase statin dose to maximum available or tolerable dose to achieve a LDL-C reduction $\geq 50\%$ from baseline
- If the initial statin is not tolerated, consider switching statins, or alternate day dosing
- If statins are contraindicated or poorly tolerated, ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred) may be considered

Additional Treatment Considerations



- If the patient is not at LDL-C treatment goal with the maximum available and tolerable dose of a statin, then combine with ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred).
- Decisions regarding selection of additional drug combinations should be based on concomitant risk factors for myopathy, concomitant medications, and the presence of other disease conditions and lipid abnormalities.

LDL Apheresis



- FDA-approved process of selectively removing Apo B-containing particles from the circulation through extracorporeal precipitation with either dextran sulphate cellulose or heparin
- Done every 1 to 2 weeks
- LDL apheresis typically removes at least 60% of the Apo B-containing lipoproteins at each procedure

Candidates for LDL Apheresis

Patients with inadequate response to maximum tolerated drug therapy:

- Functional homozygous FH patients with LDL-C ≥ 300 mg/dL (or non-HDL-C ≥ 330 mg/dL).
- Functional heterozygous FH patients with LDL-C ≥ 300 mg/dL (or non-HDL-C ≥ 330 mg/dL) and 0-1 risk factors.
- Functional heterozygous FH patients with LDL-C ≥ 200 mg/dL (or non-HDL-C ≥ 230 mg/dL) and high risk characteristics such as ≥ 2 risk factors or high lipoprotein (a) ≥ 50 mg/dL using an isoform insensitive assay.
- Functional heterozygous FH patients with LDL-C ≥ 160 mg/dL (or non-HDL-C ≥ 190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes).

LDL Apheresis Referrals

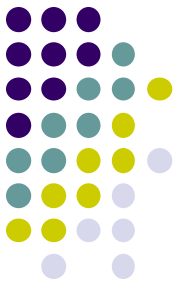
- Healthcare practitioners should refer candidates for LDL apheresis to qualified sites. Self-referrals are also possible. A listing of sites qualified to perform LDL apheresis is in development and will be posted on the National Lipid Association website (www.lipid.org).
- More than 400 patients in North America are receiving LDL apheresis therapy at more than 40 centers.
- There is a significant gap between the number of patients receiving LDL apheresis therapy and the number that, according to FDA guidelines, may qualify for LDL apheresis.

Women of Childbearing Age



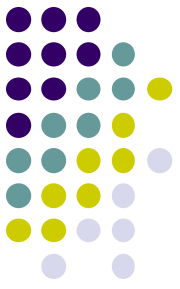
- Women with FH should receive pre-pregnancy counseling and instructions to stop statins, ezetimibe, and niacin at least four weeks before discontinuing contraception and should not use them during pregnancy and lactation.
- Consultation with her healthcare practitioner regarding continuation of any other lipid medications is recommended.
- In case of unintended pregnancy, a woman with FH should discontinue statins, ezetimibe, and niacin immediately and should consult with her healthcare practitioner promptly.

Treatment Options During Pregnancy



- Statins, ezetimibe, and niacin should not be used during pregnancy. Use of other lipid lowering medications (e.g., colesvelam) may be considered under the guidance of the healthcare practitioner.
- Consider LDL apheresis during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous FH.

Conclusions



- FH is a treatable disease
- It is underdiagnosed and undertreated
- Earlier recognition and appropriate treatment can decrease the risk of developing CHD
- Screen earlier and screen family members
- Potent statin and possibly combination therapy
- LDL apheresis for patients with inadequate response to therapy