**Introduction**

The Adult Treatment Panel III (ADT III) of the National Cholesterol Education Program (NCEP) recently issued a modification of their 2001 guidelines. Based on five major clinical trials of statin therapy involving more than 50,000 patients, more aggressive goals are established for patients in a newly created very high risk category. For people in the lower-risk categories, the goals and cut points of therapy remain the same.

**Relation of Serum LDL-C Concentrations to CHD Risk**

The new clinical trials verify the association between low-density lipoprotein cholesterol (LDL-C) concentrations and coronary heart disease (CHD). The risk is continuous but it is not linear. The risk rises more steeply with increasing LDL-C levels. For every 30 mg/dl increase in LDL-C, the relative risk for CHD is changed in proportion by about 30% (Figure 1). The new studies provide strong evidence to support the log-linear relationship between LDL-C levels and CHD risk. Note that no threshold effect exists for low LDL-C levels. The risk of CHD continues to improve as LDL-C concentration decreases.

**Risk factors have not changed**

The traditional risk factors for coronary artery disease include cigarette smoking, hypertension, hypertension under treatment, HDL-C below 40 mg/dl in males and below 50 mg/dl in females, family history of premature CHD (<55 y/o in a male first degree relative or <65 y/o in a female first degree relative), diabetes mellitus, and age (males >45 y/o and females >55 y/o).

**Therapeutic lifestyle changes to lower LDL**

- Cholesterol <200 mg/day
- Weight reduction to ideal body weight
- Increase physical activity (30 minutes/day)
- Increase fiber to 20ñ30 g/day

**Very High Risk**

For high-risk patients the goal is still LDL-C levels <100mg/dl, but for those at very high risk the new optional goal is LDL-C <70mg/dl. The factors that determine very high risk are as follows:

Established cardiovascular disease (includes stroke, peripheral vascular disease, aortic aneurysm) or CHD PLUS:

- Multiple major risk factors including diabetes and hypertension and family history.
- Poorly controlled risk factors (especially continued cigarette smoking).
- Multiple risk factors of the metabolic syndrome
  - High triglycerides > 200 mg/dl plus
  - Non-HDL-C > 130 mg/dl with
  - Low HDL-C < 40 mg/dl,
- An acute coronary event within the last two years

**What is non-HDL Cholesterol?**

The 2001 NCEP ADT III guidelines recommend use of non-HDL cholesterol (non-HDL-C) to judge risk in patients with triglycerides >200 mg/dl. The cholesterol inside of the beta lipoproteins (Apo B) is called the non-HDL-C. Non-HDL-C was added as a secondary target of therapy to take into account for the atherogenic potential associated with remnant lipoproteins (VLDL and IDL) in patients with

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hypertriglyceridemia. It is the beta lipoproteins particles that invade the blood vessel wall and form an atherosclerotic plaque, not just cholesterol. The non-HDL-C goal is 30 mg/dl higher than the LDL-C goal, eg, <160 or <130 mg/dl for the moderate and high-risk patients. The non-HDL-C is determined by subtracting HDL-C from the total cholesterol level.

Non-HDL-C is an estimation of beta lipoprotein concentration. If non HDL-C is elevated there are too many beta lipoprotein particles. The HDL particle has a surface apoprotein termed "A" or alpha. Accordingly, HDLs are referred to as the alpha lipoproteins. (A more definitive test for characterization of lipoprotein particle concentration (LDL, HDL, IDL, and VLDL) is the lipoprotein profile using NMR Spectroscopy: by LipoScience, Inc. in Raleigh, NC.)

**Formula for non-HDL-cholesterol**

Non-HDL cholesterol = Total cholesterol ñ HDL c

Additional Recommendations of the ADT III

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce risk through several mechanisms beyond LDL-C lowering.
- TLC should be initiated in all persons whose LDL-C level is > 130 mg/dl.
- Any person at high or moderate risk who has lifestyle-related factors (eg, obesity, physical inactivity, elevated triglycerides, low HDL-C or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
- Whenever the baseline LDL-C concentration is >100 mg/dl in moderate or high-risk patients, simultaneous initiation of an LDL-C lowering drug and dietary therapy is recommended.
- The optional goal of <70 mg/dl applies only to individuals who are very high risk.
- Drug therapy for moderate and high-risk persons should be sufficient to achieve at least 30% to 40% reduction in LDL-C levels.
- Although there is a potential benefit of raising HDL-C, current evidence of risk reduction is not sufficient to warrant setting a specific goal value for raising HDL-C. The recent lipid-lowering drug trials provide no new evidence for raising HDL-C when LDL-C is at desired level.

Screening Obstetric Patients For Hemoglobinopathies

In July 2000, the American College of Obstetrics and Gynecology (ACOG) Committee on Genetics issued an opinion statement, which recommended the screening of selected patients for hemoglobinopathies. (1) The United States is experiencing a constant diversification with an associated increase in the lines of ethnicity and a concomitant broadening of the geographic distribution of genetic diseases. Nevertheless, widespread screening of all individuals for possible hemoglobin disorders is not recommended. ACOG recommends that the obstetrician-gynecologist attempt to identify and screen patients/couples at increased risk for thalassemia or sickle cell disease. High-risk ethnic groups include those of African-American, Southeast Asian, or Mediterranean descent. Low risk groups include those of northern European, Japanese, Korean, Mexican, Native American, and Inuit (Eskimo) heritage.

Within the high-risk groups - those of African-American origin are at increased risk for sickle cell anemia, Southeast Asians are at increased risk for alpha thalassemia, and those with Mediterranean heritage are at increased risk for beta thalassemia. For this reason, a two-tiered approach to screening is recommended. A complete blood count including mean corpuscular volume (MCV) is recommended as an initial study for patients at increased risk for alpha or beta thalassemia. Patients with microcytic RBCs (low MCV) may have a hemoglobinopathy. Due to the risk of sickle cell disease, hemoglobin electrophoresis is recommended for all patients of African-American ancestry. After excluding iron deficiency, a hemoglobin electrophoresis is recommended to evaluate for the presence of an abnormal hemoglobin (e.g. Hb C or Hb S) or beta thalassemia (elevated Hb A2).

Hemoglobin electrophoresis will not detect the carrier state of alpha thalassemia state. Alpha-globin gene analysis (Mayo Medical Laboratories test #9499, $527) by Southern blot and polymerase chain reaction is necessary for diagnosis of alpha-thalassemia or the carrier state. Patients, especially those with Southeast Asian heritage, who have low MCV, normal iron studies, and a normal hemoglobin electrophoresis, should be considered for molecular testing to detect alpha thalassemia. Testing of the partners of any obstetric patients with abnormal screening results is recommended to assess reproductive risk. The recommendations are summarized in the accompanying algorithm (Antepartum Evaluation for Hemoglobinopathy).

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References


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**References**


(In the interest of full public disclosure - the author of this report owns stock in Merck and Pfizer, while the editor of this bulletin owns stock in Pfizer.)
Surgical Tissue Procurement for UNC Tissue Bank

Rex has been providing tissue for the UNC Lineberger Comprehensive Cancer Center Tissue Procurement Facility for a little over two years. The UNC tissue bank was developed in 1995 to provide high quality neoplastic (and non-neoplastic) tissue for research protocols involving the diagnosis and management of cancer. While formalin fixed, paraffin-embedded tissue may be used for some research protocols, fresh frozen tissue is preferred. All specimens are coded to assure patient confidentiality. The Institutional Review Boards (IRB) at UNC and Rex has approved the program. Tissue is released only to research protocols approved by the UNC IRB. Dr. Lisa Tolnitch and Dr. Keith Nance began the program at Rex in 2001-2002, with an emphasis on obtaining tissue from breast cancer cases. In 2003 the procurement program was expanded to include a wider variety of specimens obtained from the operating rooms at Rex. As a result, 313 specimens were collected at Rex last year for the tissue bank.

Examples of Tissue Use to Date (No Clinical Follow-Up)

1. Methods Development
   a. Optimize/characterize antibodies for immunohistochemistry stains (IHC)
   b. Development of dual/sequential assay methods: IHC/IHC; IHC/fluorescence in situ hybridization (FISH)
   c. RNA expression assays

2. Evaluation of gene expression/protein expression/gene amplification/gene mutation in neoplasms
   a. DNA studies
      i. DNA mutational analysis (e.g. frequency of p53 missense mutations vs. frame shift; correlation w/ IHC.)
      ii. DNA arrays (e.g. unique genes in comedo DCIS of breast vs. proliferative non-neoplastic breast tissue)
   b. RNA expression studies
      i. Breast cancer
      ii. Head and neck cancer

Examples of Potential Tissue Use (Coded specimens with clinical follow-up)

1. Predict prognosis
   a. Single marker studies (e.g. p53, Her2-neu, ERA, PRA, EGFR)
   b. Multiple marker studies (e.g. CD34/p53, Her2-neu/ERA, e-cadherin/PR or DNA/RNA arrays)

2. Predict response to therapy
   a. Her2-neu in breast cancer
   b. EGFR in lung cancer

3. Predict toxic responses
   a. Response to oral capecitabine
   b. Polymorphisms in DNA (racial, ethnic, geographic variations predispose to toxic side effects)

Advantages to Rex Patients

There is no direct benefit to Rex patients for participation in the tissue procurement. Neither patients nor their physicians receive results from any research performed on tissue samples. Donation of tissue to the bank may benefit future cancer patients by the development of new tools and therapies for cancer management, with a particular emphasis on individualized therapy based on the genetic/molecular characteristics of the tumor and/or patient.

Risks to Patients

Minimal. Tissue is donated only after the attending pathologist determines that there is sufficient tissue to adequately characterize the neoplasm and determine relevant parameters (e.g. tumor size, margin status) necessary for patient care. No specimen is released to the tissue bank until a final pathologic diagnosis is obtained. If the Rex pathologist determines that tissue originally donated to the tissue bank requires microscopic review, the tissue is returned to the Rex Pathology Department. All specimens donated to the tissue bank have a representative area sampled for microscopic review by the UNC tissue bank pathologist to confirm that representative tissue was procured for quality assurance purposes.

All specimens are de-identified and assigned a code number at the time of accessioning by tissue bank staff. The database has restricted access and the consent forms are stored securely. No patient identifying data is stored with tissue samples or released to investigators.

There are no costs to patients or their insurance providers for participating in the tissue procurement program.

Patient Eligibility

Only adult patients (18 y.o. or older) who consent prior to surgery are eligible. Patients with infections known to render tissue a biohazard (e.g. HIV infection, hepatitis B, tuberculosis) should be excluded from consideration.
Individuals undergoing excision of a relatively large neoplasm are ideal candidates for participation in this project. Patients undergoing diagnostic needle, endoscopic or incisional biopsy should not be considered candidates.

**Rex Tissue Procurement Protocol**

The following protocol was developed with the cooperation of the UNC Tissue Bank, Rex Pathology Laboratory and Rex Surgical Services with the intention of developing a standardized approach to obtaining patient consent with minimal disruption to workflow in the operating room and pathology laboratory. Surgeons/gynecologists may elect to consent their patients individually, but OR surgical nurses will consent the majority of patients as follows:

a. Rex pathologist and Rex Tissue Bank technologist review OR schedule the day prior to surgery, highlighting potential candidates for tissue donation.

b. Rex OR staff approach potential candidates in pre-operative or surgical prep area to inform them of tissue procurement program and invite their participation. Informational brochures are provided.

c. Patients agreeing to participate sign pink consent forms.

d. Consent form accompanies surgical specimen and histology requisition delivered to pathology laboratory. Specimen may be submitted in formalin or fresh at the discretion of the attending surgeon. Fresh specimens are encouraged in cases where a large volume of recognizable tumor is anticipated. It is important to communicate to the pathologist whether the specimen is being sent fresh for an OR Consult/Frozen Section requested by the attending surgeon/gynecologist, or simply to facilitate harvesting of fresh tissue for UNC Tissue Bank. There is no OR Consult charge to the patient for pathologist evaluation of a fresh specimen submitted only for tissue procurement purposes. However, those specimens will not receive the same (hopefully immediate) attention given to fresh specimens sent for OR Consult/Frozen Section evaluation, particularly in situations where specimens from several patients are received simultaneously.

e. The Rex pathologist will evaluate the specimen and determine if there is sufficient/appropriate tissue for donation to the tissue bank.

f. The Rex tissue bank technologist will assign a code to the specimen and process the tissue further depending on the nature of the specimen (fresh vs. formalin-fixed). Portions of fresh specimens are snap-frozen in liquid N2. The only information recorded with the code is the patient's age, gender, and final pathology diagnosis.

g. Tissue transferred to UNC Tissue Bank for storage and quality assurance studies. Consent forms secured at UNC Tissue Bank.

**Calling All Rex Surgeons/Gynecologists**

Your cooperation in procuring tissue for the UNC Tissue Bank is solicited. We ask that you and your patients consider this opportunity to assist in cancer research, particularly for patients who will undergo resection of large tumors. Generally only a few (quality) blocks are needed to characterize most neoplasms. Any excess tumor removed is currently destroyed in a relatively short time after the final diagnosis is rendered. The tissue procurement program provides patients the opportunity to benefit society by use of excess tissue in the development of novel therapies to fight cancer. A few words from you during a pre-operative evaluation will assist the OR nursing staff obtaining consent on the day of surgery. If a relatively large amount of tumor is expected, consider sending the specimen to the lab fresh for tissue procurement.

John D. Benson, MD

Reference:

1. Dressler, L (Director of UNC Tissue Procurement Facility). Lecture notes and personal communication (August 3, 2004).
Southeast Asian or Mediterranean descent

- CBC with RBC indices
  - No abnormality
  - Microcytic anemia (low MCV) and normal iron studies
    - Hemoglobin electrophoresis
      - Normal
        - If Southeast Asian, consider studies for alpha thalassemia
          - Not a carrier
          - Alpha thalassemia carrier
            - Offer testing to partner to assess risk to offspring

African-American descent

Modified from reference #1