UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HIKMA PHARMACEUTICALS USA INC.,
HIKMA PHARMACEUTICALS PLC,
Petitioner,

v.

AMARIN PHARMACEUTICALS IRELAND LIMITED,
Patent Owner.

Case IPR2022-00215
Patent 8,642,077 B2
Issued: February 4, 2014

Title: STABLE PHARMACEUTICAL
COMPOSITION AND METHODS OF USING SAME

DECLARATION OF SYLVIA D. HALL-ELLIS, PH.D.

I. INTRODUCTION

1. My name is Sylvia D. Hall-Ellis. I have been retained as an expert by Hikma Pharmaceuticals USA Inc. and Hikma Pharmaceuticals PLC (together, "Hikma"), the Petitioner.

2. I have written this declaration at the request of Hikma to provide my expert opinion regarding the authenticity and public availability of several journal publications, books, and documents. My declaration sets forth my opinions in detail and provides the basis for my opinions regarding the authenticity and public availability of these publications.

3. I reserve the right to supplement or amend my opinions, and bases for them, in response to any additional evidence, testimony, discovery, argument, and/or other additional information that may be provided to me after the date of this declaration.

4. I am being compensated for my time spent working on this matter at my normal consulting rate of $325 per hour, plus reimbursement for any additional reasonable expenses. My compensation is not in any way tied to the content of this declaration, the substance of my opinions, or the outcome of this proceeding. I have no other interests in this proceeding or with any of the parties.

5. All of the materials that I considered are discussed explicitly in this declaration.

II. QUALIFICATIONS

6. I am currently an Adjunct Professor in the School of Information at San José State University. I obtained a Master of Library Science from the University of North Texas in 1972 and a Ph.D. in Library and Information Science from the University of Pittsburgh in 1985. Over the last fifty years, I have held various positions in the field of library and information resources. I was first employed as a librarian in 1966 and have been involved in the field of library sciences since, holding numerous positions.

7. I am a member of the American Library Association (ALA) and its Association for Library Collections & Technical Services (ALCTS) Division, and I served on the Committee on Cataloging: Resource and Description (which wrote the new cataloging rules) and as the chair of the Committee for Education and Training of Catalogers and the Competencies and Education for a Career in Cataloging Interest Group. I also served as the Chair of the ALCTS Division's Task Force on Competencies and Education for a Career in Cataloging. Additionally, I have served as the Chair for the ALA Office of Diversity's Committee on Diversity, as a member of the national Board of Directors for REFORMA, and as a member of the Editorial Board for the ALCTS premier cataloging journal, *Library Resources and Technical Services*. Currently I serve as a Co-Chair for the Library Research Round Table of the American Library Association.

8. I have also given over one hundred presentations in the field, including several on library cataloging systems and Machine-Readable Cataloging ("MARC") standards. My current research interests include library cataloging systems, metadata, and organization of electronic resources.

9. My full curriculum vitae is attached hereto as Attachment 9 to this declaration.

III. LIBRARY CATALOGING PRACTICES

10. I am fully familiar with the library cataloging standard known as the MARC standard, which is an industry-wide standard method of storing and organizing library catalog information.[1] MARC was first developed in the 1960s by the Library of Congress. A MARC-compatible library is one that has a catalog consisting of individual MARC records for each of its items. Today, MARC is the primary communications protocol for the transfer and storage of bibliographic metadata in libraries.[2]

---

[1] The full text of the standard is available from the Library of Congress at http://www.loc.gov/marc/bibliographic/.

[2] Almost every major library in the world is MARC-compatible. *See, e.g.*, *MARC Frequently Asked Questions (FAQ)*, Library of Congress, https://www.loc.gov/marc/faq.html (last visited October 18, 2021) ("MARC is the acronym for MAchine-Readable Cataloging. It defines a data format that emerged from a Library of Congress-led initiative that began nearly fifty years ago. It provides the mechanism by which computers exchange, use, and interpret bibliographic information, and its data elements make up the foundation of most

11. A MARC record comprises several fields, each of which contains specific data about the work. Each field is identified by a standardized, unique, three-digit code corresponding to the type of data that follow. For example, a work's title is recorded in field 245, the primary author of the work is recorded in field 100, an item's International Standard Book Number ("ISBN") is recorded in field 020, an item's International Standard Serial Number ("ISSN") is recorded in field 022, an item's Library of Congress call number is recorded in field 050, and the publication date is recorded in field 260 under the subfield "c." If a work is a periodical, then its publication frequency is recorded in field 310, and the publication dates (e.g., the first and last publication) are recorded in field 362, which is also referred to as the enumeration/chronology field.

12. The library that created the record is recorded in field 040 in subfield "a" with a unique library code. When viewing the MARC record online via Online Computer Library Center's ("OCLC") bibliographic database, hovering over this code with the mouse reveals the full name of the library. I used this method of "mousing over" the library codes in the OCLC database to identify the originating library for the MARC records discussed in this declaration. Where this "mouse over" option was not available, I consulted the Directory of OCLC Libraries in order

---

library catalogs used today."). MARC is the ANSI/NISO Z39.2-1994 (reaffirmed 2016) standard for Information Interchange Format.

to identify the institution that created the MARC record.[3]

13. MARC records also include several fields that include subject matter classification information. An overview of MARC record fields is available through the Library of Congress.[4] For example, 6XX fields are termed "Subject Access Fields."[5] Among these, for example, is the 650 field; this is the "Subject Added Entry – Topical Term" field.[6] The 650 field is a "[s]ubject added entry in which the entry element is a topical term." These entries "are assigned to a bibliographic record to provide access according to generally accepted thesaurus-building rules (e.g., *Library of Congress Subject Headings* (LCSH), *Medical Subject Headings* (MeSH))." Further, MARC records include call numbers, which themselves include a classification number. For example, the 050 field is the "Library of Congress Call Number."[7] A defined portion of the Library of Congress Call Number is the classification number, and "source of the classification number is *Library of Congress Classification* and the *LC Classification-Additions and Changes*." Thus, included in the 050 field is a subject matter classification. Each item in a library has a single classification number. A library selects a classification scheme (*e.g.*, the

[3] https://www.oclc.org/en/contacts/libraries.html.
[4] http://www.loc.gov/marc/bibliographic/.
[5] http://www.loc.gov/marc/bibliographic/bd6xx.html.
[6] http://www.loc.gov/marc/bibliographic/bd650.html.
[7] http://www.loc.gov/marc/bibliographic/bd050.html.

Library of Congress Classification scheme just described or a similar scheme such as the Dewey Decimal Classification scheme) and uses it consistently. When the Library of Congress assigns the classification number, it appears as part of the 050 field. If a local library assigns the classification number, it appears in a 090 field. In either scenario, the MARC record includes a classification number that represents a subject matter classification.

14. The OCLC was created "to establish, maintain and operate a computerized library network and to promote the evolution of library use, of libraries themselves, and of librarianship, and to provide processes and products for the benefit of library users and libraries, including such objectives as increasing availability of library resources to individual library patrons and reducing the rate of rise of library per-unit costs, all for the fundamental public purpose of furthering ease of access to and use of the ever-expanding body of worldwide scientific, literary and educational knowledge and information."[8] Among other services, OCLC and its members are responsible for maintaining the WorldCat database,[9] used by independent and institutional libraries throughout the world.

15. OCLC also provides its members online access to MARC records

---

[8] Third Article, Amended Articles of Incorporation of OCLC Online Computer Library Center, Incorporated (available at https://www.oclc.org/content/dam/oclc/membership/articles-of-incorporation.pdf).
[9] http://www.worldcat.org/.

through its OCLC bibliographic database. When an OCLC member institution acquires a work, it creates a MARC record for this work in its computer catalog system in the ordinary course of its business. MARC records created at the Library of Congress are directly uploaded or may be tape-loaded into the OCLC database through a subscription to MARC Distribution Services daily or weekly. Once the MARC record is created by a cataloger at an OCLC member institution or is tape-loaded from a participating institution, the MARC record is then made available to any other OCLC members online, and therefore made available to the public. Accordingly, once the MARC record is created by a cataloger at an OCLC member institution or is tape-loaded from the Library of Congress or another library anywhere in the world, any publication corresponding to the MARC record has been cataloged and indexed according to its subject matter such that a person interested in that subject matter could, with reasonable diligence, locate and access the publication through any library with access to the OCLC bibliographic database or through the Library of Congress.

16. When an OCLC member institution creates a new MARC record, OCLC automatically supplies the date of creation for that record. The date of creation for the MARC record appears in the fixed field (008), characters 00 through 05. The MARC record creation date reflects the date on which, or shortly after which, the item was first acquired or cataloged. Initially, field 005 of the MARC

record is automatically populated with the date the MARC record was created in year, month, day format (YYYYMMDD) (some of the newer library catalog systems also include hour, minute, second (HHMMSS)). Thereafter, the library's computer system may automatically update the date in field 005 every time the library updates the MARC record (*e.g.*, to reflect that an item has been moved to a different shelving location within the library). Field 005 is visible when viewing a MARC record via an appropriate computerized interface, but when a MARC record is printed to hardcopy, no "005" label appears. The initial field 005 date (*i.e.*, the date the MARC record was created) does appear, however, next to the label "Entered."[10] The date upon which the most recent update to field 005 occurred also appears, next to the label "Replaced." Thus, when an item's MARC record has been printed to hardcopy—as is the case with the exhibits to this declaration—the date reflected next to the label "Entered" is necessarily on or after the date the library first cataloged and indexed the underlying item.

17. Once one library has cataloged and indexed a publication by creating a MARC record for that publication, other libraries that receive the publication do not

[10] In this declaration, I sometimes refer to the "Entered" entry as Field 008, characters 00-05. Field 005 is visible when viewing a MARC record via an appropriate computerized interface. But when a MARC record is printed directly to hardcopy from the OCLC database, the "005" label is not shown. The date in the 005 field instead appears next to the label "Replaced."

create additional MARC records—the other libraries instead rely on the original MARC record. They may update or revise the MARC record to ensure accuracy, but they do not replace or duplicate it. This practice does more than save libraries from duplicating labor. It also enhances the accuracy of MARC records. Further, it allows librarians around the world to know that a particular MARC record is authoritative (in contrast, a hypothetical system wherein duplicative records were created would result in confusion as to which record is authoritative).

18. The date of creation of the MARC record by a cataloger at an OCLC member institution reflects when the underlying item is accessible to the public. Upwards of two-thirds to three-quarters of book sales to libraries come from a jobber or wholesaler for online and print resources. These resellers make it their business to provide books to their customers as fast as possible, often providing turnaround times of only a single day after publication. Libraries purchase a significant portion of the balance of their books directly from publishers themselves, which provide delivery on a similarly expedited schedule. In general, libraries make these purchases throughout the year as the books are published and shelve the books as soon thereafter as possible in order to make the books available to their patrons. Thus, books are generally available at libraries across the country within just a few days of publication.

19. Catalogers can create MARC records for all types of print, online, and

digital resources. For example, MARC records cover serial publications, including both serially-published monographs and journals. OCLC hosts MARC records for more than 320 million serial publications. Serial publications are those publications that have the same collective title but are intended to be continued indefinitely with enumeration such as a volume or issue number (*e.g.*, magazines, journals, etc.). In the OCLC bibliographic database, the first issue or volume of the monographic serial is typically cataloged (*i.e.*, a corresponding MARC record is created), but the date is left open-ended with the use of a punctuation mark such as a dash. MARC records for serial publications represent the entire run of the title. With knowledge of the first issue or volume published, future issues or volumes can be predicted based on the information provided in the MARC record, for example in field 362. In my extensive professional experience, is it highly unusual for a library to stop collecting and shelving a serial publication prior to the time of its cessation. If a subscription to a serial publication ends or is cancelled, the library will denote that it has stopped receiving new issues or volumes by filling in the end date in the MARC record.

20. The handling of printed journal subscriptions is shown on the covers of individual issues. As was the best practice among libraries, issues arrived at a central facility and were immediately received, verified as part of a subscription, checked in, and stamped with the institution's name and date. Determining that the issue was part of the library subscription ensured that the entire set of publications for the year

had been received so that they could be professionally bound and retained. This process also verified that each of the published issues arrived so that the library staff did not have to request or claim an issue that did not arrive as expected. In large public libraries with branches and multi-campus libraries within academic institutions, the journals were sorted and delivered to the subscribing unit. The issues were frequently stamped again to acknowledge receipt. The new issue was placed in the public area; the older issue was stored so that it remained available.

21. The foregoing process has been standard library practice longer than I have been working in the profession. I first learned the steps in the process in the late 1970s and later supervised it. Although the checking in process has become automated and now links electronically to holdings records for the MARC record for each serial title, the manual stamping and placing the issue in a public area has not changed for 50 years. Unless I note otherwise below in reference to a specific serial publication, it is my expert opinion that this standard protocol was followed for each of the serial publications discussed below.

22. In preparing this declaration, I used authoritative databases, such as the OCLC bibliographic database and the Library of Congress Online Catalog, to confirm citation details of the various publications discussed.

23. *Indexing*. A researcher may discover material relevant to his or her topic in a variety of ways. One common means of discovery is to search for relevant

information in an index of periodical and other publications. Having found relevant material, the researcher will then normally obtain it online, look for it in libraries, or purchase it from the publisher, a bookstore, a document delivery service, or other provider. Sometimes, the date of a document's public accessibility will involve both indexing and library date information. However, date information for indexing entries is often unavailable. This is especially true for online indices.

24. Indexing services use a wide variety of controlled vocabularies to provide subject access and other means of discovering the content of documents. The formats in which these access terms are presented vary from service to service.

25. Online indexing services commonly provide bibliographic information, abstracts, and full-text copies of the indexed publications, along with a list of the documents cited in the indexed publication. These services also often provide lists of publications that cite a given document. A citation of a document is evidence that the document was publicly available and in use by researchers no later than the publication date of the citing document.

26. Before the widespread development of online databases to index articles in journals, magazines, conference papers, and technical reports, libraries purchased printed volumes of indices. Graduate library school education mandated that students learn about the bibliographic control of disciplines, the prominent indexing volumes, and searching strategies required to use them effectively and

efficiently. Half of the courses that I studied in library school were focused on the bibliography and resources in academic disciplines.

27. Librarians consulted with information seekers to verify citations, check availability in union catalogs, printed books catalogs, the OCLC database, and make formal requests for materials (e.g., books, conference proceedings, journal articles). Requests were transmitted using Telex machines, rudimentary email systems, and the United States Postal Service. During my career, I have performed and supervised staff who handled these resource sharing tasks.

28. A major firm known for the breadth of subjects and comprehensive treatment in the preparation of index volumes, the H. W. Wilson Company offered these reference resources since the firm was founded in 1898. The *Reader's Guide to Periodical Literature* is one of the best-known titles available from H. W. Wilson. Each volume includes a comprehensive index for 300 of the most popular and important periodicals in the United States and Canada. Information seekers have subject access expressed in plain language terminology, author access, and cross references to find the desired results from their searches. The family of index titles included *Science & Technology Index*, *Business Periodicals*, *Applied Science & Technology Index, Humanities Index, Biological & Agricultural Index*, and *Industrial Arts Index*. These printed indices have been superseded by digital database offerings available to information seekers through Ebsco.

29. Information seekers also used printed versions of *Chemical Abstracts* and *Index Medicus* to locate articles, scientific reports, and research papers. *Chemical Abstracts* began publication in 1907 and by 2007 its databases "contained more than 27 million records of journal and patent literature."[11] In 2010, *Chemical Abstracts* discontinued the print index. Access is now available through two electronic databases: *CAplus* and *Registry*.[12] *Index Medicus* is a bibliographic index to medical science information, started in 1879.[13] Currently, *PubMed* includes the content that had been published as *Index Medicus*.[14]

30. Established in 1836 as part of the Surgeon General of the Army's Office, the National Library of Medicine (NLM) has been instrumental in the development of access to medical books, journals, and research publications. In the

---

[11] Chemical Abstracts Service, "CAS History," *available at* https://www.cas.org/about/cas-history (last accessed October 18, 2021); American Chemical Society, "Chemical Abstracts Service," *available at* https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/cas.html (last accessed October 18, 2021).

[12] American Chemical Society, "Chemical Abstracts Service," *available at* https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/cas.html (last accessed October 18, 2021).

[13] Stephen Greenberg and Patricia Gallagher, "The great contribution: *Index Medicus*, *Index-Catalogue*, and IndexCast," *Journal of Medical Library Association*, April 2009, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2670211/ (last accessed October 18, 2021).

[14] U.S. National Library of Medicine, "List of All Journals Cited in PubMed®," https://www.nlm.nih.gov/bsd/serfile_addedinfo.html (last accessed October 18, 2021).

1970s, NLM introduced MEDLINE, followed by "the establishment of the National Center for Biotechnology Information in 1988, the introduction of free MEDLINE in 1997, the creation of consumer-friendly MedlinePlus in 1998, and the introduction of ClinicalTrials.gov in 2000."[15]

31. Online indexing services such as Google Scholar[16] or ScienceDirect[17] commonly provide bibliographic information, abstracts, and full-text copies of the indexed publications, along with a list of the documents cited in the indexed publication. These services also often provide lists of publications that cite a given document.

32. A citation of a document by another is evidence that the document was publicly available and in use no later than the publication date of the citing document.

IV. PRELIMINARIES

33. *Scope of this declaration.* I am not an attorney and will not offer opinions on the law. I am, however, rendering my expert opinion on the authenticity of the documents referenced herein and when and how each of these documents was disseminated or otherwise made publicly available to the extent that persons

---

[15] U.S. National Library of Medicine, "A Brief History of NLM," available at https://www.nlm.nih.gov/about/briefhistory.html.
[16] https://scholar.google.com/.
[17] https://www.sciencedirect.com/.

interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, could have located the documents before April 29, 2008.

34. I am informed by counsel that a printed publication qualifies as publicly accessible as of the date it was disseminated or otherwise made available such that a person interested in and ordinarily skilled in the relevant subject matter could locate it through the exercise of ordinary diligence.

35. While I understand that the determination of public accessibility under the foregoing standard rests on a case-by-case analysis of the facts particular to an individual publication, I also understand that a printed publication is rendered "publicly accessible" if it is cataloged and indexed by a library such that a person interested in the relevant subject matter could locate it exercising reasonable diligence (*i.e.*, I understand that cataloging and indexing by a library in a manner that permits a person of ordinary skill in the relevant subject matter to locate the publication is sufficient, though there are other ways that a printed publication may qualify as publicly accessible). One manner of sufficient indexing is indexing according to subject matter category. I understand that the cataloging and indexing by a single library of a single instance of a particular printed publication is sufficient, even if the single library is in a foreign country. I understand that, even if access to a library is restricted, a printed publication that has been cataloged and indexed therein is publicly accessible so long as a presumption is raised that the portion of

the public concerned with the relevant subject matter would know of the printed publication. I also understand that the cataloging and indexing of information that would guide a person interested in the relevant subject matter to the printed publication, such as the cataloging and indexing of an abstract for the printed publication, is sufficient to render the printed publication publicly accessible.

36. I understand that routine business practices, such as general library cataloging and indexing practices, can be used to establish an approximate date on which a printed publication became publicly accessible.

37. *Persons of ordinary skill in the art*. I am told by counsel that the subject matter of this proceeding relates generally to the field of treating cardiovascular-related diseases and lipid disorders.

38. I have been informed by counsel that a person of ordinary skill in the art ("POSA") is a hypothetical person who is presumed to be familiar with the relevant field and its literature at the time of the alleged invention. This hypothetical person is also a person of ordinary creativity, capable of understanding the scientific principles applicable to the pertinent field.

39. I am informed by counsel that a POSA for purposes of this proceeding would have had (1) a medical degree; (2) several years of experience in the development and/or clinical use of fatty acids to treat cardiovascular, endocrine, and/or lipid disorders, including fish-oil-based fatty acids, i.e., EPA and/or DHA,

and their dosage forms; and (3) access to a team including one or more of an analytical chemist, pharmaceutical chemist, formulator, or biostatistician.

40. It is my opinion that such a person would have been engaged in research, learning through study and practice in the field and possibly through formal instruction the bibliographic resources relevant to his or her research. In the late-1990s such a person would have had access to a vast array of long-established print resources in cardiology and/or lipidology and/or endocrinology as well as to a rich set of online resources providing indexing information, abstracts, and full text services for cardiology and/or lipidology and/or endocrinology references.

41. Based on my experience working in research libraries with researchers having the qualifications described above, or even lesser qualifications, it is my opinion that such researchers would have been able to locate the material discussed herein on their own or with the assistance of a research librarian with relative ease using the tools and resources described herein.

V. PUBLICATIONS

A. Document 1: Exhibit 1008 ("ATP-III")

42. Attached hereto as Attachment 1 is a copy of a report from Volume 106, Number 25 of the journal *Circulation* found in the National Agricultural Library (Beltsville, Maryland). The "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment

of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report" (hereafter "ATP-III") appears beginning on page 3143 of this issue dated December 17, 2002. Attachment 1 is a true and correct copy of the nine-part report. Attachment 1 is a true and correct copy of the issue cover, table of contents, and the nine parts (pages 3157-3421). I obtained copies of Parts 1 through 8 from the National Agricultural Library and downloaded Part 9 from the journal website. Specifically, the text of the column is complete; no pages are missing, and the text on each page appears to flow seamlessly from one page to the next; further, there are no visible alterations to the document. Attachment 1 was found within the custody of a library and/or the publisher itself – places where, if authentic, a copy of this journal would likely be. Attachment 1 is a true and correct copy in a condition that creates no suspicion about its authenticity.

43. The cover of the December 17, 2002, issue of the journal *Circulation* has a stamp affixed at the National Agricultural Library which shows that it was received, verified, and checked in on December 28, 2002. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals to show when a reference was received, verified, and checked. Therefore, in my experience, the issue of the journal *Circulation* in which ATP-III appears would have been available to users at the National Agricultural Library on that date.

44. Attached hereto as Attachment 1a is a true and correct copy of the MARC record for the journal *Circulation* in the National Agricultural Library online catalog. The library ownership is indicated by the presence of the library's code (AGL) in the 049 field. The most recent enhancement to Attachment 1a occurred on June 26, 2020, as shown in field 005 ("20200626"). I personally identified and retrieved the MARC record that is Attachment 1a. Attachment 1a also shows that ATP-III was catalogued with three descriptor terms reading "Cardiology $v Periodicals" (see Attachment 1b, Library of Congress subject heading sh2008117649), "Cardiovascular system $v Periodicals" (see Attachment 1c, National Library of Congress subject heading sh85020226 and Attachment 1d, Library of Congress subject heading sh85099890), and "Hypertension $v Periodicals" (see Attachment 1e, Library of Congress subject heading sh85063723 and Attachment 1d, Library of Congress subject heading sh85099890) in the 650 fields.

45. Based on finding a print copy of ATP-III in the National Agricultural Library and MARC record in its online library catalog attached as Attachment 1a, it is my opinion that ATP-III published in the journal *Circulation* was publicly available on December 28, 2002.

46. As noted in the holdings information (field 362), the National Agricultural Library has subscribed to the journal *Circulation* since publication

began in January 1950 and continues to receive the publication in print and digital versions. In view of the MARC record for ATP-III, ATP-III was publicly available in print on December 28, 2002, because the serial title had been received, cataloged, and indexed in the National Agricultural Library and made part of its catalog.

47. Attached hereto as Attachment 1f is a true and correct copy of the MARC record for the journal *Circulation* obtained from the OCLC bibliographic database. I personally identified and retrieved the MARC record that is Attachment 1f. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 1f, that library code is "MUL," which means that the MARC record for this serial was cataloged as part of the Minnesota Union List of Serials at the University of Minnesota Libraries (Minneapolis, Minnesota). As can be seen in the "Entered" field in the MARC record for this exhibit, a cataloger at the University of Minnesota Libraries created OCLC record number 1554748 on August 17, 1975. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 1f occurred on July 31, 2020, as shown in the "Replaced" field ("20200731"). The "BLvl" entry in Attachment 1f is "s," which indicates that the journal *Circulation* is a serial publication. Field 310 of Attachment 1f reads "Weekly (except the first two weeks in Jan. and the last two weeks in Dec.), $b <Apr. 8, 2003-." Accordingly, the MARC record for ATP-III corresponds to

those issues of the journal *Circulation* during the time that ATP-III was published.

48. Attachment 1f further includes an entry in field 050 ("RC681.A1 $b C5")—as described above, this includes a subject matter classification number consistent with the Library of Congress classification system (analogous to the Dewey Decimal classification system); an entry in field 060 ("W1 $b CI743")—as described above, this includes a subject matter classification number consistent with the National Library of Medicine classification system (analogous to the Dewey Decimal classification system); and an entry in field 082 ("616.105")—as described above, this includes a subject matter classification number consistent with the Dewey Decimal classification system. Attachment 1f further includes three descriptor terms reading "Cardiology $v Periodicals" (see Attachment 1b, Library of Congress subject heading sh2008117649), "Cardiovascular system $v Periodicals" (see Attachment 1c, National Library of Congress subject heading sh85020226 and Attachment 1d, Library of Congress subject heading sh85099890), and "Hypertension $v Periodicals" (see Attachment 1e, Library of Congress subject heading sh85063723 and Attachment 1d, Library of Congress subject heading sh85099890) in the 650 fields. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 1f was indexed according to its subject matter by virtue of at least four independently sufficient classifications: the field 050 entry, the field 060 entry, the field 082 entry, and the

field 650 entries. Further, as of August 17, 1975, the MARC record attached hereto as Attachment 1f was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that subscribed to the serial, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library. Therefore, ATP-III was publicly accessible in print as early as December 28, 2002, because by that time it had been received, cataloged, and indexed at the National Agricultural Library.

49. Attachment 1f indicates that the journal *Circulation* as cataloged at the University of Minnesota Libraries is currently available from 1,155 libraries. In view of the above, this issue of the journal *Circulation* was publicly available in print on December 28, 2002, because by that date it had been cataloged and indexed at the University of Minnesota Libraries, made part of the OCLC bibliographic database, and received at the National Agricultural Library. For these reasons, it is my opinion that ATP-III was published and accessible to the public on December 28, 2002.

50. Further supporting my opinion that ATP-III was publicly accessible to ordinarily skilled and interested researchers in the field is the fact that the journal *Circulation* was included in several well-known indices, including *BIOSIS, CAB Abstracts, Chemical Abstracts, Current Contents, EMBASE,* and *MEDLINE* (s*ee*

field 510 entry in Attachment 1a and Attachment 1f, and publisher's website.[18] As noted above, this would have provided a POSA with keyword searching capabilities and other tools to locate this article.

51. I have examined Exhibit 1008, provided by counsel, which is a copy of ATP-III. The text of Exhibit 1008 is substantively identical to the corresponding material in Attachment 1. Thus, in my opinion, Exhibit 1008 and Attachment 1 are authentic copies of ATP-III, which is a printed publication that was publicly accessible before April 29, 2008.

B. Document 2: Exhibit 1007 ("Grimsgaard")

52. Attached hereto as Attachment 2 is a copy of an article from Volume 66, Issue 3 of *The American Journal of Clinical Nutrition* found in the University of Wisconsin – Oshkosh Libraries. The article "Highly Purified Eicosapentaenoic Acid and Docosahexaenoic Acid in Humans Have Similar Triacylglycerol-Lowering Effects but Divergent Effects on Serum Fatty Acids" by Sameline Grimsgaard, Kaare H. Bønaa, John-Bjame Hansen and Arne Nordøy (hereafter "Grimsgaard") appears beginning on page 649 of this issue dated September 1997. Attachment 2 is a true and correct copy of the issue cover, table of contents, and the Grimsgaard article (pages 649-659). I obtained this copy of the article from the University of

[18] https://www.ahajournals.org/circ/about

Wisconsin – Oshkosh Libraries. Specifically, the text of the article is complete; no pages are missing, and the text on each page appears to flow seamlessly from one page to the next; further, there are no visible alterations to the document. Attachment 2 was found within the custody of a library – a place where, if authentic, a copy of this journal would likely be. Attachment 2 is a true and correct copy in a condition that creates no suspicion about its authenticity.

53. The cover of the September 1997 issue of *The American Journal of Clinical Nutrition* has a stamp affixed at the University of Wisconsin – Oshkosh Libraries which shows that it was received, verified, and checked in on September 3, 1997. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals to show when a reference was received, verified, and checked. Therefore, in my experience, this issue of *The American Journal of Clinical Nutrition* would have been available to users in print on that date.

54. Attached hereto as Attachment 2a is a true and correct copy of the online catalog record for *The American Journal of Clinical Nutrition* in the University of Wisconsin – Oshkosh Libraries. I personally identified and retrieved the MARC record that is Attachment 2a. Attachment 2a also shows that Grimsgaard was catalogued with two descriptor terms reading "Nutrition $v Periodicals" (see Attachment 2b, Library of Congress subject heading sh2008108541) and "Diet in disease $v Periodicals" (see Attachment 2c, Library of Congress subject heading

sh85037854 and Attachment 1d, Library of Congress subject heading sh85099890) in the 650 fields.

55. Based on finding a print copy of Grimsgaard in the University of Wisconsin – Oshkosh Libraries and MARC record in its online library catalog attached as Attachment 2a, it is my opinion that the Grimsgaard article published in *The American Journal of Clinical Nutrition* was publicly available on September 3, 1997.

56. As noted in the holdings information (field 362), the University of Wisconsin – Oshkosh Libraries has received *The American Journal of Clinical Nutrition* since publication began in 1954 and continues to receive the journal. In view of the MARC record for Grimsgaard, Grimsgaard was publicly available in print on September 3, 1997, because the serial title had been received, cataloged, and indexed in the University of Wisconsin – Oshkosh Libraries and made part of its online catalog database.

57. Attached hereto as Attachment 2d is a true and correct copy of the MARC record for *The American Journal of Clinical Nutrition* obtained from the OCLC bibliographic database. I personally identified and retrieved the MARC record that is Attachment 2d. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 2d, that library code is "MUL," which means that the MARC record for this serial was cataloged as

part of the Minnesota Union List of Serials at the University of Minnesota Libraries (Minneapolis, Minnesota). As can be seen in the "Entered" field in the MARC record for this exhibit, a cataloger at the University of Minnesota Libraries created OCLC record number 1480127 on July 26, 1975. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 2d occurred on August 16, 2021, as shown in the "Replaced" field ("20210816"). The "BLvl" entry in Attachment 2d is "s," which indicates that *The American Journal of Clinical Nutrition* is a serial publication. Field 310 of Attachment 2d reads "Monthly, $b <1965-." Accordingly, the MARC record for Grimsgaard corresponds to those issues of *The American Journal of Clinical Nutrition* during the time that the Grimsgaard article was published.

58. Attachment 2d further includes an entry in field 050 ("RC584 $b .A5")—as described above, this includes a subject matter classification number consistent with the Library of Congress classification system (analogous to the Dewey Decimal classification system). Attachment 2d further includes an entry in field 060 ("W1 $b AM45J"), a subject matter consistent with the National Library of Medicine classification system, and an entry in field 082 ("612.3"), a subject matter consistent with the Dewey Decimal classification system. Attachment 2d further includes two descriptor terms reading "Nutrition $v Periodicals" (see

Attachment 2b, Library of Congress subject heading sh2008108541) and "Diet in disease $v Periodicals" (see Attachment 2c, Library of Congress subject heading sh85037854 and Attachment 1d, Library of Congress subject heading sh85099890) in the 650 fields. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 2d was indexed according to its subject matter by virtue of at least four independently sufficient classifications: the field 050 entry, the field 060 entry, the field 082 entry, and the field 650 entries. Further, as of July 26, 1975, the MARC record attached hereto as Attachment 2d was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that subscribed to the serial, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library. Therefore, Grimsgaard was publicly accessible in print as early as September 3, 1997, because by that time it had been cataloged and indexed at the University of Minnesota Libraries, made part of the OCLC bibliographic database, and received at the University of Wisconsin – Oshkosh Libraries.

59. Attachment 2d indicates that *The American Journal of Clinical Nutrition* as cataloged at the University of Minnesota Libraries is currently available from 1,199 libraries. For these reasons, it is my opinion that Grimsgaard was published and accessible to the public in print on or shortly after than September 3,

1997.

60. Further supporting my opinion that Grimsgaard was publicly accessible to ordinarily skilled and interested researchers in the field is the fact that *The American Journal of Clinical Nutrition* was included in the well-known index *Chemical Abstracts*. *See* field 510 entry in Attachment 2d. As noted above, this would have provided a POSA with keyword searching capabilities and other tools to locate this article.

61. I have examined Exhibit 1007, provided by counsel, which is a copy of Grimsgaard. The text of Exhibit 1007 is substantively identical to the corresponding material in Attachment 2. Thus, in my opinion, Exhibit 1007 and Attachment 2 are authentic copies of Grimsgaard, which is a printed publication that was publicly accessible before April 29, 2008.

C. Document 3: Exhibit 1014 ("Lovaza PDR")

62. Attached hereto as Attachment 3 is an excerpt from a book, *Physicians' Desk Reference*, 62nd edition, issued by Thomson Healthcare in 2008. Attachment 3 is a true and correct copy of the title page, title page verso, table of contents, and the entry for "Lovaza™" (pages 2699-2701) (hereafter "Lovaza PDR") as held by the University of Wisconsin – River Falls Libraries. I obtained this document from the University of Wisconsin – River Falls Libraries. Specifically, the text of Attachment 3 is complete; no pages are missing, and the text on each page appears

to flow seamlessly from one page to the next; further, there are no visible alterations to the document. Attachment 3 was found within the custody of a library – a place where, if authentic, a copy of this book would likely be. Attachment 3 is a true and correct copy in a condition that creates no suspicion about its authenticity.

63. Attached hereto as Attachment 3a is a true and correct copy of the MARC record for this monograph from the University of Wisconsin – River Falls Libraries online catalog. The library ownership is indicated by the presence of the library's code (WRF) in the 049 field. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 3a occurred on July 7, 2021, as shown in field 005 ("20210707"). I personally identified and retrieved the library catalog record which is Attachment 3a. Attachment 3a also shows that Lovaza PDR was catalogued with descriptor term "Drugs $v Dictionaries" (see Attachment 3b, Library of Congress subject heading sh2008102453) in the 650 field.

64. Attached hereto as Attachment 3c is a true and correct copy of the MARC record for the book *Physicians' Desk Reference*, 62nd edition, obtained from the OCLC bibliographic database. I personally identified and retrieved the MARC record that is Attachment 3c. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 3c, that library code is "AJP," which means that the MARC record for this book was created at the

White County Regional Library System (Searcy, Arkansas). As can be seen in the "Entered" field in the MARC record for this exhibit, a cataloger at the White County Regional Library System created OCLC record number 182846164 on December 5, 2007.

65. Attachment 3c further includes an entry in field 050 ("RS75 $b .P578")—as described above, this includes a subject matter classification number consistent with the Library of Congress classification system (analogous to the Dewey Decimal classification system); an entry in field 060 ("QV772 $b P5781"), a subject matter consistent with the National Library of Medicine classification system; and an entry in field 082 ("615.1"), subject matters consistent with the Dewey Decimal classification system. Attachment 3c further includes five descriptor terms reading "Drugs $v Dictionaries" (see Attachment 3b, Library of Congress subject heading sh2008102453), "Pharmacology $v Dictionaries" (see Attachment 3d, Library of Congress subject heading sh85100599 and Attachment 3e, Library of Congress subject heading sh85099890), "Pharmacy" (see Attachment 3f, Library of Congress subject heading sh85100603), "Materia medica" (see Attachment 3g, Library of Congress subject heading sh85082055), and "Biological products" (see Attachment 3h, Library of Congress subject heading sh85014183) in the 650 fields. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 3c was indexed according to its subject

matter by virtue of at least four independently sufficient classifications: the field 050 entry, the field 060 entry, the field 082 entry, and the field 650 entries. Further, as of December 5, 2007, the MARC record attached hereto as Attachment 3c was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that added this book to its collection, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library.

66. Attachment 3c indicates that the book *Physicians' Desk Reference*, 62nd edition, as cataloged at the White County Regional Library System is currently available from 299 libraries. In view of above, this monograph *Physicians' Desk Reference*, 62nd edition, was publicly available no later than December 5, 2007, because by that date it had been received, cataloged, and indexed at the White County Regional Library System and added to the OCLC bibliographic database. For these reasons, it is my opinion that Lovaza PDR was published and accessible to the public no later than December 5, 2007.

67. I have examined Exhibit 1014, provided by counsel, which is a copy of Lovaza PDR. The text of Exhibit 1014 is substantively identical to the corresponding material in Attachment 3. Thus, in my opinion, Exhibit 1014 and Attachment 3 are authentic copies of Lovaza PDR, which is a printed publication

that was publicly accessible before April 29, 2008.

D. Document 4: Exhibit 1004 ("Mori")

68. Attached hereto as Attachment 4 is a copy of an article from Volume 71, Issue 5 of *The American Journal of Clinical Nutrition* found in the University of Wisconsin – Stevens Point Libraries. The article "Purified Eicosapentaenoic and Docosahexaenoic Acids Have Differential Effects on Serum Lipids and Lipoproteins, LDL Particle Size, Glucose, and Insulin in Mildly Hyperlipidemic Men" by Trevor R. Mori, Valerie Burke, Ian B. Puddey, Gerald F. Watts, David N. O'Neal, James D. Best, and Lawrence J. Beilin (hereafter "Mori") appears beginning on page 1085 of this issue dated May 2000. Attachment 4 is a true and correct copy of the issue cover, table of contents, and the Mori article (pages 1085-1094). I obtained this copy of the article from the University of Wisconsin – Stevens Point Libraries. Specifically, the text of the article is complete; no pages are missing, and the text on each page appears to flow seamlessly from one page to the next; further, there are no visible alterations to the document. Attachment 4 was found within the custody of a library – a place where, if authentic, a copy of this journal would likely be. Attachment 4 is a true and correct copy in a condition that creates no suspicion about its authenticity.

69. The online catalog at the University of Wisconsin – Stevens Point indicates that the library subscribed to the print and digital versions (see Attachment

4a, field 530) of *The American Journal of Clinical Nutrition*. The cover of the May 2000 issue of *The American Journal of Clinical Nutrition*, as shown in Attachment 4, has a receipt stamp affixed at the University of Wisconsin – Stevens Point Libraries which shows that it was received, verified, and checked in.[19] This stamp has the general appearance of stamps that libraries have long affixed to periodicals to show that a reference was received, verified, and checked. The publisher's website indicates that Mori was published digitally on May 1, 2000. Therefore, in my experience, this issue of *The American Journal of Clinical Nutrition* would have been available to users digitally on that date.

70. Attached hereto as Attachment 4a is a true and correct copy of the MARC record for *The American Journal of Clinical Nutrition* in the University of Wisconsin – Stevens Point Libraries. I personally identified and retrieved the MARC record that is Attachment 4a. Attachment 4a also shows that Mori was catalogued with two descriptor terms reading "Nutrition $v Periodicals" (see Attachment 2b, Library of Congress subject heading sh2008108541) and "Diet in disease $v Periodicals" (see Attachment 2c, Library of Congress subject heading

[19] https://wisconsin-uwsp.primo.exlibrisgroup.com/discovery/jsearch?query=any,contains,0002-9165&tab=jsearch_slot&vid=01UWI_SF:SP&offset=0&journals=any,0002-9165

sh85037854 and Attachment 1d, Library of Congress subject heading sh85099890) in the 650 fields.

71. Based on finding a copy of Mori in the University of Wisconsin – Stevens Point Libraries and MARC record in its online library catalog attached as Attachment 4a, it is my opinion that the Mori article published in *The American Journal of Clinical Nutrition* was publicly available on May 1, 2000.

72. As noted in the holdings information (field 362), the University of Wisconsin – Stevens Point Libraries has received *The American Journal of Clinical Nutrition* since publication began in 1954 and continues to receive the journal. In view of the MARC record for Mori, Mori was publicly available on May 1, 2000, because the serial title had been received, cataloged, and indexed in the University of Wisconsin – Stevens Point Libraries and made part of its online catalog database.

73. Attached hereto as Attachment 4b is a true and correct copy of the MARC record for *The American Journal of Clinical Nutrition* obtained from the OCLC bibliographic database. I personally identified and retrieved the MARC record that is Attachment 4b. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 4b, that library code is "MUL," which means that the MARC record for this serial was cataloged as part of the Minnesota Union List of Serials at the University of Minnesota Libraries (Minneapolis, Minnesota). As can be seen in the "Entered" field in the MARC

record for this exhibit, a cataloger at the University of Minnesota Libraries created OCLC record number 1480127 on July 26, 1975. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 4b occurred on August 16, 2021, as shown in the "Replaced" field ("20210816"). The "BLvl" entry in Attachment 4b is "s," which indicates that *The American Journal of Clinical Nutrition* is a serial publication. Field 310 of Attachment 4b reads "Monthly, $b <1965-." Accordingly, the MARC record for Mori corresponds to those issues of *The American Journal of Clinical Nutrition* during the time that the Mori article was published.

74. Attachment 4b further includes an entry in field 050 ("RC584 $b .A5")—as described above, this includes a subject matter classification number consistent with the Library of Congress classification system (analogous to the Dewey Decimal classification system). Attachment 4b further includes an entry in field 060 ("W1 $b AM45J"), a subject matter consistent with the National Library of Medicine classification system; and an entry in field 082 ("612.3"), a subject matter consistent with the Dewey Decimal classification system. Attachment 4b further includes two descriptor terms reading "Nutrition $v Periodicals" (see Attachment 2b, Library of Congress subject heading sh2008108541) and "Diet in disease $v Periodicals" (see Attachment 2c, Library of Congress subject heading sh85037854 and Attachment 1d, Library of Congress subject heading sh85099890)

in the 650 fields. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 4b was indexed according to its subject matter by virtue of at least four independently sufficient classifications: the field 050 entry, the field 060 entry, the field 082 entry, and the field 650 entries. Further, as of July 26, 1975, the MARC record attached hereto as Attachment 4b was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that subscribed to the serial, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library. Therefore, Mori was publicly accessible digitally as early as May 1, 2000, because by that time it had been cataloged and indexed at the University of Minnesota Libraries, made part of the OCLC bibliographic database, and received at the University of Wisconsin – Stevens Point Libraries.

75. Attachment 4b indicates that *The American Journal of Clinical Nutrition* as cataloged at the University of Minnesota Libraries is currently available from 1,199 libraries. For these reasons, it is my opinion that Mori was published and accessible to the public digitally on May 1, 2000.

76. Further supporting my opinion that Mori was publicly accessible to ordinarily skilled and interested researchers in the field is the fact that *The American Journal of Clinical Nutrition* was included in the well-known index *Chemical*

Abstracts. *See* field 510 entry in Attachment 4b. As noted above, this would have provided a POSA with keyword searching capabilities and other tools to locate this article.

77. I have examined Exhibit 1004, provided by counsel, which is a copy of Mori. The text of Exhibit 1004 is substantively identical to the corresponding material in Attachment 4. Thus, in my opinion, Exhibit 1004 and Attachment 4 are authentic copies of Mori, which is a printed publication that was publicly accessible before April 29, 2008.

E. Document 5: Exhibit 1015 ("Nozaki")

78. Attached hereto as Attachment 5 is a copy of an article from Volume 62, Number 3 of the *International Journal for Vitamin and Nutrition Research* found in the University of Wisconsin – Madison Libraries.[20] The article "Effects of Purified Eicosapentaenoic Acid Ethyl Ester on Plasma Lipoproteins in Primary Hypertholesterolemia" by Shuichi Nozaki, Yuji Matsuzawa, Ken-Ichi Hirano, Naohiko Sakai, Masahuro Kubo, and Seiichiro Tarui (hereafter "Nozaki") appears beginning on page 256 of this issue dated November 1992. Attachment 5 is a true and correct copy of the issue cover, masthead, table of contents, and Nozaki article (pages 256-260). I obtained this copy of the article from the University of Wisconsin

[20] The publication text is in German, English or French with summaries in one or more languages.

– Madison Libraries. Specifically, the text of the article is complete; no pages are missing, and the text on each page appears to flow seamlessly from one page to the next; further, there are no visible alterations to the document. Attachment 5 was found within the custody of a library – a place where, if authentic, a copy of this journal would likely be. Attachment 5 is a true and correct copy in a condition that creates no suspicion about its authenticity.

79. The table of contents (Attachment 5, page 3) of Nozaki indicates that the issue arrived and was checked in on November 2, 2002. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals to show when a reference was received, verified, and checked. Therefore, in my experience, this issue of the *International Journal for Vitamin and Nutrition Research* was available to users at the University of Wisconsin – Madison Libraries on that date.

80. Attached hereto as Attachment 5a is a true and correct copy of the MARC record for the *International Journal for Vitamin and Nutrition Research* at the University of Wisconsin – Madison Libraries. The library ownership is indicated by the presence of the library's code (GZM) in field 049. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 5a occurred on April 20, 2015, as shown in field 005 ("20150420"). I personally identified and retrieved

the MARC record that is Attachment 5a. Attachment 5a also shows that Nozaki was catalogued with two descriptor terms "Vitamins $v Periodicals" (*see* Attachment 5b, Library of Congress subject heading sh85144006 and Attachment 1d, Library of Congress subject headings sh85099890) and "Nutrition $v Periodicals" (*see* Attachment 2b, Library of Congress subject heading sh2008108541) in the 650 fields.

81. Based on finding a print copy of Nozaki in the University of Wisconsin – Madison Libraries and MARC record in its online library catalog attached as Attachment 5a, it is my opinion that the Nozaki article published in the *International Journal for Vitamin and Nutrition Research* was available to users on November 2, 2002.

82. As noted in the holdings information (field 362), the University of Wisconsin – Madison Libraries has received the *International Journal for Vitamin and Nutrition Research* since publication began in 1932 and continues to receive the journal.[21] In view of the MARC record for Nozaki, Nozaki was publicly available on November 2, 2002, because the serial title had been received, cataloged, and

[21] The original title was *Zeitschrift für Vitaminforschung* (1932-1970) which changed to *Internationale Zeitschrift für Vitaminforschung = International journal for vitamin research = Journal international de vitaminologie* (1947-1970). In 1970, the publication adopted the current title *International Journal for Vitamin and Nutrition Research Health.*

indexed in the University of Wisconsin – Madison Libraries and made part of its online catalog database.

83. Attached hereto as Attachment 5c is a true and correct copy of the MARC record for the *International Journal for Vitamin and Nutrition Research* obtained from the OCLC bibliographic database. I personally identified and retrieved the MARC record that is Attachment 5c. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 5c, that library code is "DLC," which means that the MARC record for this serial was cataloged in the Library of Congress. As can be seen in the "Entered" field in the MARC record for this exhibit, a cataloger at the Library of Congress created OCLC record number 1785670 on August 7, 1973. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 5c occurred on July 19, 2021, as shown in the "Replaced" field ("20210719"). The "BLvl" entry in Attachment 5c is "s," which indicates that the *International Journal for Vitamin and Nutrition Research* is a serial publication. Field 310 of Attachment 5c reads "Six no. a year, $b <May 2002-." Accordingly, the MARC record for Nozaki corresponds to those issues of the *International Journal for Vitamin and Nutrition Research* during the time that the Nozaki article was published.

84. Attachment 5c further includes an entry in field 050 ("QP771 $b

.I57")—as described above, this includes a subject matter classification number consistent with the Library of Congress classification system (analogous to the Dewey Decimal classification system); an entry in field 060 ("W1 $b IN7652Q"), a subject matter consistent with the National Library of Medicine classification system; and an entry in field 082 ("612/.399/05"), subject matters consistent with the Dewey Decimal classification system. Attachment 5c further includes two descriptor terms reading "Vitamins $v Periodicals" (see Attachment 5b, Library of Congress subject heading sh85144006 and Attachment 1d, Library of Congress subject headings sh85099890) and "Nutrition $v Periodicals" (see Attachment 2b, Library of Congress subject heading sh2008108541) in the 650 fields. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 5c was indexed according to its subject matter by virtue of at least four independently sufficient classifications: the field 050 entry, the field 060 entry, the field 082 entry, and the field 650 entries. Further, as of August 7, 1973, the MARC record attached hereto as Attachment 5c was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that subscribed to the serial, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library. Therefore, Nozaki was publicly accessible as early as November 2, 2002, because by that time it had

been cataloged and indexed at the Library of Congress, made part of the OCLC bibliographic database, and received in the University of Wisconsin – Madison Libraries.

85. Attachment 5c indicates that the *International Journal for Vitamin and Nutrition Research* as cataloged at the Library of Congress is currently available from 207 libraries. For these reasons, it is my opinion that Nozaki was published and accessible to the public on November 2, 2002.

86. Further supporting my opinion that Nozaki was publicly accessible to ordinarily skilled and interested researchers in the field is the fact that the *International Journal for Vitamin and Nutrition Research* was included in the several well-known indexes including *Life Sciences Collection, PESTDOC, RINGDOC, VETDOC, Excerpta Medica, Biological Abstracts, Chemical Abstracts, Nuclear Science Abstracts, Index Medicus,* and *Bibliography of Agriculture. See* field 510 entries in Attachment 5a. As noted above, this would have provided a POSA with keyword searching capabilities and other tools to locate this article.

87. I have examined Exhibit 1015, provided by counsel, which is a copy of Nozaki. The text of Exhibit 1015 is substantively identical to the corresponding material in Attachment 5. Thus, in my opinion, Exhibit 1015 and Attachment 5 are authentic copies of Nozaki, which is a printed publication that was publicly accessible before April 29, 2008.

F. Document 6: Exhibit 1006 ("Satoh")

88. Attached hereto as Attachment 6 is a copy of an article from Volume 30, Number 1 of the journal *Diabetes Care* found in the University of Wisconsin – Milwaukee Libraries. The article "Purified Eicosapentaenoic Acid Reduces Small Dense LDL, Remnant Lipoprotein Particles, and C-Reactive Protein in Metabolic Syndrom" by Noriko Satoh, Akira Shimatsu, Kazuhiko Kotani, Naoki Sakane, Kazunori Yamada, Takayoshi Suganami, Hideshi Kuzuya, and Yoshihiro Ogawa (hereafter "Satoh") appears beginning on page 144 of this issue dated January 2007. Attachment 6 is a true and correct copy of the issue cover, masthead, table of contents, and Satoh article (pages 144-146). I obtained this copy of the article from the University of Wisconsin – Milwaukee Libraries. Specifically, the text of the article is complete; no pages are missing, and the text on each page appears to flow seamlessly from one page to the next; further, there are no visible alterations to the document. Attachment 6 was found within the custody of a library – a place where, if authentic, a copy of this journal would likely be. Attachment 6 is a true and correct copy in a condition that creates no suspicion about its authenticity.

89. The table of contents (Attachment 6, page 3) of Satoh indicates that the issue arrived and was checked in on January 17, 2007. This date information is consistent with how libraries have long identified when a reference was received, verified, and checked. Therefore, in my experience, this issue of the journal *Diabetes*

Care was available to users at the University of Wisconsin – Milwaukee Libraries on that date.

90. Attached hereto as Attachment 6a is a true and correct copy of the online catalog record for the journal *Diabetes Care* at the University of Wisconsin – Milwaukee Libraries. I personally identified and retrieved the online catalog record that is Attachment 6a. Attachment 6a also shows that Satoh was catalogued with two descriptor terms reading "Diabetes $v Periodicals" (see Attachment 6b, Library of Congress subject heading sh2009123299) and "Diabetes $x Rehabilitation $v Periodicals" (see Attachment 6c, Library of Congress subject heading sh85037456, Attachment 6d, Library of Congress subject heading sh85112401 and Attachment 1d, Library of Congress subject heading sh85099890) in the 650 fields.

91. Based on finding a print copy of Satoh in the University of Wisconsin – Milwaukee Libraries and MARC record in its online library catalog attached as Attachment 6a, it is my opinion that the Satoh article published in the journal *Diabetes Care* was available to users on January 17, 2007.

92. As noted in the holdings information (field 362), the University of Wisconsin – Milwaukee Libraries has received the journal *Diabetes Care* since publication began in 1978 and continues to receive the journal. In view of the MARC record for Satoh, Satoh was publicly available on January 17, 2007, because

the serial title had been received, cataloged, and indexed in the University of Wisconsin – Milwaukee Libraries and made part of its online catalog database.

93. Attached hereto as Attachment 6e is a true and correct copy of the MARC record for the journal *Diabetes Care* obtained from the OCLC bibliographic database. I personally identified and retrieved the MARC record that is Attachment 6e. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 6e, that library code is "NSD," which means that the MARC record for this serial was cataloged as part of the National Serials Program at the Library of Congress. As can be seen in the "Entered" field in the MARC record for this exhibit, a cataloger at the Library of Congress created OCLC record number 3524314 on December 30, 1977. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 6e occurred on November 6, 2021, as shown in the "Replaced" field ("20211106"). The "BLvl" entry in Attachment 6e is "s," which indicates that the journal *Diabetes Care* is a serial publication. Field 310 of Attachment 6e reads "Monthly, $b 1991-." Accordingly, the MARC record for Satoh corresponds to those issues of the journal *Diabetes Care* during the time that the Satoh article was published.

94. Attachment 6e further includes an entry in field 050 ("RC660.A1 $b D49")—as described above, this includes a subject matter classification number

consistent with the Library of Congress classification system (analogous to the Dewey Decimal classification system); an entry in field 060 ("W1 $b DI161Q"), a subject matter consistent with the National Library of Medicine classification system; and an entry in field 082 ("616.4/62/005"), subject matters consistent with the Dewey Decimal classification system. Attachment 6e further includes two descriptor terms reading "Diabetes $v Periodicals" (see Attachment 6b, Library of Congress subject heading sh2009123299) and "Diabetes $x Rehabilitation $v Periodicals" (see Attachment 6c, Library of Congress subject heading sh85037456, Attachment 6d, Library of Congress subject heading sh85112401 and Attachment 1d, Library of Congress subject heading sh85099890) in the 650 fields. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 6e was indexed according to its subject matter by virtue of at least four independently sufficient classifications: the field 050 entry, the field 060 entry, the field 082 entry, and the field 650 entries. Further, as of December 30, 1977, the MARC record attached hereto as Attachment 6e was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that subscribed to the serial, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library. Therefore, Satoh was publicly accessible as early as January 17, 2007, because by that time it had been

cataloged and indexed at the Library of Congress, made part of the OCLC bibliographic database, and received in the University of Wisconsin – Milwaukee Libraries.

95. Attachment 6e indicates that the journal *Diabetes Care* as cataloged at the Library of Congress is currently available from 847 libraries. For these reasons, it is my opinion that Satoh was published and accessible to the public on January 17, 2007.

96. Further supporting my opinion that Satoh was publicly accessible to ordinarily skilled and interested researchers in the field is the fact that the journal *Diabetes Care* was included in the well-known index *Chemical Abstracts. See* field 510 entries in Attachment 6a. As noted above, this would have provided a POSA with keyword searching capabilities and other tools to locate this article.

97. I have examined Exhibit 1006, provided by counsel, which is a copy of Satoh. The text of Exhibit 1006 is substantively identical to the corresponding material in Attachment 6. Thus, in my opinion, Exhibit 1006 and Attachment 6 are authentic copies of Satoh, which is a printed publication that was publicly accessible before April 29, 2008.

G. Document 7: Exhibit 1016 ("Shinozaki")

98. Attached hereto as Attachment 7 is a copy of an article from Volume 2, Number 2 of the *Journal of Atherosclerosis and Thrombosis* found in the National

Library of Medicine (Bethesda, Maryland). The article "The Long-Term Effect of Eicosapentaenoic Acid on Serum Levels of Lipoprotein (a) and Lipids in Patients with Vascular Disease" by Koji Shinozaki, Jun-ichi Kambayashi, Tomio Kawasaki, Yoshio Uemura, Masato Sakon, Eiichi Shiba, Takashi Shibuya, Takashi Nakamura, and Takesada Mori (hereafter "Shinozaki") appears beginning on page 107 of this issue dated January 1996. Attachment 7 is a true and correct copy of the Shinozaki article (pages 107-109). I obtained this copy of the article from the publisher's website[22] through the National Library of Medicine. Specifically, the text of the article is complete; no pages are missing, and the text on each page appears to flow seamlessly from one page to the next; further, there are no visible alterations to the document. Attachment 7 was found within the custody of the publisher – a place where, if authentic, a copy of this journal would likely be. Attachment 7 is a true and correct copy in a condition that creates no suspicion about its authenticity.

99. Attached hereto as Attachment 7a is a true and correct copy of the MARC record for the *Journal of Atherosclerosis and Thrombosis* at the National Library of Medicine. I personally identified and retrieved the MARC record that is Attachment 7a. Attachment 7a also shows that Shinozaki was catalogued with two descriptor terms reading "Atherosclerosis" (see Attachment 7b, National Library of

[22] https://www.jstage.jst.go.jp/article/jat1994/2/2/2_2_107/_article

Medicine subject heading D050197) and "Thrombosis" (see Attachment 7c, National Library of Medicine subject heading D013927) in the 650 fields.

100. As noted in the holdings information (field 362), the National Library of Medicine has received the *Journal of Atherosclerosis and Thrombosis* since publication began in 1994 and continues to receive the journal. The "BLvl" entry in Attachment 7a is "s," which indicates that the *Journal of Atherosclerosis and Thrombosis* is a serial publication. Field 310 of Attachment 7a reads "Two no. a year." Accordingly, the MARC record for Shinozaki corresponds to those issues of the *Journal of Atherosclerosis and Thrombosis* from the time of the serial title began publication to the present day. In view of the MARC record for Shinozaki, Shinozaki was publicly available on or shortly after January 31, 1996, because the serial title had been received, cataloged, and indexed in the National Library of Medicine and made part of its online catalog database.[23]

101. Attached hereto as Attachment 7d is a true and correct copy of the MARC record for the *Journal of Atherosclerosis and Thrombosis* obtained from the OCLC bibliographic database. I personally identified and retrieved the MARC

[23] The *Journal of Atherosclerosis and Thrombosis* was published twice a year and, therefore, new issues were available approximately 180 days. Based on the frequency of publication (see Attachment 7a, field 310) and my years of experience working with serials, it is my opinion that issues would be published by the end of the month. Therefore, a public availability date of January 31, 1996, is reasonable.

record that is Attachment 7d. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 7d, that library code is "NLM," which means that the MARC record for this serial was cataloged at the National Library of Medicine. As can be seen in the "Entered" field in the MARC record for this exhibit, a cataloger at the National Library of Medicine created OCLC record number 32826477 on July 17, 1995. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 7d occurred on August 24, 2021, as shown in the "Replaced" field ("20210824"). The "BLvl" entry in Attachment 7d is "s," which indicates that the *Journal of Atherosclerosis and Thrombosis* is a serial publication. Accordingly, the MARC record for Shinozaki corresponds to those issues of the *Journal of Atherosclerosis and Thrombosis* during the time that the Shinozaki article was published.

102. Attachment 7d further includes an entry in field 050 ("RC692 $b .J68")—as described above, this includes a subject matter classification number consistent with the Library of Congress classification system (analogous to the Dewey Decimal classification system); and an entry in field 060 ("W1 $b JO545M"), a subject matter consistent with the National Library of Medicine classification system. Attachment 7d further includes two descriptor terms reading "Atherosclerosis $v Periodicals" (see Attachment 7e, Library of Congress subject

heading sh85009129 and Attachment 1d, Library of Congress subject heading sh85099890) and "Thrombosis $v Periodicals" (see Attachment 7f, Library of Congress subject heading sh85135077 and Attachment 1d, Library of Congress subject heading sh85099890) in the 650 fields. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 7d was indexed according to its subject matter by virtue of at least three independently sufficient classifications: the field 050 entry, the field 060 entry, and the field 650 entries. Further, as of July 17, 1995, the MARC record attached hereto as Attachment 7d was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that subscribed to the serial, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library. Therefore, Shinozaki was publicly accessible as early as January 31,1996, because by that time it had been received, cataloged, and indexed at the National Library of Medicine and made part of the OCLC bibliographic database.

103. Attachment 7d indicates that the *Journal of Atherosclerosis and Thrombosis* as cataloged at the National Library of Medicine is currently available from 34 libraries. For these reasons, it is my opinion that Shinozaki was published and accessible to the public on January 31, 1996.

104. Further supporting my opinion that Shinozaki was publicly accessible to ordinarily skilled and interested researchers in the field is the fact that the *Journal of Atherosclerosis and Thrombosis* was included in the well-known index *Chemical Abstracts*. *See* field 510 entries in Attachment 7a. As noted above, this would have provided a POSA with keyword searching capabilities and other tools to locate this article.

105. I have examined Exhibit 1016, provided by counsel, which is a copy of Shinozaki. The text of Exhibit 1016 is substantively identical to the corresponding material in Attachment 7. Thus, in my opinion, Exhibit 1016 and Attachment 7 are authentic copies of Shinozaki, which is a printed publication that was publicly accessible before April 29, 2008.

H. Document 8: Exhibit 1005 ("Yokoyama II")

106. Attached hereto as Attachment 8 is a copy of an article from Volume 369, Issue 9567 of the journal *The Lancet*, North American edition, found in the Health Sciences Library at the University of Washington (Seattle, Washington). The article "Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolaemic Patients (JELIS): A Randomised Open-Label, Blinded Endpoint Analysis" by Mitsuhiro Yokoyama, Hideki Origasa, Masunori Matsuzaki, Yuji Matsuzawa, Yasushi Saito, Yuichi Ishikawa, Shinichi Oikawa, Jun Sasaki, Hitoshi Hishida, Hiroshige Itakura, Toru Kita, Akira Kitabatake, Noriaki Nakaya,

Toshiie Sakata, Kazuyuki Shimada and Kunio Shirato (hereafter "Yokoyama II") appears beginning on page 1090 of this issue dated March 31-April 6, 2007. Attachment 8 is a true and correct copy of the issue cover, masthead with the table of contents, and Yokoyama II (pages 1090-1098). I obtained this copy of the article from the Health Sciences Library at the University of Washington. Specifically, the text of the article is complete; no pages are missing, and the text on each page appears to flow seamlessly from one page to the next; further, there are no visible alterations to the document. Attachment 8 was found within the custody of a library – a place where, if authentic, a copy of this journal would likely be. Attachment 8 is a true and correct copy in a condition that creates no suspicion about its authenticity.

107. The cover (Attachment 8, page 1) of Yokoyama II indicates that the issue arrived and was checked in on April 12, 2007. This date information is consistent with how libraries have long identified when a reference was received, verified, and checked. Therefore, in my experience, this issue of the journal *The Lancet*, North American edition, was available to users in the Health Sciences Library at the University of Washington on that date.

108. Attached hereto as Attachment 8a is a true and correct copy of the online catalog record for the journal *The Lancet*, North American edition, from the

Health Sciences Library at the University of Washington.[24] I personally identified and retrieved the MARC record that is Attachment 8a. Attachment 8a also shows that Yokoyama II was catalogued with two descriptor terms reading "Medicine" (*see* Attachment 8b, National Library of Medicine subject heading D008511) and "Medicine $v Periodicals" (*see* Attachment 8c, Library of Congress subject heading sh2008107665) in the 650 fields.

109. Based on finding a copy of Yokoyama II in the Health Sciences Library at the University of Washington and catalog record in its online library catalog attached as Attachment 8a, it is my opinion that Yokoyama II published in the journal *The Lancet*, North American edition, was available to users on April 12, 2007.

110. As noted in the holdings information, the Health Sciences Library at the University of Washington has received the journal *The Lancet*, North American edition, since publication began in 1966 and continues to receive the journal. In view of the catalog record for Yokoyama II, Yokoyama II was publicly available on April 12, 2007, because the serial title had been received, cataloged, and indexed in

[24] https://alliance-primo.hosted.exlibrisgroup.com/primo-explore/fulldisplay?docid=CP71137296750001451&context=L&vid=UW&lang=en_US&search_scope=all&adaptor=Local%20Search%20Engine&tab=default_tab&query=any,contains,lancet&offset=0

the Health Sciences Library at the University of Washington and made part of its online catalog database.

111. Attached hereto as Attachment 8d is a true and correct copy of the MARC record for the journal *The Lancet*, North American edition, obtained from the OCLC bibliographic database. I personally identified and retrieved the MARC record that is Attachment 8d. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 8d, that library code is "NSD," which means that the MARC record for this serial was cataloged as part of the National Serials Data Program at the Library of Congress. As can be seen in the "Entered" field in the MARC record for this exhibit, a cataloger at the Library of Congress created OCLC record number 2141608 on April 27, 1976. The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 8d occurred on June 6, 2020, as shown in the "Replaced" field ("20200606"). The "BLvl" entry in Attachment 8d is "s," which indicates that the journal *The Lancet*, North American edition, is a serial publication. Accordingly, the MARC record for Yokoyama II corresponds to those issues of the journal *The Lancet*, North American edition, during the time that Yokoyama II was published.

112. Attachment 8d further includes an entry in field 050 ("R31 $b .L3")—as described above, this includes a subject matter classification number consistent

with the Library of Congress classification system (analogous to the Dewey Decimal classification system); and an entry in field 060 ("W1 $b LA453B"), a subject matter consistent with the National Library of Medicine classification system. Attachment 8d further includes a descriptor term reading "Medicine $v Periodicals" (see Attachment 8c, Library of Congress subject heading sh2008107665 in the 650 field. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 8d was indexed according to its subject matter by virtue of at least three independently sufficient classifications: the field 050 entry, the field 060 entry, and the field 650 entry. Further, as of April 27, 1976, the MARC record attached hereto as Attachment 8d was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that subscribed to the serial, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library. Therefore, Yokoyama II was publicly accessible as early as April 12, 2007, because by that time it had been cataloged and indexed at the Library of Congress, made part of the OCLC bibliographic database, and received in the Health Sciences Library at the University of Washington.

113. Attachment 8d indicates that the journal *The Lancet*, North American edition, as cataloged at the Library of Congress is currently available from 1,078

libraries. For these reasons, it is my opinion that Yokoyama II was published and accessible to the public on April 12, 2007.

114. Further supporting my opinion that Yokoyama II was publicly accessible to ordinarily skilled and interested researchers in the field is the fact that the journal *The Lancet*, North American edition, was included in the well-known indexes including *Chemical Abstracts, CrossRef, Cumulative Indexing to Nursing and Allied Health Literature, Current Contents – Clinical Medicine, Current Contents – Life Sciences, Embase, Essential Science Indicators, PubMed, MEDLINE, Science Citation Index Expanded,* and *Scopus* (*see* publisher's website).[25] As noted above, this would have provided a POSA with keyword searching capabilities and other tools to locate this article.

115. I have examined Exhibit 1005, provided by counsel, which is a copy of Yokoyama II. The text of Exhibit 1005 is substantively identical to the corresponding material in Attachment 8. Thus, in my opinion, Exhibit 1005 and Attachment 8 are authentic copies of Yokoyama II, which is a printed publication that was publicly accessible before April 29, 2008.

VI. SUMMARY OF OPINIONS

116. In view of the foregoing, it is my opinion that the publications described

[25] https://www.sciencedirect.com/journal/the-lancet/about/abstracting-and-indexing

above were publicly available on or about the corresponding date listed in the table below:

Document	Publication	Publicly Available
Exhibit 1008 (Attachment 1) ATP-III	American Heart Association, Council on Arteriosclerosis (American Heart Association) and American Heart Association, Abstracts. "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel 111) Final Report." *Circulation*, vol. 106, no. 25 (17 December 2002): 3157-3421.	December 28, 2002
Exhibit 1007 (Attachment 2) Grimsgaard	Grimsgaard, Sameline, Kaare H. Bønaa, John-Bjame Hansen and Arne Nordøy. "Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids." *The American Journal of Clinical Nutrition*, vol. 66, issue 3 (September 1997): 649-659.	September 3, 1997
Exhibit 1014 (Attachment 3) Lovaza PDR	"Lovaza™." *Physicians' Desk Reference* (pp. 2699-2701). 62nd ed., 2008. Montvale, NJ: Thomson Healthcare Inc., ©2007.	December 5, 2007
Exhibit 1004 (Attachment 4) Mori	Mori, Trevor R., Valerie Burke, Ian B. Puddey, Gerald F. Watts, David N. O'Neal, James D. Best, and Lawrence J. Beilin. "Purified Eicosapentaenoic and Docosahexaenoic Acids Have Differential Effects on Serum Lipids and Lipoproteins, LDL Particle Size, Glucose, and Insulin in Mildly Hyperlipidemic Men." *The American Journal of Clinical Nutrition*, vol. 71, issue 5 (May 2000): 1085-1094.	May 1, 2000

Document	Publication	Publicly Available
Exhibit 1015 (Attachment 5) Nozaki	Nozaki, Shuichi, Yuji Matsuzawa, Ken-Ichi Hirano, Naohiko Sakai, Masahuro Kubo, and Seiichiro Tarui. "Effects of Purified Eicosapentaenoic Acid Ethyl Ester on Plasma Lipoproteins in Primary Hypertholesterolemia." *International Journal for Vitamin and Nutrition Research*, vol. 62, no. 3 (November 1992): 256-260.	November 2, 2002
Exhibit 1006 (Attachment 6) Satoh	Satoh, Noriko, Akira Shimatsu, Kazuhiko Kotani, Naoki Sakane, Kazunori Yamada, Takayoshi Suganami, Hideshi Kuzuya, and Yoshihiro Ogawa. "Purified Eicosapentaenoic Acid Reduces Small Dense LDL, Remnant Lipoprotein Particles, and C-Reactive Protein in Metabolic Syndrome." *Diabetes Care*, vol. 30, no. 1 (January 2007): 144-146.	January 17, 2007
Exhibit 1016 (Attachment 7) Shinozaki	Shinozaki, Koji, Jun-ichi Kambayashi, Tomio Kawasaki, Yoshio Uemura, Masato Sakon, Eiichi Shiba, Takashi Shibuya, Takashi Nakamura, and Takesada Mori. "The Long-Term Effect of Eicosapentaenoic Acid on Serum Levels of Lipoprotein (A) and Lipids in Patients with Vascular Disease." *Journal of Atherosclerosis and Thrombosis*, vol. 2, no. 2 (January 1996): 107-109.	January 31, 1996
Exhibit 1005 (Attachment 8) Yokoyama II	Yokoyama, Mitsuhiro, Hideki Origasa, Masunori Matsuzaki, Yuji Matsuzawa, Yasushi Saito, Yuichi Ishikawa, Shinichi Oikawa, Jun Sasaki, Hitoshi Hishida, Hiroshige Itakura, Toru Kita, Akira Kitabatake, Noriaki Nakaya, Toshiie Sakata, Kazuyuki Shimada and Kunio Shirato, "Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolaemic Patients (JELIS): A Randomised Open-Label, Blinded Endpoint Analysis." *The Lancet*, vol. 369, issue 9567 (31 March-6 April 2007): 1090-1098.	April 12, 2007

109. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

110. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

DATED: November 30, 2021 By: Sylvia D. Hall-Ellis

Sylvia D. Hall-Ellis, Ph.D.

ATTACHMENT 1 (Part 1)

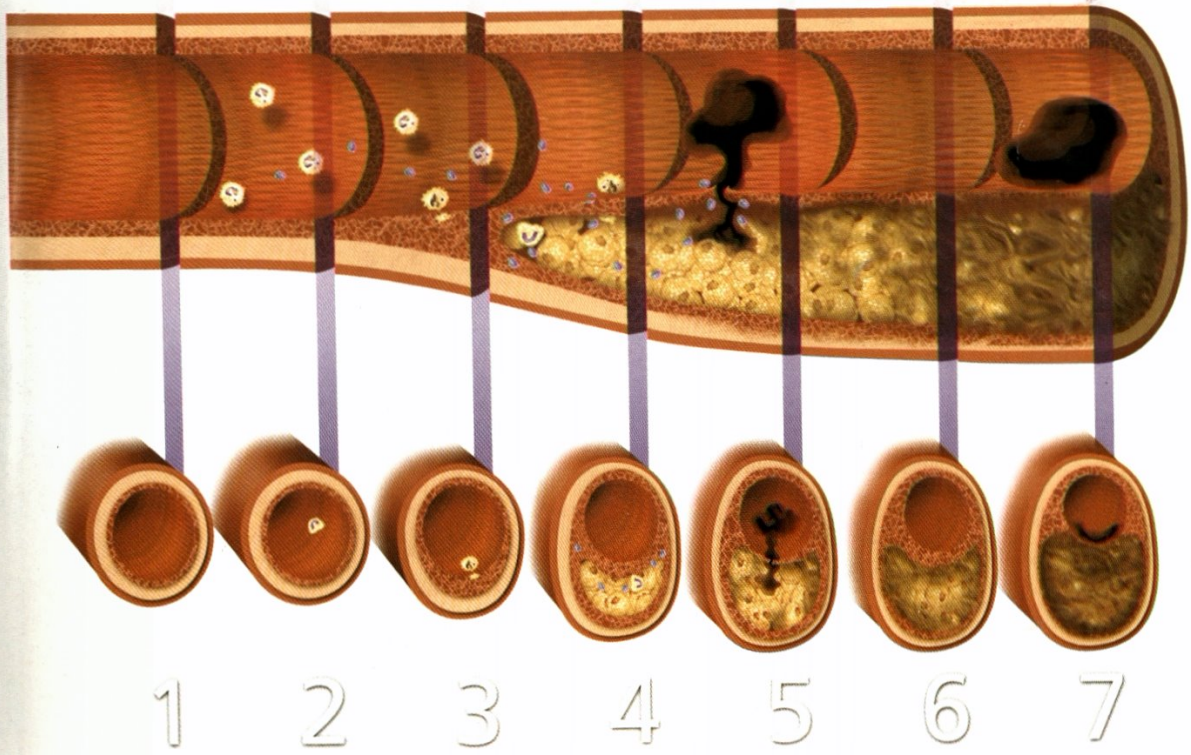
(ATP-III)

Vol 106, No 25, December 17/24, 2002
ISSN 0009-7322
http://circ.ahajournals.org

American Heart Association®
Fighting Heart Disease and Stroke

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection

Evaluation

Treatment

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Final Report

National Cholesterol Education Program

National Heart, Lung, and Blood Institute

National Institutes of Health

NIH Publication No. 02-5215
September 2002

Contents

I. Background and Introduction

I. Background and Introduction

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) presents the National Cholesterol Education Program's (NCEP's) updated recommendations for cholesterol testing and management. It is similar to Adult Treatment Panel II (ATP II)[1,2] in general outline and fundamental approach to therapy. It focuses on the role of the clinical approach to prevention of coronary heart disease (CHD).* This report continues to identify low-density lipoprotein (LDL) as the primary target of cholesterol-lowering therapy. Since ATP II, a number of controlled clinical trials with newer cholesterol-lowering drugs have been reported. These trials demonstrated remarkable reductions in risk for CHD, in both primary and secondary prevention. Their results enrich the evidence base upon which the new guidelines are founded.

1. Development of an evidence-based report

The ATP III panel extensively analyzed the results of recent clinical trials whose findings strongly influenced the development of the new guidelines. The panel's major goals were to review the literature objectively and to document and display the scientific evidence for ATP III recommendations. Prior to the appointment of the ATP III panel, the NCEP Coordinating Committee developed a list of important issues for the panel's consideration. This list was presented to the panel, discussed, and modified appropriately. The literature pertaining to each defined issue was identified by the panel members and by a MEDLINE search. Panel members produced a series of issue papers that carefully reviewed the literature; these issue papers became the foundation for writing the first draft of the report. Modifications of drafts were made following review and discussion of additional evidence arising from the literature search. ATP III contains both evidence statements and specific recommendations based on these statements. Each evidence statement is qualified according to category of evidence (A–D) and strength of evidence (1–3), as follows:

Type of Evidence

Category of Type of Evidence	Description of Type of Evidence
A	Major randomized controlled clinical trials (RCTs)
B	Smaller RCTs and meta-analyses of other clinical trials
C	Observational and metabolic studies
D	Clinical experience

Strength of Evidence

Category of Strength of Evidence	Description of Strength of Evidence
1	Very strong evidence
2	Moderately strong evidence
3	Strong trend

Empirical data provide the foundation for recommendations; but research in the cholesterol field, as in almost any other, generally has addressed large questions and has not necessarily provided answers to every specific question of clinical intervention. Thus, in the panel's view, the general evidence (including type and strength) often fails to carry a one-to-one correspondence with needed specific recommendations. Consequently, ATP III recommendations are based on the panel's best interpretation of the relation between empirical evidence and issues of clinical intervention. The recommendations are crafted in language that best links general evidence to specific issues; they are not qualified quantitatively according to category and strength of evidence, which is implicit in the language of the recommendation. Finally, for complex issues, several evidence statements or recommendations may be grouped together.

* In ATP III, CHD is defined as symptomatic ischemic heart disease, including myocardial infarction, stable or unstable angina, demonstrated myocardial ischemia by noninvasive testing, and history of coronary artery procedures.

This evidence-based report should not be viewed as a standard of practice. Evidence derived from empirical data can lead to generalities for guiding practice, but such guidance need not hold for individual patients. Clinical judgment applied to individuals can always take precedence over general management principles. Recommendations of ATP III thus represent general guidance that can assist in shaping clinical decisions, but they should not override a clinician's considered judgment in the management of individuals.

The ATP III panel played four important roles in forging this evidence-based report. First, it systematically reviewed the literature and judged which reports provided relevant information. Second, it synthesized the existing literature into a series of evidence statements. This synthesis also required a judgment as to the category and strength of evidence. Third, the panel developed recommendations based on the evidence statements; these recommendations represent a consensus judgment about the clinical significance of each evidence statement. Lastly, the panel created an integrated set of recommendations and guidelines based on individual recommendations.

2. Features of ATP III similar to those of ATP I and II

ATP III represents an update of recommendations for clinical management of high blood cholesterol and related abnormalities. It is constructed on the foundation of previous reports, ATP I[3,4] and ATP II.[1,2] The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management. Each report has a major thrust. ATP I outlined a strategy for primary prevention of CHD in persons with high LDL cholesterol (≥160 mg/dL) or in those with borderline-high LDL cholesterol (130–159 mg/dL) and multiple (2+) other risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For CHD patients, ATP II set a new, lower LDL-cholesterol goal of ≤100 mg/dL. ATP III maintains continuity with ATP I and ATP II. Before considering the new constituents of ATP III, some of the important features shared with previous reports are shown in Table I.2–1.

Table I.2–1. Shared Features of ATP III and ATP II

- Continued identification of LDL cholesterol lowering as the primary goal of therapy
- Consideration of high LDL cholesterol (≥160 mg/dL) as a potential target for LDL-lowering drug therapy, specifically as follows:
  - For persons with multiple risk factors whose LDL levels are high (≥160 mg/dL) after dietary therapy, consideration of drug therapy is recommended
  - For persons with 0–1 risk factor whose LDL levels are 160–189 mg/dL after dietary therapy, drug treatment is optional; if LDL levels are ≥190 mg/dL after dietary therapy, drug treatment should be considered
- Emphasis on intensive LDL-lowering therapy in persons with established CHD
- Identification of three categories of risk for different LDL goals and different intensities of LDL-lowering therapy:
  - CHD and CHD risk equivalents* (other forms of clinical atherosclerotic disease)
  - Multiple (2+) risk factors†
  - 0–1 risk factor
- Identification of population groups, besides middle-aged men, for detection of high LDL cholesterol (and other lipid risk factors) and for clinical intervention. These include:
  - Young adults
  - Postmenopausal women
  - Older persons
- Emphasis on weight loss and physical activity to enhance risk reduction in persons with elevated LDL cholesterol

* A CHD risk equivalent is a condition that carries an absolute risk for developing new CHD equal to the risk for having recurrent CHD events in persons with established CHD.

† Risk factors that continue to modify the LDL goal include cigarette smoking, hypertension, a low level of high-density lipoprotein (HDL) cholesterol, family history of premature CHD, age, and diabetes. Note that in ATP III, diabetes is regarded as a CHD risk equivalent. A high HDL cholesterol remains a "negative" risk factor: its presence subtracts one risk factor from the risk factor count.

3. New features of ATP III

While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature is a focus on primary prevention in persons with multiple risk factors. Many of these persons have a relatively high risk for CHD and will benefit from more intensive LDL-lowering treatment than is recommended in ATP II. Table I.3–1. shows the new features of ATP III.

Table I.3–1. New Features of ATP III

Focus on Multiple Risk Factors

- Raises persons with diabetes without CHD (most of whom display multiple risk factors) to the risk level of CHD risk equivalent
- Uses Framingham projections of 10-year absolute CHD risk (i.e., the percent probability of having a CHD event in 10 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes

Modifications of Lipid and Lipoprotein Classification

- Identifies LDL cholesterol <100 mg/dL as optimal
- Raises categorical low HDL cholesterol from <35 mg/dL to <40 mg/dL because the latter is a better measure of a depressed HDL
- Lowers the triglyceride classification cutpoints to give more attention to moderate elevations

Support for Implementation

- Recommends lipoprotein analysis (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) as the preferred initial test, rather than screening for total cholesterol and HDL alone
- Encourages use of plant stanols/sterols and viscous (soluble) fiber as therapeutic dietary options to enhance lowering of LDL cholesterol
- Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies
- Recommends treatment beyond LDL lowering for persons with triglycerides ≥200 mg/dL

4. Relation of ATP III to NCEP's public health approach

To reduce the burden of coronary atherosclerosis in society, LDL-cholesterol concentrations and other CHD risk factors must be kept as near to an optimal level as possible through the *public health (population) approach*. Lowering LDL-cholesterol levels in the whole population and keeping them low requires adoption of a low saturated fat and low cholesterol diet, maintenance of a healthy weight, and regular physical activity. NCEP has separately produced a Population Panel Report[5,6] that outlines a strategy for the public health approach. The population approach for controlling CHD risk factors will, in the long term, have the greatest impact on reducing the magnitude of cardiovascular disease in the United States. Nonetheless, for persons in whom LDL-cholesterol concentrations are significantly elevated, a *clinical strategy* is also required. NCEP's recommendations for the clinical approach are contained in the Adult Treatment Panel reports. The clinical and population approaches are complementary.[7] ATP III updates NCEP's clinical guidelines for cholesterol management. It also attempts to provide a bridge between clinical management and population strategy. Clinical professionals are integral to the public health approach. The clinical approach alone cannot overcome the burden of atherosclerotic disease in the general population. A parallel and simultaneous effort must be made to promote changes in population life habits to retard atherogenesis. The clinical approach can, however, delay or prevent the onset of CHD and prolong the lives of many persons at increased risk.

5. Relation of ATP III to other clinical guidelines

Since the publication of ATP II, other bodies have published guidelines for CHD risk reduction. For persons with established CHD, ATP III recommendations largely match other guidelines. Recent clinical trials confer a strong scientific base for the benefit of cholesterol-lowering therapy in secondary prevention, making it easier to achieve common ground with other guidelines. There is less congruence on guidelines for primary prevention through clinical therapy. Several recent guidelines place almost exclusive priority for treatment on persons at high risk in the short term, (i.e., ≤10 years). This priority is dictated largely by cost considerations, particularly the costs of cholesterol-lowering drugs. ATP III likewise identifies individuals at high short-term risk who need intensive intervention. However, an important feature of the ATP III guidelines (as in ATP I and ATP II) is extension of the clinical approach to the reduction of long-term (i.e., >10-year) risk. By so doing, ATP III links clinical therapy to the public health approach and goes beyond the more restrictive recommendations of some guideline committees. The panel concluded that clinical guidelines should not be truncated to include only persons at high short-term risk. High serum cholesterol itself is a major cause of the build-up of coronary atherosclerosis, and hence of the development of CHD in the long term. For this

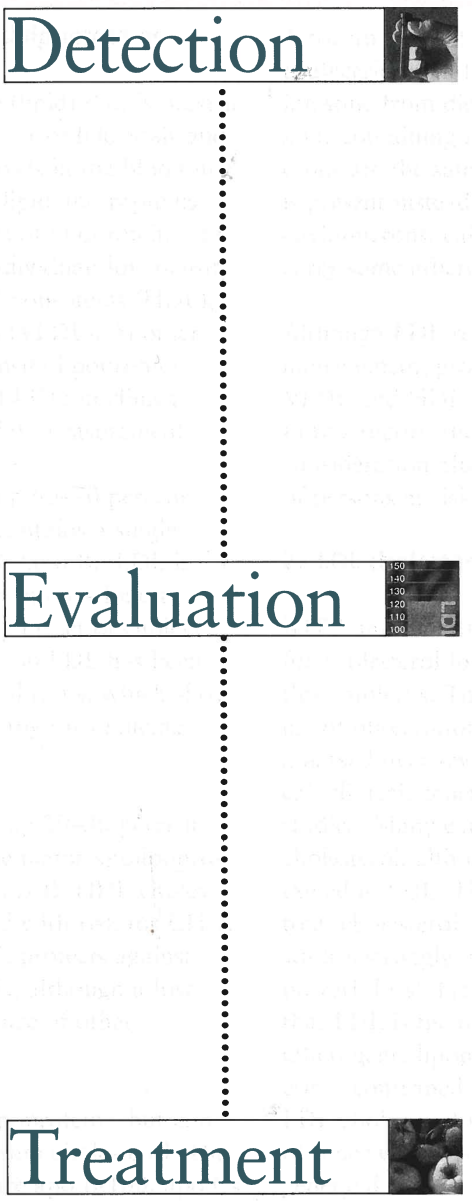
reason, ATP III stresses the need for long-term prevention of coronary atherosclerosis, as well as short-term prevention of acute coronary syndromes resulting from advanced atherosclerosis.

A comment is required about the relationship of ATP III to what is commonly called *global risk assessment* for CHD. In recent clinical guidelines, assessment of absolute risk (global risk) for experiencing acute coronary syndromes over the short term (≤10 years) has assumed increasing importance for primary prevention. These estimates provide a guide for selecting persons for clinical intervention. Accordingly, ATP III can be considered the "cholesterol component" of integrated, short-term risk reduction. At the same time, ATP III can be viewed as a broad-based approach to reducing CHD risk through short-term and long-term control of high serum cholesterol and related disorders of lipid and lipoprotein metabolism. Thus, on the one hand, high serum cholesterol can be identified in the context of global risk assessment that employs all other risk factors. Alternatively, risk assessment can be performed for persons in whom high serum cholesterol and related lipid disorders are detected independently. Thus, ATP III guidelines are designed to be flexible for use in various approaches to primary prevention.

II. Rationale for Intervention

ATTACHMENT 1 (Part 2)

(ATP-III)



II. Rationale for Intervention

II. Rationale for Intervention

1. Basic description of lipids and lipoproteins

Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids and steroid hormones. Cholesterol travels in the blood in distinct particles containing both lipid and proteins (lipoproteins). Three major classes of lipoproteins are found in the serum of a fasting individual: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). Another lipoprotein class, intermediate density lipoprotein (IDL), resides between VLDL and LDL; in clinical practice, IDL is included in the LDL measurement.

LDL cholesterol typically makes up 60–70 percent of the total serum cholesterol. It contains a single apolipoprotein, namely apo B-100 (apo B). LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol-lowering therapy. This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD.

HDL cholesterol normally makes up 20–30 percent of the total serum cholesterol. The major apolipoproteins of HDL are apo A-I and apo A-II. HDL-cholesterol levels are inversely correlated with risk for CHD. Some evidence indicates that HDL protects against the development of atherosclerosis, although a low HDL level often reflects the presence of other atherogenic factors.

The VLDL are triglyceride-rich lipoproteins, but contain 10–15 percent of the total serum cholesterol. The major apolipoproteins of VLDL are apo B-100, apo Cs (C-I, C-II, and C-III), and apo E. VLDL are produced by the liver and are precursors of LDL; some forms of VLDL, particularly VLDL remnants, appear to promote atherosclerosis, similar to LDL. VLDL remnants consist of partially degraded VLDL and are relatively enriched in cholesterol ester. Strictly speaking, IDL belongs to remnant lipoproteins although, in clinical practice, IDL is included in the LDL fraction.

A fourth class of lipoproteins, chylomicrons, are also triglyceride-rich lipoproteins; they are formed in the intestine from dietary fat and appear in the blood after a fat-containing meal. The apolipoproteins of chylomicrons are the same as for VLDL except that apo B-48 is present instead of apo B-100. Partially degraded chylomicrons, called chylomicron remnants, probably carry some atherogenic potential.

Although LDL receives primary attention for clinical management, growing evidence indicates that both VLDL and HDL play important roles in atherogenesis. In this report, therefore, VLDL and HDL receive consideration after LDL in the overall management of persons at risk for CHD.

2. LDL cholesterol as the primary target of therapy

ATP I and ATP II identified LDL as the primary target for cholesterol-lowering therapy, and ATP III continues this emphasis. This designation is based on a wide variety of observational and experimental evidence amassed over several decades from animal, pathological, clinical, genetic, and different types of population studies. Many earlier studies measured only serum total cholesterol, although most of total cholesterol is contained in LDL. Thus, the robust relationship between total cholesterol and CHD found in epidemiological studies strongly implies that an elevated LDL is a powerful risk factor. Subsequent studies have shown that LDL is the most abundant and clearly evident atherogenic lipoprotein. The role of LDL in atherogenesis is confirmed by genetic disorders in which serum LDL cholesterol is markedly increased in the absence of other CHD risk factors. Notable examples of such genetic disorders are homozygous and heterozygous forms of familial hypercholesterolemia; in both, atherogenesis is markedly accelerated. Finally, a causal role for LDL has been corroborated by controlled clinical trials of LDL lowering; recent trials especially have revealed a striking reduction in incidence of CHD. Evidence for LDL being both a major cause of CHD and a primary target of therapy will be examined in some detail.

II. Rationale for Intervention

1. Basic description of lipids and lipoproteins

Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids and steroid hormones. Cholesterol travels in the blood in distinct particles containing both lipid and proteins (lipoproteins). Three major classes of lipoproteins are found in the serum of a fasting individual: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). Another lipoprotein class, intermediate density lipoprotein (IDL), resides between VLDL and LDL; in clinical practice, IDL is included in the LDL measurement.

LDL cholesterol typically makes up 60–70 percent of the total serum cholesterol. It contains a single apolipoprotein, namely apo B-100 (apo B). LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol-lowering therapy. This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD.

HDL cholesterol normally makes up 20–30 percent of the total serum cholesterol. The major apolipoproteins of HDL are apo A-I and apo A-II. HDL-cholesterol levels are inversely correlated with risk for CHD. Some evidence indicates that HDL protects against the development of atherosclerosis, although a low HDL level often reflects the presence of other atherogenic factors.

The VLDL are triglyceride-rich lipoproteins, but contain 10–15 percent of the total serum cholesterol. The major apolipoproteins of VLDL are apo B-100, apo Cs (C-I, C-II, and C-III), and apo E. VLDL are produced by the liver and are precursors of LDL; some forms of VLDL, particularly VLDL remnants, appear to promote atherosclerosis, similar to LDL. VLDL remnants consist of partially degraded VLDL and are relatively enriched in cholesterol ester. Strictly speaking, IDL belongs to remnant lipoproteins although, in clinical practice, IDL is included in the LDL fraction.

A fourth class of lipoproteins, chylomicrons, are also triglyceride-rich lipoproteins; they are formed in the intestine from dietary fat and appear in the blood after a fat-containing meal. The apolipoproteins of chylomicrons are the same as for VLDL except that apo B-48 is present instead of apo B-100. Partially degraded chylomicrons, called chylomicron remnants, probably carry some atherogenic potential.

Although LDL receives primary attention for clinical management, growing evidence indicates that both VLDL and HDL play important roles in atherogenesis. In this report, therefore, VLDL and HDL receive consideration after LDL in the overall management of persons at risk for CHD.

2. LDL cholesterol as the primary target of therapy

ATP I and ATP II identified LDL as the primary target for cholesterol-lowering therapy, and ATP III continues this emphasis. This designation is based on a wide variety of observational and experimental evidence amassed over several decades from animal, pathological, clinical, genetic, and different types of population studies. Many earlier studies measured only serum total cholesterol, although most of total cholesterol is contained in LDL. Thus, the robust relationship between total cholesterol and CHD found in epidemiological studies strongly implies that an elevated LDL is a powerful risk factor. Subsequent studies have shown that LDL is the most abundant and clearly evident atherogenic lipoprotein. The role of LDL in atherogenesis is confirmed by genetic disorders in which serum LDL cholesterol is markedly increased in the absence of other CHD risk factors. Notable examples of such genetic disorders are homozygous and heterozygous forms of familial hypercholesterolemia; in both, atherogenesis is markedly accelerated. Finally, a causal role for LDL has been corroborated by controlled clinical trials of LDL lowering; recent trials especially have revealed a striking reduction in incidence of CHD. Evidence for LDL being both a major cause of CHD and a primary target of therapy will be examined in some detail.

a. Serum LDL cholesterol as a major cause of CHD

The induction of hypercholesterolemia is a prerequisite for atherogenesis, and sometimes myocardial ischemia, in various experimental animals. In addition, certain species have hereditary forms of hypercholesterolemia and develop atherosclerosis spontaneously; a classical example is the WHHL rabbit, which carries the same molecular defect as human familial hypercholesterolemia. In contrast, low LDL-cholesterol levels are well tolerated. LDL cholesterol as low as 25–60 mg/dL is physiologically sufficient.[8] Animal species that do not develop atherosclerosis generally have LDL-cholesterol levels below 80 mg/dL. The LDL-cholesterol concentration in the newborn infant is approximately 30 mg/dL, indicating that such low levels are safe. Moreover, persons who have extremely low levels of LDL throughout life due to familial hypobetalipoproteinemia have documented longevity.[9]

Epidemiological investigations of human populations incriminate high levels of LDL cholesterol as being atherogenic. In population studies, the serum total cholesterol is a good surrogate for LDL-cholesterol levels. The Framingham Heart Study,[10] the Multiple Risk Factor Intervention Trial (MRFIT),[11] and the Lipid Research Clinics (LRC) trial[12,13] found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new-onset CHD in men and women who were initially free of CHD. The same relation holds for recurrent coronary events in people with established CHD.[14-16] Any LDL cholesterol above 100 mg/dL appears to be atherogenic. The prevalance of elevated levels in large part accounts for the near-universal development of coronary atherosclerosis in the United States and the high attendant risk for developing CHD over a lifetime—49 percent for men and 32 percent for women.[17]

Studies across different populations reveal that those with higher cholesterol levels have more atherosclerosis and CHD than do those having lower levels.[18-20] People who migrate from regions where average serum cholesterol in the general population is low to areas with high cholesterol levels show increases in their cholesterol levels as they acculturate. These higher levels in turn are accompanied by more CHD.[21,22]

The positive relationship between serum cholesterol levels and the development of first or subsequent attacks of CHD is observed over a broad range of LDL-cholesterol levels; the higher the level, the greater the risk.[11] Early prospective data suggested that the risk of CHD plateaued at lower cholesterol levels, but this apparent plateau has disappeared in larger studies.[11,23,24] Only in populations that maintain very low levels of serum cholesterol, e.g., total cholesterol <150 mg/dL (or LDL cholesterol <100 mg/dL) throughout life do we find a near-absence of clinical CHD.[19,23-28]

Atherosclerosis generally can first be identified by gross pathological examination of coronary arteries in adolescence or early adulthood.[29-31] The subsequent rate of atherogenesis is proportional to the severity of ambient risk factors including serum cholesterol levels. Moreover, the cholesterol level in young adulthood predicts development of CHD later in life. In three prospective studies with long-term followup,[32-34] detection of elevated serum cholesterol in early adulthood predicted an increased incidence of CHD in middle-age.

The power of elevated LDL to cause CHD is shown most clearly in persons with genetic forms of hypercholesterolemia.[8] In these persons, advanced coronary atherosclerosis and premature CHD occur commonly even in the complete absence of other risk factors. These disorders provide the strongest evidence that LDL is a powerful atherogenic lipoprotein.

Since LDL-cholesterol levels <100 mg/dL throughout life are associated with a very low risk for CHD in populations, they can be called *optimal.* Even when LDL-cholesterol concentrations are *near optimal* (100–129 mg/dL), atherogenesis occurs; hence, such levels must also be called *above optimal.* At levels that are *borderline high* (130–159 mg/dL), atherogenesis proceeds at a significant rate, whereas at levels that are *high* (160–189 mg/dL) and very high (≥190 mg/dL) it is markedly accelerated. These relationships are confirmed by the log-linear relationship between serum cholesterol levels and CHD risk observed in many populations.[23,24]

The relation of elevated LDL cholesterol to the development of CHD must be viewed as a multi-step process beginning relatively early in life.[35-37] The first stage of atherogenesis is the fatty streak, which consists largely of cholesterol-filled macrophages; most of the

a. Serum LDL cholesterol as a major cause of CHD

The induction of hypercholesterolemia is a prerequisite for atherogenesis, and sometimes myocardial ischemia, in various experimental animals. In addition, certain species have hereditary forms of hypercholesterolemia and develop atherosclerosis spontaneously; a classical example is the WHHL rabbit, which carries the same molecular defect as human familial hypercholesterolemia. In contrast, low LDL-cholesterol levels are well tolerated. LDL cholesterol as low as 25–60 mg/dL is physiologically sufficient.[8] Animal species that do not develop atherosclerosis generally have LDL-cholesterol levels below 80 mg/dL. The LDL-cholesterol concentration in the newborn infant is approximately 30 mg/dL, indicating that such low levels are safe. Moreover, persons who have extremely low levels of LDL throughout life due to familial hypobetalipoproteinemia have documented longevity.[9]

Epidemiological investigations of human populations incriminate high levels of LDL cholesterol as being atherogenic. In population studies, the serum total cholesterol is a good surrogate for LDL-cholesterol levels. The Framingham Heart Study,[10] the Multiple Risk Factor Intervention Trial (MRFIT),[11] and the Lipid Research Clinics (LRC) trial[12,13] found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new-onset CHD in men and women who were initially free of CHD. The same relation holds for recurrent coronary events in people with established CHD.[14-16] Any LDL cholesterol above 100 mg/dL appears to be atherogenic. The prevalance of elevated levels in large part accounts for the near-universal development of coronary atherosclerosis in the United States and the high attendant risk for developing CHD over a lifetime—49 percent for men and 32 percent for women.[17]

Studies across different populations reveal that those with higher cholesterol levels have more atherosclerosis and CHD than do those having lower levels.[18-20] People who migrate from regions where average serum cholesterol in the general population is low to areas with high cholesterol levels show increases in their cholesterol levels as they acculturate. These higher levels in turn are accompanied by more CHD.[21,22]

The positive relationship between serum cholesterol levels and the development of first or subsequent attacks of CHD is observed over a broad range of LDL-cholesterol levels; the higher the level, the greater the risk.[11] Early prospective data suggested that the risk of CHD plateaued at lower cholesterol levels, but this apparent plateau has disappeared in larger studies.[11,23,24] Only in populations that maintain very low levels of serum cholesterol, e.g., total cholesterol <150 mg/dL (or LDL cholesterol <100 mg/dL) throughout life do we find a near-absence of clinical CHD.[19,23-28]

Atherosclerosis generally can first be identified by gross pathological examination of coronary arteries in adolescence or early adulthood.[29-31] The subsequent rate of atherogenesis is proportional to the severity of ambient risk factors including serum cholesterol levels. Moreover, the cholesterol level in young adulthood predicts development of CHD later in life. In three prospective studies with long-term followup,[32-34] detection of elevated serum cholesterol in early adulthood predicted an increased incidence of CHD in middle-age.

The power of elevated LDL to cause CHD is shown most clearly in persons with genetic forms of hypercholesterolemia.[8] In these persons, advanced coronary atherosclerosis and premature CHD occur commonly even in the complete absence of other risk factors. These disorders provide the strongest evidence that LDL is a powerful atherogenic lipoprotein.

Since LDL-cholesterol levels <100 mg/dL throughout life are associated with a very low risk for CHD in populations, they can be called *optimal.* Even when LDL-cholesterol concentrations are *near optimal* (100–129 mg/dL), atherogenesis occurs; hence, such levels must also be called *above optimal.* At levels that are *borderline high* (130–159 mg/dL), atherogenesis proceeds at a significant rate, whereas at levels that are *high* (160–189 mg/dL) and very high (≥190 mg/dL) it is markedly accelerated. These relationships are confirmed by the log-linear relationship between serum cholesterol levels and CHD risk observed in many populations.[23,24]

The relation of elevated LDL cholesterol to the development of CHD must be viewed as a multi-step process beginning relatively early in life.[35-37] The first stage of atherogenesis is the fatty streak, which consists largely of cholesterol-filled macrophages; most of the

cholesterol in fatty streaks is derived from LDL cholesterol. The second stage consists of fibrous plaques in which a layer of scar tissue overlies a lipid-rich core. Other risk factors contribute to plaque growth at this phase. The third stage is represented by the development of unstable plaques that are prone to rupture and formation of luminal thrombosis. Plaque rupture (or erosion) is responsible for most acute coronary syndromes (myocardial infarction, unstable angina, and coronary death).[38-41] Elevated LDL cholesterol plays a role in the development of the mature coronary plaque, which is the substrate for the unstable plaque. Recent evidence also indicates that elevated LDL cholesterol contributes to plaque instability as well; conversely, LDL cholesterol lowering stabilizes plaques and reduces the likelihood of acute coronary syndromes. Clinical intervention with LDL-lowering therapy in patients with advanced coronary atherosclerosis (short-term risk reduction) thus aims to stabilize plaques and to prevent acute coronary sydromes.[42,43] In contrast, LDL lowering earlier in life slows atherosclerotic plaque development, the foundation of the unstable plaque. This fact provides a rationale for long-term lowering of LDL cholesterol using both public-health and clinical approaches.

b. Serum LDL cholesterol as target of therapy

Notwithstanding this diverse evidence, the ultimate proof of the benefits of lowering LDL cholesterol is through clinical trial. A large number of clinical trials of cholesterol-lowering therapy have been carried out over the past four decades.[44] The history of cholesterol-lowering trials records one of the major advances in modern medicine.[44] The initial encouraging findings of earlier trials have recently been reinforced by the robust findings of a large number of studies, especially those using HMG CoA reductase inhibitors (statins). Clinical outcomes in terms of CHD incidence and CHD mortality are summarized in Table II.2–1 for pre-statin and statin trials in which LDL-cholesterol reduction was the major lipid response. The pre-statin trials provided strong evidence that CHD incidence is reduced by cholesterol-lowering therapy; statin trials extend the benefit to reduction of CHD mortality, and even to total mortality (see Section II.9).

Additional evidence of the benefit of LDL lowering is provided by study of coronary lesion architecture through coronary angiography. A summary of the evidence from different categories of angiographic trials reveals that LDL-lowering therapy produces favorable outcomes for coronary lesions, with a strong trend for a beneficial outcome for major coronary events (Table II.2–2).

Both clinical trials and angiographic studies show reductions in CHD risk that are broadly consonant with what was projected from cohort studies. The issue of whether cholesterol-lowering therapy reduces total mortality is considered in detail subsequently (see Section II.9).

In recent trials, statin therapy reduced risk for CHD in men and women, in those with or without heart disease, in older and younger subjects, in those with diabetes and hypertension, and at most levels of cholesterol. These benefits for different subgroups are shown by meta-analysis prepared for ATP III by panel members and statistical consultants at NHLBI (Table II.2–3) and by a recent analysis from two combined secondary prevention trials (CARE and LIPID).[47,48]

Table II.2–1.* CHD Outcomes in Clinical Trials of LDL-Cholesterol-Lowering Therapy†

Intervention	No. trials	No. treated	Person-years	Mean cholesterol reduction (%)	CHD Incidence (% change)	CHD Mortality (% change)
Surgery	1	421	4,084	22	**-43**	-30
Sequestrants	3	1,992	14,491	9	**-21**	-32
Diet	6	1,200	6,356	11	**-24**	-21
Statins	12	17,405	89,123	20	**-30**	**-29**

* This table is adapted from the meta-analysis of Gordon.[45]

† Not included among these clinical trials are those employing fibrates, nicotinic acid, and hormones. The major actions of fibrates and nicotinic acid are on triglyceride and HDL, whereas hormone trials have effects beyond serum lipids.

Table II.2–2. Odds Ratios for Coronary Lesion Regression vs. Progression and for Cardiovascular Event Rates in Angiographic Trials of LDL-Lowering Therapy (Including Comparison with Placebo and Trials of Calcium Channel Blockers)

Trials	Coronary Lesion Regression vs. Progression Odds Ratio (Number >1 means greater regression than progression)	Cardiovascular Event Rates Odds Ratio (Number <1 means fewer events on therapy)
Statins	2.1 (1.6, 2.7)* (p<0.0001)(vs. placebo)† (p<0.0001) vs. (calcium blocker)‡	0.67 (0.57, 0.80)* (p<0.0001)† (p=0.012)‡
Ileal Exclusion (POSCH)	4.7 (2.5, 9.0)* (p<0.0001)† (p=0.002)‡	0.57 (0.41, 0.78)* (p<0.0005)† (p=0.0082)‡
Sequestrants	3.2 (0.9, 11.4)* NS† NS‡	0.41 (0.17, 1.00)* NS† NS‡
Lifestyle	10.7 (4.0, 29.0)* (p<0.0001)† (p=0.0004)‡	0.57 (0.23, 1.46)* NS† NS‡
Combination Therapy	3.0 (1.8, 5.1)* (p<0.0001)† (p=0.03)‡	0.54 (0.36, 0.81)* (p=0.0031)† (p=0.021)‡
Calcium Channel Blockers	1.0 (0.6, 1.4)* NS†	1.33 (0.94, 1.89)* NS†

* Confidence intervals.
† Statistical significance compared to placebo.
‡ Statistical significance compared to calcium channel blocker trials.
NS Not significant.
This table was modified from a recently published meta-analysis provided by G.B.J. Mancini.[46] In this analysis, to assess trends and to synthesize the results of disparate trials, the reported trial results were examined with respect to the main angiographic and clinical endpoints. Odds ratios were calculated comparing progression and regression as dichotomous responses, excluding mixed or no-change responses. Odds ratios also were calculated for reported events. Tests of homogeneity were performed and were not significant, i.e., it may be assumed that the different trials in each category estimate a common odds ratio even though definitions of progression and regression and of clinical events differ somewhat among the trials. The significance of the calculated pooled odds ratios as well as 95 percent confidence intervals (CI) were calculated. Paired comparisons between combined odds ratios for different trial groups were carried out using Bonferroni's correction for multiple comparisons. The clinical trials compared in these studies were the following:
Statin trials:Δ LCAS, CIS, CARS, Post-CABG, REGRESS, PLAC I, CCAIT, MAAS, MARS
Surgical therapy:Δ POSCH
Sequestrant trials:Δ STARS, NHLBI Type II
Lifestyle intervention:Δ Heidelberg, STARS, Lifestyle Heart Trial
Combination drug therapy:Δ HARP, SCRIP, SCOR, FATS (lovastatin/colestipol), FATS (nicotinic acid/colestipol), CLAS
Calcium channel blocker monotherapy trialsΔ: Montreal Heart Institute Study, INTACT

Δ See List of Studies appendix for listing of the full names of these clinical trials.

Results of clinical trials of LDL lowering find support from a review of world-wide prospective studies on the relation between serum cholesterol levels and CHD incidence. In fact, Law et al.[23,24] reported a high congruence between results of prospective epidemiology studies and clinical trials. One advantage of epidemiological studies is their ability to examine and predict long-term influences. Earlier clinical trials found that a 1 percent reduction in serum total cholesterol level reduces risk for CHD by about 2 percent. Recent clinical trials with statins indicate that a 1 percent decrease in LDL cholesterol reduces risk by about 1 percent. However, across-country epidemiological studies strongly suggest that maintaining a lower serum cholesterol for periods longer than the duration of clinical trials yields a greater reduction in risk than is predicted from clinical trials. In populations that maintain very low cholesterol levels throughout life, the population risk for CHD is much lower than in populations that habitually carry higher cholesterol levels.[19,20] In contrast, in high-risk populations, the reduction in CHD attained with aggressive cholesterol-lowering therapy still leaves absolute CHD rates far above those in low-risk populations. From another point of view, epidemiological studies suggest that beginning cholesterol-lowering therapy at an earlier age will lead to a greater risk reduction than starting later in life. For example, using data from a large number of cohort studies, Law et al.[23,24] found that a 10 percent reduction in serum cholesterol level attained at age 40 yields a reduction in relative risk for CHD of 50 percent at age 40, whereas a 10 percent cholesterol reduction gives only a 20 precent reduction in risk if begun at age 70. This finding implies that the greatest long-term benefit is attained by early intervention; conversely, later intervention yields lesser benefit in risk reduction.

Evidence statement: Multiple lines of evidence from experimental animals, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled clinical trials indicate a strong causal relationship between elevated LDL cholesterol and CHD (A1, B1, C1).

Recommendation: LDL cholesterol should continue to be the primary target of cholesterol-lowering therapy.

Table II.2–3. CHD Risk Reduction (RR) in Cholesterol Trial Subgroups

CHD Risk Reduction in Cholesterol Trial Subgroups						
Trait	**Subgroup**	**N**	**Mean RR**	**95% CI**	**P-Interaction***	**Trials†**
Gender	Male Female	21651 4147	32% 34%	26–36% 20–45%	0.759	AFCAPS, POSCH, CARE, LIPID, PLAC1, 4S, CCAIT
Age	Younger Older	19119 16549	33% 30%	27–39% 24–36%	0.514	AFCAPS, POSCH, Upjohn, VAHIT, WOSCOPS, CARE, LIPID, PLAC1, CCAIT
Hypertension	No Yes	14623 8520	33% 22%	25–39% 12–31%	0.068	AFCAPS, POSCH, VAHIT, CARE, LIPID
Smoker	No Yes	18343 12193	23% 32%	16–30% 25–39%	0.075	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Newcastle, CCAIT
Diabetes	No Yes	25147 2443	27% 31%	21–32% 17–42%	0.596	AFCAPS, POSCH, VAHIT, CARE, LIPID, 4S
Cholesterol	Lower Higher	14180 7519	27% 32%	20–34% 22–40%	0.480	POSCH, Upjohn, WOSCOPS, CARE, LIPID
LDL	Lower Higher	11715 16071	29% 40%	22–36% 35–45%	0.012	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki
HDL	Lower Higher	16739 17021	33% 34%	27–38% 28–39%	0.865	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki
TG	Lower Higher	10791 12192	30% 27%	22–38% 20–34%	0.567	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki

* P-Interaction refers to the difference in treatment effect between the subgroups for each trait. The higher the number, the less is the difference in risk reduction between the two subgroups. The P-interaction term provides a statistical interpretation of the difference in relative risk reduction noted for the two subgroups. In statistical terms, the higher the number, the more homogeneous is the effect between the two subgroups. The dichotomous categories shown in this table vary in cutpoints depending on the results reported for each of the individual studies.

† See List of Studies appendix for listing of the full names of these clinical trials.

c. Categories and classification of total cholesterol and LDL cholesterol

ATP III maintains a classification of serum total cholesterol and LDL cholesterol similar to that in ATP II[1,2] with some minor modifications. The ATP III classification is shown in Table II.2–4.

Table II.2–4. ATP III Classification of Total Cholesterol and LDL Cholesterol

Total Cholesterol (mg/dL)		LDL Cholesterol (mg/dL)	
		<100	Optimal
<200	Desirable	100–129	Near optimal/ above optimal
200–239	Borderline High	130–159	Borderline High
≥240	High	160–189	High
		≥190	Very High

3. Other lipid risk factors

a. Triglycerides

1) *Elevated serum triglycerides (and triglyceride-rich lipoproteins) as a risk factor*

Many prospective epidemiological studies have reported a positive relationship between serum triglyceride levels and incidence of CHD.[49,50] However, early

multivariate analyses generally did not identify serum triglycerides as an independent risk factor for CHD.[51] This failure results from the large number of intercorrelated variables associated with elevated triglycerides. Lipoprotein metabolism is integrally linked, and elevations of serum triglycerides can be confounded by significant correlations with total, LDL, and HDL-cholesterol levels. Nonlipid risk factors of obesity, hypertension, diabetes, and cigarette smoking are also interrelated with triglycerides[52] as are several emerging risk factors (insulin resistance, glucose intolerance, and prothrombotic state [see Section II.5]). Thus, many persons with elevated triglycerides are at increased risk for CHD, even when this greater risk cannot be independently explained by triglycerides. Still, renewed interest in the importance of elevated triglycerides has been stimulated by the publication of meta-analyses that found that raised triglycerides are in fact an *independent risk factor* for CHD.[49,50] This independence suggests that some triglyceride-rich lipoproteins (TGRLP) are atherogenic.

2) *Lipoprotein remnants as atherogenic lipoproteins*

The most likely candidates for atherogenic TGRLP are remnant lipoproteins. These lipoproteins include small very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). They are cholesterol-enriched particles and have many of the properties of LDL. Reviews of several independent lines of evidence support the atherogenicity of remnants.[52-54] Specific evidence can be cited. In experimental animals, cholesterol-enriched remnants definitely cause atherosclerosis.[55,56] Genetic hyperlipidemias characterized by the accumulation of lipoprotein remnants commonly produce premature CHD and peripheral vascular disease in humans.[57,58] In several clinical studies in which remnants were specifically identified, their elevations emerged as strong predictors of coronary atherosclerosis or CHD.[59-69] This relation of remnants to CHD was also noted in several reviews.[52,54] Finally, drug therapies that reduce remnant lipoproteins (fibrates, nicotinic acid, and statins) are accompanied by reduced risk for CHD (see Section II.3.d).

3) *VLDL cholesterol as a marker for remnant lipoproteins*

Although a variety of methods have been developed to identify lipoprotein remnants, most are not applicable to clinical practice; the most readily available measure for clinical practice is VLDL cholesterol. Some cholesterol in VLDL may reside in non-atherogenic TGRLP, but most of it apparently occurs in atherogenic remnants.[59,70-72] Thus, VLDL cholesterol, as a marker for remnant lipoproteins, is a potential target of cholesterol-lowering therapy.

4) *Causes of elevated serum triglycerides*

Several causes underlie elevated triglycerides in the general population.[73,74]

- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Excess alcohol intake
- Very high-carbohydrate diets (>60 percent of total energy)
- Other diseases (type 2 diabetes, chronic renal failure, nephrotic syndrome)
- Certain drugs (corticosteroids, protease inhibitors for HIV, beta-adrenergic blocking agents, estrogens)
- Genetic factors

In persons with none of these factors, serum triglyceride levels typically are less than 100 mg/dL.[75] As some of these triglyceride-raising factors develop, levels commonly rise into the range of 150 to 199 mg/dL.[76,77] Although several factors can elevate triglycerides (see above), most common are overweight/obesity and physical inactivity.[76-81] When triglycerides rise to ≥200 mg/dL, these latter factors may contribute, but genetic influences play an increasing role as well.[82]

5) *Categories of serum triglycerides*

ATP II[1,2] adopted conservative definitions of serum triglyceride ranges based on the perceived weak independent relationship of triglycerides to CHD. Multivariate analysis of prospective studies at that time suggested that higher triglycerides carry little independent risk for CHD. After review of more recent evidence, the ATP III panel concluded that the link between serum triglycerides and CHD is stronger than previously recognized. Elevated triglycerides are widely recognized as a marker for increased risk, as revealed in univariate analysis.[49-51] In this context elevations in serum triglycerides can be considered a marker for atherogenic remnant lipoproteins, for other lipid risk factors (small LDL particles and low HDL), for other

Table II.3–1. Classification of Serum Triglycerides

Triglyceride Category	ATP II Levels	ATP III Levels
Normal triglycerides	<200 mg/dL	<150 mg/dL
Borderline-high triglycerides	200–399 mg/dL	150–199 mg/dL
High triglycerides	400–1000 mg/dL	200–499 mg/dL
Very high triglycerides	>1000 mg/dL	≥500 mg/dL

nonlipid risk factors (elevated blood pressure), and for emerging risk factors (insulin resistance, glucose intolerance, prothrombotic state).[52] Thus, the finding of elevated serum triglycerides helps to identify persons who are at risk and who need intervention for risk reduction. In addition, when triglyceride levels are ≥200 mg/dL, the presence of increased quantitites of atherogenic remnant lipoproteins can heighten CHD risk substantially beyond that predicted by LDL cholesterol alone.[60,83] For these reasons, ATP III modified the triglyceride classification to give more attention to moderate elevations.

Table II.3–1 compares the older ATP II classification with the new ATP III classification for serum triglycerides.

6) Elevated serum triglycerides and triglyceride-rich lipoproteins as targets of therapy

Elevated triglycerides represent one factor within a set of risk-factor targets in persons who are overweight, obese, sedentary, or cigarette smokers. Life-habit changes—weight control, exercise, and smoking cessation—will favorably modify multiple risk factors including elevated triglycerides.[78,79] Thus, elevated serum triglycerides are a potential target for therapeutic lifestyle changes.

Among triglyceride targets, remnant lipoproteins are the strongest candidates for direct clinical intervention designed to reduce risk for CHD. Atherogenic remnants can be lowered by weight reduction in overweight and obese persons[84] and by lipid-lowering drugs (statins, fibrates, and nicotinic acid).[85-88] However, none of these therapies reduce only remnants; they modify either concentrations or characteristics of all lipoprotein species. This makes it difficult to confirm the efficacy of lowering remnants per se through clinical trials. Nonetheless, the strong evidence for independent atherogenicity of elevated remnants makes them appropriate targets for cholesterol-lowering therapy.[60,83,89]

Evidence statements: Elevated serum triglycerides are associated with increased risk for CHD (C1). In addition, elevated triglycerides are commonly associated with other lipid and nonlipid risk factors (C1).

Recommendation: Greater emphasis should be placed on elevated triglycerides as a marker for increased risk for CHD. First-line therapy for elevated serum triglycerides should be therapeutic lifestyle changes.

Evidence statement: Some species of triglyceride-rich lipoproteins, notably, cholesterol-enriched remnant lipoproteins, promote atherosclerosis and predispose to CHD (C1).

Recommendation: In persons with high serum triglycerides, elevated remnant lipoproteins should be reduced in addition to lowering of LDL cholesterol.

b. Non-HDL cholesterol

1) Non-HDL cholesterol as a risk factor

Since VLDL cholesterol is highly correlated with atherogenic remnant lipoproteins, it can reasonably be combined with LDL cholesterol to enhance risk prediction when serum triglycerides are high. The sum of VLDL+LDL cholesterol is called non-HDL cholesterol. It is calculated routinely as total cholesterol minus HDL cholesterol. Non-HDL cholesterol includes all lipoproteins that contain apo B. In persons with high triglycerides (200–499 mg/dL) most cholesterol occurring in the VLDL fraction is contained in smaller (remnant) VLDL.[59,60,70-72] Few prospective studies have explicitly examined the predictive power of non-HDL-cholesterol levels versus LDL-cholesterol levels in a large group of persons with hypertriglyceridemia. However, Gordon et al.[90] reported that because non-HDL cholesterol and HDL cholesterol are

intercorrelated, they overlap in prediction, whereas LDL cholesterol is independent of HDL cholesterol as a predictor. Thus, some of the predictive power usually attributed to HDL cholesterol could be explained by elevations of non-HDL cholesterol. Frost and Havel[91] proposed that existing data actually favor use of non-HDL cholesterol over LDL cholesterol in clinical evaluation of risk. This proposal is strengthened by a recent report from the follow-up of the Lipid Research Clinic cohort which showed a stronger correlation with coronary mortality for non-HDL cholesterol than for LDL cholesterol.[92] Moreover, non-HDL cholesterol is highly correlated with total apolipoprotein B (apo B);[93,94] apolipoprotein B is the major apolipoprotein of all atherogenic lipoproteins. Serum total apo B also has been shown to have a strong predictive power for severity of coronary atherosclerosis and CHD events.[63,95-105] Because of the high correlation between non-HDL cholesterol and apolipoprotein B levels,[93,94] non-HDL cholesterol represents an acceptable surrogate marker for total apolipoprotein B in routine clinical practice; standardized measures of apolipoprotein B are not widely available for routine measurement. Potential uses of non-HDL cholesterol are for initial testing or for monitoring of response in the nonfasting state; the measurement is reliable in nonfasting serum, whereas calculated LDL cholesterol can be erroneous in the presence of postprandial hypertriglyceridemia.

In most persons with triglyceride levels <200 mg/dL, VLDL cholesterol is not substantially elevated,[106] and further, non-HDL cholesterol correlates highly with LDL cholesterol;[93,94] therefore, adding VLDL cholesterol to LDL cholesterol at lower triglyceride levels would be expected to provide little additional power to predict CHD. When triglyceride levels are ≥200 mg/dL, VLDL cholesterol levels are distinctly raised,[106] and LDL-cholesterol concentrations are less well correlated with VLDL and LDL (non-HDL) cholesterol levels;[93,94] consequently, LDL cholesterol alone inadequately defines the risk associated with atherogenic lipoproteins. In the presence of high serum triglycerides, non-HDL cholesterol therefore will better represent the concentrations of all atherogenic lipoproteins than will LDL cholesterol alone. On the other hand, when triglyceride levels become very high (e.g., ≥500 mg/dL) some of the cholesterol in TGRLP resides in nonatherogenic forms of larger VLDL and chylomicrons, and non-HDL cholesterol may be less reliable as a predictor of CHD risk.

2) Non-HDL cholesterol as a secondary target of therapy

Clinical trials of cholesterol-lowering therapy have not specifically identified non-HDL cholesterol (independent of LDL) as a target of therapy; thus, it has been difficult to isolate the impact of lowering non-HDL cholesterol per se on CHD risk. However, the same statement could be made about LDL itself. For example, it has been widely assumed from primary and secondary prevention trials of statin therapy that risk reduction is a response to LDL cholesterol lowering. Of interest, however, the percentage reductions of LDL cholesterol and VLDL cholesterol on statin therapy are similar.[93]

Consequently, it is not possible to differentiate risk reduction due to LDL lowering from non-HDL cholesterol lowering. Most clinical trials have not specifically included persons with hypertriglyceridemia; thus it can be assumed that lowering of VLDL cholesterol was a minor contributor to risk reduction in statin trials. However, in clinical practice, the situation may be different; when triglycerides are high, a significant fraction of non-HDL cholesterol is contained in VLDL. Here LDL cholesterol may not be the only significant lipid risk factor. Consequently, when triglycerides are high, non-HDL cholesterol (including VLDL cholesterol) can serve as a secondary target of therapy.

A "normal" VLDL cholesterol can be defined as that present when triglycerides are <150 mg/dL; this value typically is ≤30 mg/dL.[106] Conversely, when triglyceride levels are >150 mg/dL, VLDL cholesterol usually is >30 mg/dL. Thus, a reasonable goal for non-HDL cholesterol is one that is 30 mg/dL higher than the LDL-cholesterol goal. A specific goal of therapy for serum triglycerides is not identified in ATP III for two reasons: (a) triglyceride levels have more day-to-day variability than non-HDL-cholesterol levels and thus are less reliable, and (b) non-HDL cholesterol as a target allows more flexibility in choice of therapies to reduce atherogenic lipoproteins contained in the combined LDL+VLDL fraction. Non-HDL cholesterol was chosen as a preferred secondary target of therapy over total apo B for three other reasons:

(a) standardized measures of total apo B are not widely available in clinical practice; (b) measures of total apo B have not been shown in a large number of prospective studies to carry greater predictive power than non-HDL cholesterol in persons with elevated triglycerides; and (c) measurement of total apo B will constitute an added expense beyond the usual lipoprotein profile.

Evidence statements: Some species of triglyceride-rich lipoproteins are independently atherogenic; notable among these are cholesterol-enriched remnant lipoproteins (C1). Moreover, VLDL cholesterol is a marker for atherogenic VLDL remnants (C1).

Recommendation: In persons with high triglycerides (≥200 mg/dL), VLDL cholesterol should be combined with LDL cholesterol, yielding non-HDL cholesterol. The latter constitutes "atherogenic cholesterol" and should be a secondary target of therapy.

c. High density lipoproteins (HDL)

1) *Low HDL cholesterol as an independent risk factor for CHD*

Strong epidemiological evidence links low levels of serum HDL cholesterol to increased CHD morbidity and mortality.[10,90,107] High HDL-cholesterol levels conversely convey reduced risk. Epidemiological data taken as a whole signify that a 1 percent decrease in HDL cholesterol is associated with a 2–3 percent increase in CHD risk.[90] Epidemiological studies consistently show low HDL cholesterol to be an *independent risk factor* for CHD. Its independent relationship holds after correction for other risk variables in multivariate analysis. In fact, in prospective studies,[108,109] HDL usually proves to be the lipid risk factor most highly correlated with CHD risk. ATP II specified low HDL cholesterol (<35 mg/dL) as one of several major risk factors used to modify the therapeutic goal for LDL cholesterol. The definition of a low HDL was set to be the same for both men and women because of the view that a given level of HDL would impart the same risk for men and women.

The mechanistic relationship between low HDL-cholesterol levels and occurrence of CHD has not been fully elucidated. One theory holds that HDL directly participates in the atherogenic process. Some research in laboratory animals backs a direct action. In genetically modified animals, high levels of HDL appear to protect against atherogenesis.[110-112] In vitro, HDL promotes efflux of cholesterol from foam cells in atherosclerotic lesions (reverse cholesterol transport).[113] Recent studies indicate that the antioxidant and anti-inflammatory properties of HDL also inhibit atherogenesis.[114-116] Further, some genetic forms of HDL deficiency are accompanied by increased risk for CHD;[117,118] others appear not to be.[119-121] This latter finding raises the possibility that some subspecies of HDL affect atherogenesis whereas others do not. Although there are conflicting data, multiple lines of evidence strongly intimate that HDL plays a direct role in the atherogenic process. If so, it is a potential target for therapy.

The direct role of HDL in atherogenesis probably cannot fully account for the strong predictive power of HDL in epidemiological studies. A low HDL level correlates with the presence of other atherogenic factors.[122] In many persons, a low HDL level correlates with elevations of serum triglycerides and remnant lipoproteins;[123,124] in addition, low HDL commonly shows linkage with small, dense LDL particles.[125-128] The tight association among low HDL, small LDL particles, and elevated triglycerides has evoked the term *lipid triad.* Moreover, a low HDL level can be a sign of insulin resistance and its associated metabolic risk factors[122] (see Section II.6 Metabolic Syndrome). Because of the association of low HDL with other atherogenic factors (some of which are not included among standard risk factors), a low HDL cholesterol is not as strongly *independent* in its prediction of CHD as suggested by usual multivariate analysis, i.e., its independence is partially confounded by some risk factors that are not routinely measured, e.g., *emerging risk factors* (see Section II.5). This confounding raises the possibility that therapeutic raising of HDL-cholesterol levels will not reduce CHD risk as much as might be predicted from prospective epidemiological studies.[122]

Evidence statement: A low HDL-cholesterol level is strongly and inversely associated with risk for CHD (C1).

2) *Causes of low HDL cholesterol*

There are several factors that contribute to low HDL-cholesterol levels that need to be identified in clinical practice.[73,74,129] These include:

- Elevated serum triglycerides
- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Very high carbohydrate intakes (>60 percent of total energy intake)
- Type 2 diabetes
- Certain drugs (beta-blockers, anabolic steroids, progestational agents)
- Genetic factors

In the general population, about 50 percent of the variability of serum HDL-cholesterol levels derives from genetic factors;[130] the other 50 percent presumably comes from the acquired factors listed above. Moreover, when a person has a genetic predisposition to reduced HDL, acquired factors often drive HDL cholesterol to categorically low levels. Among these acquired factors, overweight and obesity appear to be most important.[78,79,131] Part of the effect of overweight and obesity can be explained by their action to raise serum triglycerides, which lowers HDL-cholesterol levels, but they probably reduce HDL cholesterol through other mechanisms as well.[132-134]

3) *Classification of serum HDL cholesterol*

The inverse association between HDL-cholesterol concentrations and CHD risk is a continuous variable; no threshold relationship has been identified.[10] For this reason, any categorical definition of low HDL cholesterol must be arbitrary. In ATP II,[1,2] a low HDL cholesterol was defined as a level <35 mg/dL; the setting of this cutpoint was influenced by the concept that low HDL is primarily a direct cause of atherosclerotic disease. More recently, the role of HDL as an indicator of other risk correlates has been emphasized.[122,135-137] This shift in perception requires a re-examination of the appropriate cutpoint for low HDL. Clearly, low HDL levels predict CHD at levels above 35 mg/dL;[10] this fact combined with the moderate reductions of HDL cholesterol caused by obesity and physical inactivity led the ATP III panel to recognize a somewhat higher HDL-cholesterol level as a categorical risk factor. The level <40 mg/dL was set as a low HDL cholesterol, both in men and women. Women typically have higher HDL cholesterol levels than men, and a cutpoint of <40 mg/dL will identify more men than women with low HDL cholesterol, i.e., approximately one-third of men and about one-fifth of women in the general population. Setting a different cutpoint for categorical low HDL cholesterol for men and women was rejected because it would make many women who are otherwise at low risk eligible for LDL-lowering drugs. On the other hand, as will be discussed subsequently, a higher level of HDL cholesterol (<50 mg/dL) is defined as a marginal risk factor in women, which will mandate more intensive lifestyle therapies (weight reduction and increased physical activity) (see Section II.6 Metabolic Syndrome).

In prospective studies, including the Framingham Heart Study,[10] a high HDL cholesterol is associated with reduced risk for CHD. In ATP II, this level *(high HDL cholesterol)* was also called a *negative risk factor,* and its presence evoked removal of one risk factor from the risk factor count used for setting treatment goals for LDL cholesterol. ATP III affirms the validity of this assignment. The ATP III classification of HDL cholesterol thus is given in Table II.3–2.

Table II.3–2. ATP III Classification of HDL Cholesterol

Serum HDL Cholesterol (mg/dL)	
<40 mg/dL	Low HDL cholesterol
≥60 mg/dL	High HDL cholesterol

Evidence statement: Population studies show a continuous rise in risk for CHD as HDL-cholesterol levels decline (C1). Higher risk for CHD at lower HDL levels is multifactorial in causation (C1). Although the inverse relationship between HDL cholesterol and CHD shows no inflection points, any reduction in HDL cholesterol from population means is accompanied by increased risk for CHD (C1).

Recommendation: A categorical low HDL cholesterol should be defined as a level of <40 mg/dL, in both men and women.

4) Low HDL cholesterol as a potential target of therapy

Persons with low HDL-cholesterol levels benefit similarly to those with higher HDL cholesterol during LDL-lowering therapy (See Table II.2–3). Whether raising HDL per se will reduce risk for CHD has not been resolved. Nonetheless, HDL levels are raised to varying degrees with lipid-modifying drugs, e.g., nicotinic acid,[138] fibrates,[48,139] and statins[140]. Furthermore, clinical trials with nicotinic acid[141] and fibrates[48,139] provide suggestive evidence that HDL raising provides one component of risk reduction with these drugs. Whether the small rise in HDL-cholesterol levels accompanying statin therapy accounts for any of the risk reduction from these drugs is uncertain. Since currently available drugs have multiple actions, it is difficult to dissect fully the benefit of HDL raising from that of reducing atherogenic lipoproteins. Regardless, use of drugs that favorably modify multiple inter-related lipid risk factors appears to reduce risk for CHD (see Section II.3.d Atherogenic Dyslipidemia). Finally, raising HDL levels by reversal of the major acquired causes of low HDL levels—overweight and obesity, physical inactivity, and smoking—provides the opportunity for further risk reduction in persons with low HDL-cholesterol levels. In addition, modifying these causes will be beneficial for other reasons besides raising HDL-cholesterol concentrations.

Evidence statements: Clinical trials provide suggestive evidence that raising HDL-cholesterol levels will reduce risk for CHD (A2). However, it remains uncertain whether raising HDL-cholesterol levels per se, independent of other changes in lipid and/or nonlipid risk factors, will reduce risk for CHD.

Recommendation: A specific HDL-cholesterol goal level to reach with HDL-raising therapy is not identified. However, nondrug and drug therapies that raise HDL-cholesterol levels and are part of management of other lipid and nonlipid risk factors should be encouraged.

d. Atherogenic dyslipidemia

A common form of dyslipidemia is characterized by three lipid abnormalities: elevated triglycerides, small LDL particles, and reduced HDL cholesterol.[49,52,54] Often the lipoprotein concentrations in this *lipid triad* are not categorically abnormal, but are only marginally deranged. More sophisticated methodology than that used in routine clinical practice can identify these multiple interrelated abnormalities. Still, in some persons, low HDL-cholesterol levels can occur in the absence of other lipoprotein abnormalities. These persons are said to have *isolated low HDL*. They are not common in the general population, however; more often, low HDL cholesterol occurs as a component of the lipid triad. Because of the common occurrence of the lipid triad, the relation of the lipid triad as a whole to CHD risk will be considered, and whether the entire triad is a target for therapy.

1) Atherogenic dyslipidemia as a "risk factor"

The lipid triad occurs commonly in persons with premature CHD,[125,142] hence the designation *atherogenic lipoprotein phenotype* or *atherogenic dyslipidemia*. Typical characteristics of persons with atherogenic dyslipidemia are obesity, abdominal obesity, insulin resistance, and physical inactivity.[78,79] Many persons with type 2 diabetes have atherogenic dyslipidemia.[143-145] In epidemiological studies in high-risk populations, the contributions of individual components of atherogenic dyslipidemia to CHD risk cannot reliably be dissected from the sum of lipid risk factors. Although there is evidence that each component of the lipid triad—low HDL, small LDL, and remnant lipoproteins—is individually atherogenic, the relative quantitative contribution of each cannot be determined. For this reason, it is reasonable to view the lipid triad as a whole as a "risk factor."

2) Atherogenic dyslipidemia as a target of therapy

Most therapies that lower triglyceride or raise HDL cholesterol actually modify all of the components of the lipid triad. Weight reduction in overweight and obese subjects favorably modifies atherogenic dyslipidemia;[78,79] so does increased physical activity.[146] Among lipid-lowering drugs, fibrates and nicotinic acid specifically improve all of the elements of the lipid triad.[87,138,147,148] Therefore, in considering clinical trial evidence of benefit from therapeutic modification of atherogenic dyslipidemia, all therapeutic responses together rather than individual responses in individual lipoprotein species likely determine efficacy. Although attempts have been made to dissect apart the

Table II.3–3. Primary Prevention Clinical Trials with CHD Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins

Primary prevention

Trial/Drug/ Duration of Intervention	Number of Subjects	Baseline or Placebo Lipid and Lipoprotein Values and On-Treatment Lipid and Lipoprotein in Drug Treatment Group					% Change in Coronary Event Rate (Drug vs. Placebo Groups)
		Group	TC (mg/dL)	TG (mg/dL)	Non-HDL-C (mg/dL)	HDL-C (mg/dL)	
WHO trial[149] Clofibrate 5 yrs	15,745 men lipids from Edinburgh (Subsets: n = 4935)	Placebo	257	210	—	—	-20% (p=0.05)
		On-Treatment	229	160	—	—	
Helsinki Heart Study[139] Gemfibrozil 5 yrs	4,081 men	Baseline	289	175	242	47	-34% (p<0.02)
		On-Treatment	247	115	196	51	

TC = total cholesterol; TG = triglycerides; non-HDL-C = non-HDL cholesterol; HDL-C = HDL cholesterol.

Table II.3–4. Secondary Prevention Clinical Trials with CHD Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins

Trial/Drug/ Duration of Intervention	Number of Subjects	Baseline or Placebo Lipid and Lipoprotein Values and On-Treatment Lipid and Lipoprotein in the Drug-Treatment Group					% Change in Coronary Event Rate (Drug vs. Placebo Groups)
		Group	TC (mg/dL)	TG (mg/dL)	Non-HDL-C (mg/dL)	HDL-C (mg/dL)	
Coronary Drug Project[141] Clofibrate 5 yrs	1,103 men on Clofibrate Treatment vs. 2,789 placebo	Baseline	250	177	—	—	-5% (NS)
		On-Treatment	234	149	—	—	
Coronary Drug Project[141] Nicotinic acid 5 yrs	1,119 Rx men; 2,789 placebo	Baseline	250	177	—	—	-22% p<0.05
		On-Treatment	226	143	—	—	
Newcastle Trial[150]	400 men	Baseline	245	337	—	—	-49% p<0.01
		On-Treatment	217	215	—	—	
Clofibrate 5 yrs	97 women	Baseline	270	—	—	—	
		On-Treatment	229	—	—	—	
Scottish Trial[151]	593 men	Baseline	264	—	—	—	-44% (NS)
		On-Treatment	229	—	—	—	
Clofibrate 6 yrs	124 women	Baseline	280	—	—	—	
		On-Treatment	228	—	—		
Stockholm Study[152] Clofibrate+ Nicotinic acid 5 yrs	219 men 60 women lipoproteins on subset	Baseline	251	208	203	48	-36% p<0.01
		On-Treatment	218	166	—	—	
VA-HIT Trial[48] Gemfibrozil 5 yrs	2,531 men	Baseline	175	161	143	32	-22% p<0.006
		On-Treatment	170	115	136	34	
BIP[153] Bezafibrate 6 yrs	2,825 men 265 women	Baseline	212	145	177	35	-9.4% p=0.26
		On-Treatment	202	115	161	41	

Table II.3–5. Clinical Trials with Angiographic Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins in Persons with Established Coronary Disease or CHD Equivalent

Trial/Drug/ Duration of Intervention	N	Baseline and Rx Lipid and Lipoprotein Values					Mean change, minimum lesion diameter (mm)*
		Group	Total Chol	TG	LDL	HDL	
BECAIT[154] Bezafibrate 600 mg 5 yr	92 men; 80% had mixed dyslipidemia	Baseline	266	216	180	34	-0.17 placebo -0.06 bezafibrate p<0.05
		On-Treatment	229	159	173	37	
LOCAT[155] Gemfibrozil 1200 mg 2–3 yr	395 men with Low HDL, all s/p CABG	Baseline	199	146	139	31	-0.04 placebo -0.01 gemfibrozil p=0.009
		On-Treatment	186	92	130	38	
DAIS[156] Fenofibrate	305 men 113 women with Type 2 Diabetes	Baseline	216	214	133	40	-0.06 placebo -0.01 fenofibrate p<0.029
		On-Treatment	~194	~154	~125	~43	

* Lower numbers signify less progression of lesions.

Table II.3–6. Treatment of Atherogenic Dyslipidemia with Drugs in Combination with LDL-Lowering Sequestrants or Statins

Trial/Drug/ Duration of Intervention	N	Baseline and Rx Lipid and Lipoprotein Values in Drug Group					Mean change, minimum lesion diameter (mm)*
		Group	Total Chol	TG	LDL	HDL	
CLAS[157] Niacin 3–12g + Colestipol 30g 2 yrs	162 male non-smokers s/p CABG	Baseline	246	151	171	45	-0.06 placebo +0.02 N+C p<0.01
		On-Treatment	180	110	97	61	
FATS[158] Niacin 4–6g + Colestipol 30g 2 yrs	146 men with CAD and high Apo B levels	Baseline	270	194	190	39	-0.05 usual care +0.04 N+C p=0.005
		On-Treatment	209	137	129	55	
HATS[159] Niacin 2–4g + Simvastatin 10–20 mg	160 (24 women, 136 men) with CAD, low HDL, normal LDL	Baseline	201	213	125	31	-0.14 -0.01 p<0.001
		On-Treatment	139	126	75	40	

* Positive numbers indicate net regression, compared to negative numbers which denote progression of lesions.
N = niacin; C = colestipol.

contributions of changes in individual lipoprotein species, the conclusions are always dubious. Tables II.3–3 and II.3–4 summarize the results of clinical trials in which drugs that modify atherogenic dyslipidemia—fibrates and nicotinic acid—were used. Table II.3–3 shows results of primary prevention trials, whereas Table II.3–4 summarizes secondary prevention trials.

The trials taken as a whole show a strong trend towards reduction in CHD risk through therapeutic modification of atherogenic dyslipidemia.

In addition to the endpoint trials shown in Tables II.3–3 and II.3–4, three trials of fibrate therapy have been carried out in which the endpoints are coronary

atherosclerosis as assessed by angiography. The results of these trials are summarized in Table II.3–5. They show that fibrate therapy on average causes a reduction in minimum lesion diameter of coronary arteries, without appreciably reducing LDL cholesterol.

Finally, two trials of combined drug therapy have assessed changes in coronary lumen diameter; in these trials, one drug was an LDL-lowering drug and another targeted atherogenic dyslipidemia (Table II.3–6). In both, drug therapy produced favorable changes in coronary lesions.

Taken together, these various clinical trials support a beneficial effect of drugs that favorably modify atherogenic dyslipidemia on coronary lesions and major coronary events.

Evidence statements: Atherogenic dyslipidemia commonly occurs in persons with premature CHD (C1). Moreover, atherogenic dyslipidemia strongly associates with abdominal obesity, obesity, and physical inactivity (C1). Weight reduction and increased physical activity will mitigate atherogenic dyslipidemia (A1).

Recommendation: For management of atherogenic dyslipidemia, emphasis in management should be given to life-habit modification—weight control and increased physical activity.

Evidence statement: Drugs that modify atherogenic dyslipidemia yield a moderate reduction in CHD risk (A2, B2).

Recommendation: Consideration should be given to treatment of atherogenic dyslipidemia with specific drug therapy, i.e., fibrates or nicotinic acid, in higher risk persons.

4. Nonlipid risk factors

A number of nonlipid risk factors are associated with increased CHD risk and must be considered in preventive efforts. Some of these factors are modifiable and are appropriate targets for intervention efforts in themselves (Table II.4–1). Several fixed risk factors cannot be modified; their presence signals the need for more intensive lowering of LDL cholesterol. ATP I/II and other guidelines have advocated adjusting the intensity of LDL-cholesterol therapy in the primary prevention setting according to the absolute risk for CHD. In addition, emerging risk factors promise to provide new insights into the atherosclerotic process and potentially refine risk assessment. Certainly not all of coronary risk can be explained by the major independent risk factors. Other risk factors, some of which are yet to be identified, undoubtedly influence risk independently of the major risk factors. Some of these other factors contributing to CHD risk include the life-habit risk factors (obesity, physical inactivity, and atherogenic diet), emerging risk factors, male sex, and genetic/racial/ethnic characteristics. This section will review the established nonlipid risk factors including the life-habit risk factors. The emerging risk factors are reviewed in Section II.5. The influence of racial/ethnic characteristics on risk are discussed in more detail in Section VIII.

Table II.4–1. Nonlipid Risk Factors for CHD

Modifiable Risk Factors	Nonmodifiable Risk Factors
Hypertension*	Age*
Cigarette Smoking*	Male Sex*
Thrombogenic/ Hemostatic State†	Family History of Premature CHD*
Diabetes‡	
Obesity	
Physical Inactivity	
Atherogenic Diet	

* Risk factors that are included in the ATP III CHD risk assessment algorithm.
† This risk factor is inferred from observations that antiplatelet drugs and anticoagulants have been shown to reduce risk for CHD.
‡ Modification of blood pressure and lipids in people with diabetes has been shown to reduce CHD risk. Clinical trials of improved glucose control show a trend to CHD risk reduction, but not a statistically significant reduction.

A first aim for people with modifiable nonlipid risk factors is to alter them to reduce CHD risk. Risk reduction therapies consist of smoking cessation, control of hypertension, weight reduction, increased physical activity, and improved nutrition. Control of diabeti hyperglycemia will prevent microvascular complications, although clinical trials have not unequivocally

demonstrated that improved glucose control lowers CHD events. Modification of blood pressure and lipids in people with diabetes, however, does reduce CHD risk (see discussion below). In addition, the recommendations for cholesterol management operationally take selected factors into account by setting lower thresholds for initiating treatment and lower goal levels for LDL cholesterol for those at higher risk (Table II.4–2). A low HDL cholesterol (<40 mg/dL) also counts as a major risk factor for setting lower LDL goals, whereas a higher HDL cholesterol (≥60 mg/dL) takes away one other risk factor. Evidence relating the nonlipid risk factors to CHD is summarized below (Sections II.4.a and II.4.b).

Table II.4–2.

Primary Prevention: Risk Status Based on Presence of CHD Risk Factors Other Than LDL Cholesterol

Positive Risk Factors

- Age

  Male: ≥45 years

  Female: ≥55 years
- Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)
- Current cigarette smoking
- Hypertension (≥140/90 mmHg,* or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL*)

Negative (protective) Risk Factor†

- High HDL cholesterol (≥60 mg/dL)

High risk, defined as a net of two or more CHD risk factors, leads to more vigorous intervention in primary prevention. Age (defined differently for men and for women) is treated as a risk factor because rates of CHD are higher in the older than in the young, and in men than in women of the same age. Obesity is not listed as a risk factor because it operates through other risk factors that are included (hypertension, hyperlipidemia, and decreased HDL cholesterol, as well as diabetes mellitus, which is treated as a CHD equivalent—see section II.12.b), but it should be considered a target for intervention. Physical inactivity is not listed as a risk factor to modify treatment goals for LDL cholesterol, but it too should be considered a target for intervention, and physical activity is recommended as desirable for everyone. High risk due to CHD or its equivalents is addressed directly in the algorithm.

* Confirmed by measurements on several occasions.

† If the HDL-cholesterol level is ≥60 mg/dL, subtract one risk factor (because high HDL-cholesterol levels decrease CHD risk).

a. Modifiable risk factors

1) Hypertension

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[160,161] defines categorical hypertension as a blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic or current use of antihypertensive medication. Numerous observational studies have demonstrated unequivocally a powerful association of high blood pressure with risk for CHD.[162-167] This association holds for men and women and younger and older persons. Even below categorical hypertension, subjects with high-normal blood pressure (130–139 mmHg systolic and/or 85–89 mmHg diastolic) are at increased risk for CHD compared with those with optimal values.[168,169] Clinical trials have established that blood pressure reduction in people with hypertension reduces risk for a variety of blood pressure-related endpoints including CHD.[170] This is true even for older people with isolated systolic hypertension.[165,171] Following the approach taken in ATP II,[1,2] JNC VI[160,161] employed the level of blood pressure and the concomitant presence of risk factors, coexisting cardiovascular disease (CVD), or evidence of target-organ damage to classify blood pressure severity and to guide treatment. Hypertension and high serum cholesterol often occur concomitantly.[172-174] Approaches to their joint management are considered in more detail under Section VII.6.

Evidence statements: Hypertension is a major, independent risk factor for CHD (A2, B1, C1). Treatment of hypertension does not remove all of the CHD risk accompanying elevated blood pressure (A2, B1).

Recommendation: Elevated blood pressure is a risk factor that should modify goals of LDL-lowering therapy in primary prevention (Table II.4–2). Treated hypertension should also count as a risk factor for setting goals of LDL cholesterol in primary prevention. Hypertension should be treated in all affected people according to JNC guidelines.

2) Cigarette smoking

Cigarette smoking has been established as a powerful contributor to risk for CHD and other forms of CVD.[175-186] The relationship of smoking to CVD risk is dose dependent and observed in men and women. Observational data suggest that smoking cessation reduces the risk for CVD events and that the decline in risk begins within months after quitting.[186] Randomized clinical trials of smoking cessation in primary prevention settings have revealed substantial reductions in risk for cardiac events in those who quit.[187-189] Cigarette smoking features prominently in the risk assessment component of ATP III because of the CVD risks associated with it and the substantial benefits to be derived from smoking cessation. Moreover, smokers benefit as much, if not more, from LDL-lowering therapy as do nonsmokers (Table II.2–3).

Evidence statements: Cigarette smoking is a strong, independent risk factor for CHD (C1). Smoking cessation is accompanied by a reduction in CHD risk (C1).

Recommendation: Prevention of smoking and smoking cessation should receive prime emphasis in the clinical strategy to reduce CHD risk.

3) Diabetes

Diabetes is defined as a fasting blood glucose of 126 mg/dL or greater.[190] Risk for all forms of CVD, including CHD is increased substantially with type 1 and type 2 diabetes mellitus.[191-195] Furthermore, the mortality rate in diabetic subjects who have experienced CHD is much higher than in non-diabetic subjects.[107,196,197] The increase in risk attributed to hyperglycemia per se is independent of the overweight/obesity and dyslipidemia commonly observed in persons with diabetes. Tighter glycemic control reduces risk for microvascular complications of diabetes such as renal impairment and retinopathy.[198-200] Thus far, however, improved glucose control in diabetic people has not been definitively shown to reduce macrovascular disease (CHD), although a trend toward benefit has been observed.[198-200] Importantly, management of other risk factors effectively reduces the incidence of major coronary events in persons with diabetes. This has been shown for tight blood pressure control.[201,202] Analyses of diabetic subgroups within large placebo-controlled trials of cholesterol- and triglyceride-lowering therapy have indicated that the benefits of treatment are comparable among diabetics and non-diabetics[48,203-209] (see also Table II.2–3).

A growing body of literature reveals that higher-risk people with diabetes carry an absolute risk for major coronary events similar to that of non-diabetic people with established CHD.[210-213] Although some populations with diabetes do not reach this risk level,[214] the very high morbidity and mortality after onset of CHD makes it appropriate to place most people with diabetes in a separate category of risk (see Section II.12.b).

Evidence statements: Diabetes is a major, independent risk factor for CHD and other forms of CVD (B1). Reducing cholesterol levels in people with diabetes reduces risk for CHD (see Section II.12.b).

Recommendation: The presence of diabetes should modify treatment goals for LDL cholesterol. Because of growing evidence that many people with diabetes carry a risk for CHD similar to that of people with established CHD, diabetes should be removed from the list of other risk factors that modify LDL-cholesterol goals. Instead, diabetes should be treated as a separate category of higher risk (see Section II.12.b).

4) Overweight/obesity

An estimated 97 million adults in the United States are overweight or obese.[78,79] *Obesity* is defined as a body mass index (BMI) (weight in kg divided by the square of height in meters) of ≥30 kg/m^2 and *overweight* as 25–29.9 kg/m^2.[78,79] Although some people classified as overweight actually have a large muscle mass, most persons with BMIs of 25 to 29.9 kg/m^2 have excess body fat. Overweight and obesity not only predispose to CHD, stroke, and numerous other conditions, they also are associated with a greater all-cause mortality.[215-218] People who are overweight or obese have a high burden of other CHD risk factors including dyslipidemia (high LDL cholesterol, low HDL cholesterol, and high VLDL and triglycerides),[76,77,219-221] type 2 diabetes[222,223] and hypertension.[224-226]

Obese individuals who do not yet have these risk factors are at increased risk for developing them. The Framingham Heart Study confirms that obesity is strongly predictive of CHD. Risk for CVD is particularly raised when abdominal obesity is present; *abdominal obesity is defined* by a waist circumference greater than 102 cm (40 inches) in men or 88 cm (35 inches) in women.[78,79]

Despite the strong association between various indicators of obesity and risk for CHD, ATP III does not list obesity among the risk factors that modify the treatment goals for LDL cholesterol. Much of the risk associated with overweight and obesity appears to be mediated through the major risk factors. The independent component of risk has not been quantified. Furthermore, the prevalence of overweight and obesity in the U.S. population is so high that counting them as risk factors to modify LDL goals would enormously expand the population having multiple risk factors, causing an even greater increase in usage of LDL-lowering drugs than will result from the intensified management of persons with multiple risk factors outlined in ATP III. Instead, ATP III identifies overweight and obesity as direct targets of weight-reduction intervention; this approach will achieve more overall risk reduction than will LDL lowering without an emphasis on weight control.

Evidence statement: Obesity is a major, modifiable risk factor for CHD (C1). Nevertheless, the incremental risk imparted by obesity independently of accompanying risk factors is uncertain.

Recommendation: Obesity should be considered a direct target for clinical intervention rather than an indicator for lipid-modifying drug treatment. Because of the association of obesity with other risk factors, obesity should not be included as a factor influencing treatment goals of LDL cholesterol in primary prevention.

5) Physical inactivity

Physical inactivity is associated with increased risk for CHD. Conversely, physical activity favorably modifies several risk factors; it has been reported to lower LDL and triglyceride levels, raise HDL cholesterol, improve insulin sensitivity, and lower blood pressure.[227-230] Evidence that physical activity can reduce risk for CHD comes from multiple observational studies.[231-236] Therefore, physical inactivity is widely designated to be a major risk factor for CHD.[1,2,237,238] In ATP III, physical inactivity also is listed as a major modifiable risk factor. The mechanisms whereby physical inactivity raises risk for CHD are not fully understood and are probably multifactorial. Physical inactivity reduces caloric expenditure and probably contributes to obesity and to its associated lipid and nonlipid risk factors,[239] as well as to insulin resistance.[240] Beyond its effects on standard risk factors, physical inactivity may have adverse effects on cardiovascular fitness and function. Many of the adverse effects of a sedentary lifestyle that raise CHD risk can be inferred from the actions of increased physical activity, which include reduction in insulin resistance, lowering of blood pressure, reducing serum triglycerides, raising HDL cholesterol, and improving cardiovascular risk.[238]

Although ATP III specifies physical inactivity as a major modifiable risk factor, it does not list it as a risk factor that modifies LDL-cholesterol goals. Because of the collinearity of physical inactivity with other independent risk factors, there is some confounding between physical inactivity and the risk factors that modify LDL goals. Nonetheless, physical inactivity is designated as a major target of intervention for therapeutic lifestyle changes. Undoubtedly some of the benefit of increased physical activity is mediated through mechanisms other than the measured risk factors. In addition, after setting LDL-cholesterol goals with standard risk factors, a physician can take into account a person's levels of physical activity and fitness when adjusting the intensity of LDL-lowering therapy.

It has been suggested that a history of regular physical activity should count as a "negative risk factor," similarly to high HDL cholesterol. Although regular physical activity undoubtedly reduces baseline risk for CHD and should be encouraged, ATP III does not specifically count it as a negative risk factor for setting the goal level for LDL cholesterol.

Evidence statements: Physical inactivity is a major, modifiable risk factor for CHD (C1). However, a portion of the increased risk for CHD accompanying physical inactivity can be explained by associated major risk factors (C2). Regardless of mechanism, increased physical activity will reduce risk for CHD (B2, C1).

Recommendations: Physical inactivity should be a direct target for clinical intervention. Increased physical activity in accord with a person's overall health status should be encouraged as part of lifestyle therapies to reduce risk for CHD. Patients undergoing clinical cholesterol management should be provided with guidance for safe forms of physical activity that will reduce CHD risk beyond LDL-lowering therapy.

A history of physical inactivity should not be counted as a risk factor for setting goals for LDL cholesterol in primary prevention. However, clinical judgment can be used to decide whether to intensify LDL-lowering therapy in physically inactive persons, or to reduce intensity of therapy in physically active persons.

6) Atherogenic diet

Prospective studies in populations show that dietary patterns modify the baseline CHD risk of populations.[241,242] In high-risk populations, some of the adverse effects of diet composition undoubtedly relate to established risk factors, e.g., effects of high intakes of saturated fatty acids and cholesterol on LDL-cholesterol levels and of high salt intakes on blood pressure. Moreover, dietary patterns appear to influence baseline risk beyond the known risk factors. For example, populations that consume diets high in fruits, vegetables, whole grains, and unsaturated fatty acids appear to be at a lower baseline risk than can be explained by standard risk factors. The particular nutrients that impart this lower risk have not been adequately defined, but strong candidates include antioxidant nutrients, folic acid, other B-vitamins, omega-3 fatty acids, and other micronutrients.[242]

Evidence statements: An atherogenic diet is a major, modifiable risk factor for CHD (C1). High intakes of saturated fatty acids and cholesterol directly raise LDL-cholesterol concentrations (see Section V.5). Further, certain dietary patterns appear to modify baseline risk for CHD, independently of effects on LDL cholesterol (see Sections V.1, V.4, and V.5.c).

Recommendation: Modification of an atherogenic diet should be employed to reduce CHD risk as part of overall therapeutic lifestyle changes for CHD risk reduction (see Section V). However, consumption of an atherogenic diet should not be included among risk factors to modify LDL-cholesterol goals in primary prevention.

b. Nonmodifiable risk factors

1) Age

Risk for coronary disease increases steeply with advancing age in men and women. At any given level of LDL cholesterol, risk for CHD is higher in older than in younger people.[10] The principal reason that risk rises with age is that age is a reflection of the progressive accumulation of coronary atherosclerosis, which in turn reflects the cumulative exposure to atherogenic risk factors, both known and unknown. On average, older persons have more coronary atherosclerosis than do younger persons. Once atherosclerosis develops, the coronary plaque itself becomes a "risk factor" for development of clinical CHD. This is because plaque ruptures produce acute coronary events (unstable angina or myocardial infarction), or when plaques grow large, coronary obstructive symptoms (angina pectoris) occur. Recent clinical trials indicate that older persons benefit from LDL-lowering therapy similarly to middle-aged individuals (Table II.2–3).

Evidence statement: Advancing age is a major, independent risk factor for CHD (C1).

Recommendation: Age should count as a risk factor to modify LDL-cholesterol goals in primary prevention.

2) Male sex

The rise in absolute risk with aging becomes most clinically significant in men in their mid-forties and in women about the time of the menopause. At any given age men are at greater risk for coronary disease than are women.[10] Risk in women lags about 10 to 15 years behind that of men. The reasons for a gender difference in CHD risk are not fully understood. Part of the difference can be explained by the earlier onset of risk factors in men, e.g., elevations of LDL cholesterol and blood pressure, and lower HDL cholesterol. However, the Framingham Heart Study has shown that the differences in absolute risk between the sexes cannot be explained entirely by standard risk factors. Nonetheless, women respond to LDL-lowering therapy with a reduction in relative risk similarly to men (Table II.2–3).

Evidence statement: Men have a higher baseline risk for CHD than do women at all ages, except perhaps in the oldest age group (>80 years) (C1).

Recommendation: An age cutpoint at which age becomes a risk factor to modify goals for LDL cholesterol should be set lower in men (≥45 years) than in women (≥55 years) in primary prevention (Table II.4–2).

3) Family history of premature CHD

CHD tends to cluster in families, and a positive family history of premature CHD counts as a risk factor. Several prospective studies[243-255] indicate that a family history of premature CHD is an *independent* risk factor even when other risk factors are taken into account. Relative risk for CHD in first-degree relatives has been reported to range from two to as high as 12 times that of the general population.[256-258] Risk increases with the number of primary relatives affected and at younger ages of onset in the probands.[259,260] The clustering of CHD risk in families most closely resembles diseases of polygenic origin and does not follow a Mendelian recessive or dominant pattern that suggests a single gene locus.[261] Among primary relatives, it appears that siblings of probands have the highest relative risk, probably due to shared sociocultural environment, exposures, and genetics. Many prospective cohort and case-control investigations, including the recent Atherosclerosis Risk In Communities Study (ARIC) in four U.S. communities, show this risk to be independent of known risk factors.[253,262] Many risk factors are under genetic control (e.g., blood pressure, lipids and lipoproteins, Lp(a), and obesity), but they account for only a portion of the aggregation of CHD seen in families.[263,264] While family history is immutable, a large number of modifiable risk factors are found in people with a history of premature CHD in a first-degree relative.[265,266] This has been demonstrated in both genders and in most races. The Framingham Heart Study family history analysis does not demonstrate sufficient incremental risk for family history to be included in risk assessment equations. Nonetheless, a body of compelling case-control and cohort studies has found family history to be independently associated with higher risk status. The variance across studies depends on the way in which family history is assessed. In the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study and in the Newcastle Family History Study, self-report of a family history of premature CHD in a first degree relative has been found to be reasonably accurate with sensitivity above 80 percent and specificity about 90 percent.[253,267,268]

Evidence statements: A positive family history for CHD in a first-degree relative (parent, sibling, or offspring) is a major risk factor for CHD. Often a positive family history is associated with a high prevalence of modifiable risk factors (C1); however, a positive family history carries excess risk beyond standard measurements of risk factors (C1). Risk for CHD is higher the younger the age of onset in the affected family member and the greater the number of affected first degree relatives (C1).

Recommendation: The presence and age of onset of CHD in all first-degree relatives should be assessed. The family history should be considered positive for premature CHD if clinical CHD or sudden death can be documented in first degree male relatives younger than 55 years of age and in first degree female relatives younger than 65 years of age. Because a positive family history of premature CHD is immutable but bears information about the risk for CHD and the probability of having modifiable risk factors, it should serve as a factor in making treatment decisions relative to setting and reaching LDL-cholesterol goals in primary prevention (Table II.4–2).

5. Emerging risk factors

The major risk factors listed in Table II.4–2, along with elevated LDL cholesterol, are powerfully associated with the development of CHD. Although several of them are directly atherogenic, their power to predict CHD is still limited. Most of the *excess* risk for CHD can be explained by the major risk factors; this is shown by the very low risk in persons who have optimal levels of all of these risk factors (see Primary Prevention [Section II.7]). Nonetheless, when major risk factors are present, they account for only about half of the *variability* in CHD risk in the U.S. population; other factors, yet to be identified, seemingly influence how much the major risk factors affect absolute CHD risk. Consequently there has been intensive research to identify new risk factors that will enhance predictive power in individuals. These newer factors can be called *emerging risk factors*. For present purposes, these can be conveniently divided into three categories: lipid risk factors, nonlipid risk factors, and subclinical atherosclerotic disease (see below).

To determine the clinical significance of the emerging risk factors, they must be evaluated against the following criteria used to identify the major risk factors:

- Significant predictive power that is independent of the other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population-reference values, and be relatively stable biologically
- Preferably, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk

In the discussion to follow, the *emerging risk factors* are evaluated against these criteria. Even when a factor does not qualify as a major risk factor for routine measurement, its association with CHD risk deserves some consideration. A review of the key literature is required to determine whether the putative risk factor deserves to be elevated to the level of a major risk factor, and if not, whether it can still be used in selected persons as an adjunct to risk assessment. Even if neither is the case, the risk factor often remains a direct target of therapy, unrelated to modifying LDL-cholesterol goals. If the emerging risk factor is a lipid parameter, its treatment will be considered in more detail elsewhere in this report. If it is a nonlipid risk factor, the reader will be referred to other sources for information on therapy.

A foundation of ATP III is that the major risk factors define absolute risk and thereby modify LDL-cholesterol goals. An initial assessment of risk is made on the basis of these risk factors before any consideration is given to whether emerging risk factors should influence goals or therapies. The same reasoning holds for underlying risk factors: obesity, physical inactivity, and atherogenic diet. On the other hand, ATP III does not discount the influence of underlying or emerging risk factors. *They can be taken into consideration according to clinical judgment as optional modifiers of therapy, but they should be used only as an adjunct to adjust the estimate of absolute risk status obtained with the major risk factors.*

a. Emerging lipid risk factors

1) Triglycerides

Elevated serum triglycerides have long been considered a risk factor by some investigators. The status of triglycerides as a risk predictor is reviewed in other sections of this report (Sections II.3.a and VII.2). Two questions about triglycerides persist: (a) whether they constitute an independent risk factor for CHD and (b) whether they should be a direct target for therapy. Although recent data point to some independence in risk prediction, their close association with other lipid risk factors (remnant lipoproteins, small LDL, low HDL cholesterol) and nonlipid risk factors makes the issue of their "independence" open to considerable question. In this report, elevated triglycerides are viewed as a marker for other lipid and nonlipid risk factors that themselves raise risk; however, elevated triglycerides per se are not designated a major risk factor to modify goals for LDL cholesterol. Nonetheless, ATP III gives increased weight to elevated triglycerides in cholesterol management in two ways: (a) as a marker for atherogenic remnant lipoproteins and (b) as a marker for other lipid and nonlipid risk factors in the metabolic syndrome (see Section II.6). The former leads to non-HDL cholesterol as a secondary target of therapy when triglycerides are high, whereas the latter calls for more intensive lifestyle therapies (see Section V).

2) Lipoprotein remnants

Many lines of evidence point to the atherogenic potential of lipoprotein remnants (see Section II.3.a.2). Although no single finding confirms remnant lipoproteins as an independent risk factor, circumstantial evidence is strong. Lipoproteins called beta-VLDL, which are apolipoprotein E-enriched remnants and are typical of dysbetalipoproteinemia, almost certainly are atherogenic, because dysbetalipoproteinemia is accompanied by increased risk for CHD (see Section VII). High serum levels of lipoproteins enriched in apolipoprotein C-III, another form of VLDL remnants, appear to be atherogenic as well.[64,65,68,69,269] Several assays are available for identification and measurement of remnant lipoproteins; these include ultracentrifugation, electrophoresis, and immunological techniques. Remnant-like particles (RLP) measured immunologically appear to be a promising risk predictor.[270-273] Even so, prospective studies relating various remnant measures to CHD risk are limited, and measurement with specific assays cannot be recommended for routine practice. Nonetheless, as discussed earlier (see Section II.3.a), ATP III identifies elevated VLDL cholesterol as the surrogate for elevated atherogenic remnants in persons with triglycerides ≥200 mg/dL.

3) Lipoprotein (a)

Several studies[274-277] report a strong association between Lp(a) levels and CHD risk. Indeed, a recent meta-analysis of reported prospective studies supports an independent predictive power for elevated Lp(a).[278] In addition, concomitant elevations of Lp(a) and LDL cholesterol have been reported to have synergy in elevating risk in both men and women with hypercholesterolemia. On the basis of these studies, some authorities hold that an elevation of Lp(a) is an independent risk factor for CHD. It must be noted nonetheless that several prospective studies[279,280] do not confirm independent prediction. Of note, Lp(a) levels are higher in African Americans than in Caucasians, but an increased risk for CHD associated with higher Lp(a) levels in African Americans has not been documented.[279] Thus, the quantitative contribution of elevated Lp(a) to CHD risk beyond the major risk factors is uncertain. This uncertainty extends both to individuals and populations; in the latter, the frequency of elevated Lp(a) is not as high as for the major risk factors.

Moreover, issues related to measurement of Lp(a) in clinical practice have not been fully resolved.[281,282] Measurement of Lp(a) is made by immunological methods, and standardized methods are available only in a few reference laboratories. Population reference levels are available from these laboratories, but they are not widely available in clinical practice. Accurate methodology has not yet been established in most clinical chemistry laboratories; samples generally must be sent to special laboratories for measurement. As a result, extra expense in measurement is required. Serum Lp(a) is relatively resistant to therapeutic lowering. Statin drugs are ineffective. Among currently available drugs, only nicotinic acid reduces Lp(a) concentrations, and only moderately.[283,284] In postmenopausal women, estrogen therapy also causes some reduction in Lp(a) concentrations.[285] Although these therapies typically lower elevated Lp(a) levels, they have not been widely adopted. At present no clinical trial evidence supports a benefit from lowering Lp(a) levels with particular agents.

Despite limitations in measurement and therapy, some authorities believe that Lp(a) measurement is a useful addition to the major risk factors for identifying persons at still higher risk than revealed by those factors. According to advocates for Lp(a), the option of measurement is best reserved for persons with a strong family history of premature CHD or those with genetic causes of hypercholesterolemia, such as familial hypercholesterolemia.[281,282] An elevated Lp(a) thus presents the option to raise a person's risk to a higher level. For example, if a person has a high LDL cholesterol and only one other risk factor, the finding of a high Lp(a) could count as a second risk factor to justify a lower goal for LDL cholesterol. ATP III did not find strong evidence to support this approach, but accepts it as an option for selected persons.

4) Small LDL particles

One component of atherogenic dyslipidemia is small LDL particles. They are formed in large part, although not exclusively, as a response to elevations of triglycerides. Their presence is associated with an increased risk for CHD;[125,286,287] however, the extent to which they predict CHD independently of other risk factors is unresolved.[288] Moreover, standard and inexpensive methodologies are not available for their measurement. For these reasons, ATP III does not recommend

measurement of small LDL particles in routine practice. If the clinical decision is made to detect and measure small LDL, their presence is best used as an indicator for atherogenic dyslipidemia and the metabolic syndrome. Their elevation also supports intensified therapeutic lifestyle changes. If small LDL particles accompany elevated triglycerides or low HDL cholesterol in high-risk persons, consideration can be given to using nicotinic acid or fibric acid as components of lipid-lowering therapy. Nonetheless, LDL cholesterol remains the primary target of treatment in persons with small LDL particles.

5) HDL subspecies

HDL comprises several components and subfractions that also have been related to CHD risk. While HDL cholesterol is the risk indicator most often used, HDL subfractions (LpAI and LpAI/AII and/or HDL_3 and HDL_2) have also been used for risk prediction. Although small studies suggest greater predictive power of one or another HDL component, their superiority over HDL cholesterol has not been demonstrated in large, prospective studies. Moreover, measures of HDL subspecies are not readily available in clinical practice. Consequently, ATP III does not recommend the routine measurement of HDL subspecies in CHD risk assessment.

6) Apolipoproteins

a) Apolipoprotein B

Apolipoprotein B is a potential marker for all atherogenic lipoproteins. It has been proposed as an alternative to LDL cholesterol as a risk factor (see Section II.3.b). Limited epidemiological and clinical trial evidence supports its superiority over LDL cholesterol in risk prediction.[289,290] Nonetheless, the body of evidence in favor of apolipoprotein B has not been developed sufficiently to justify replacing LDL cholesterol, which itself is a powerful independent predictor of CHD (see Section II.2). In addition, from the viewpoint of ATP III, the question is whether apolipoprotein B is preferred as a target of therapy, not as a factor in risk assessment. Although LDL cholesterol and apolipoprotein B are highly correlated in persons with normal triglyceride levels, the apolipoprotein B level typically is disproportionately higher in persons with hypertriglyceridemia. ATP III takes this difference into account and sets a secondary target, non-HDL cholesterol, in persons with hypertriglyceridemia. Non-HDL cholesterol is significantly correlated with apolipoprotein B and can serve as a "surrogate" for it. The non-HDL-cholesterol measure is readily available in clinical practice, whereas standardized apolipoprotein B measures are not widely available, and in any case, would add expense beyond routine lipoprotein analysis.

b) Apolipoprotein A-I

Apolipoprotein A-I is carried in HDL, and it is usually low when HDL is reduced. A low apolipoprotein A-I thus is associated with increased risk for CHD, but not independently of low HDL. Whether it has independent predictive power beyond HDL cholesterol is uncertain. In any case, standardized methodology for estimating apolipoprotein A-I is not widely available. Its measurement thus is not recommended for routine risk assessment in ATP III.

7) Total cholesterol/HDL-cholesterol ratio

Many studies show that the total cholesterol/HDL-cholesterol ratio is a powerful predictor of CHD risk. Some investigators[291-294] propose that this "cholesterol ratio" is a simple approach for lipid risk assessment. This ratio reflects two powerful components of risk. A high total cholesterol is a marker for atherogenic lipoproteins, whereas a low HDL cholesterol correlates with the multiple risk factors of the metabolic syndrome and probably imparts some independent risk. In fact, however, the total cholesterol/HDL-cholesterol ratio is subsumed in the Framingham global risk equations that are the basis of the 10-year risk assessment used in ATP III. In this way, ATP III incorporates cholesterol ratios into risk assessment. If risk assessment is done using Framingham risk factors as continuous variables (e.g., by risk equations), then the ratio is essentially incorporated. If risk assessment is made using total cholesterol and HDL cholesterol in graded incremental steps (see Section III), then the ratio is applied approximately. Regardless, ATP III does not define the total cholesterol/HDL-cholesterol ratio as a specified lipid target of therapy. Instead, LDL cholesterol is retained as the primary target of lipid-lowering therapy. Nor is the total cholesterol/HDL-cholesterol ratio recommended as a secondary target of therapy. Treatment of ratios will divert priority from specific lipoprotein fractions as targets of therapy.

b. Emerging nonlipid risk factors

1) *Homocysteine*

Elevations of serum homocysteine are positively correlated with risk for CHD.[295-303] The mechanism of the link between homocysteine and CHD is not well understood, although persons with inherited forms of severe homocysteinemia have premature vascular injury and atherosclerosis. In any case, the strength of association between homocysteine and CHD is not as great as that for the major risk factors. Moreover, an elevation of homocysteine is not as common as that of the major risk factors. For these reasons, ATP III does not list elevated homocysteine as a major risk factor to modify LDL-cholesterol goals.

Even though elevated homocyteine is not classified as a major risk factor, some investigators hold that the association with CHD is strong enough to make it a direct target of therapy. The available intervention for elevated homocysteine is dietary folic acid, perhaps combined with other B vitamins (B_6 and B_{12}).[298] Measurement of homocysteine is an option favored by some authorities, with the aim of treating with supplemental B vitamins. Others, however, contend that measurement of homocysteine adds little to risk reduction provided that persons are consuming recommended dietary allowances of folic acid. Several clinical trials are underway to test whether homocysteine lowering will reduce CHD risk.[304] It had been predicted that the recent institution of folate fortification of foods would reduce average levels of homocysteine in the U.S. population.[305,306] Recent data show that this has occurred.[307] Substantial increases in serum folate in young women have also been documented.[308]

ATP III does not recommend routine measurement of homocysteine as part of risk assessment to modify LDL-cholesterol goals for primary prevention. This lack of recommendation is based on uncertainty about the strength of the relation between homocysteine and CHD, a lack of clinical trials showing that supplemental B vitamins will reduce risk for CHD, and the relatively low prevalence of elevated homocysteine in the U.S. population. Measurement of homocysteine nonetheless remains an option in selected cases, e.g., with a strong family history of premature CHD in an otherwise low-risk patient. If elevated, the clinical approach favored by ATP III is to determine vitamin B_{12} level and, if this is normal, to ensure adequate folate intake rather than modifying the LDL-cholesterol goal.

2) *Thrombogenic/hemostatic factors*

Thrombosis plays a key role in acute coronary syndromes, including myocardial infarction.[309] Both platelets and coagulation factors are involved in the thrombotic process. Although the precise hemostatic or prothrombotic mechanisms that predispose to myocardial infarction have not been worked out, the evidence that aspirin and other antiplatelet therapy can reduce risk is compelling and suggests a role for platelet hyperaggregability.[310-312] Another hemostatic factor associated with CHD risk is fibrinogen.[313-316] A high fibrinogen level associates significantly with increased risk for coronary events, independent of cholesterol level; and conversely, a low fibrinogen level indicates a reduced risk, even in the presence of high total cholesterol levels. Other hemostatic factors that have been found to be associated with increased coronary risk include activated factor VII, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), von Willebrand factor, factor V Leiden, protein C, and antithrombin III. Studies have shown that some of these prothrombotic factors are elevated as a component of the metabolic syndrome.

ATP III does not recommend measurement of prothrombotic factors as part of routine assessment of CHD risk. The strength of the association between any of these factors and CHD risk has not been defined. Specific therapeutic interventions, other than aspirin or warfarin therapy, are not available in clinical practice. Clinical trials have not been carried out that target specific prothrombotic factors. Laboratory measurements for prothrombotic factors are not widely available, nor have they been standardized. This said, it is worth noting that the metabolic syndrome is often accompanied by a prothrombotic state, and life-habit intervention to reverse the metabolic syndrome reduces serum levels of prothrombotic factors.

3) Inflammatory markers

The increasing recognition that atherosclerosis involves a chronic inflammatory process has brought greater attention to arterial "inflammation" as a risk factor for major coronary events. In fact, recent reports indicate that serum inflammatory markers, such as C-reactive protein (CRP), carry predictive power for coronary events.[317-322] High sensitivity (hs) CRP appears to be the most reliable inflammatory marker available at present. Cigarette smoking, which apparently promotes arterial inflammation and predisposes to major coronary events, is associated with higher levels of CRP.[323] Because of the growing evidence that inflammation within coronary plaques predisposes to plaque rupture, one theory holds that an elevation of hs-CRP reflects the presence of "unstable" plaques. The recent observations that obesity and the metabolic syndrome are commonly accompanied by increases in CRP also suggest a close link between metabolic derangement and inflammation.[324-326] Although adverse metabolism could activate immune mechanisms and predispose to major coronary events, some investigations suggest that chronic, low-grade infections of the arterial wall accelerate atherogenesis and lead to CHD. Infectious agents that have been implicated are Chlamydia pneumoniae and cytomegalovirus.

ATP III does not recommend routine measurement of inflammatory markers for the purpose of modifying LDL-cholesterol goals in primary prevention. A growing body of literature nonetheless suggests that inflammatory markers such as hs-CRP carry some independent predictive power beyond lipid risk factors.[321] The extent to which they provide extra prediction beyond all the major risk factors combined is uncertain. Nonetheless, in the opinion of some investigators,[321] in persons with elevated hs-CRP, consideration can be given to more aggressively lowering LDL-cholesterol levels than indicated by the goals set by the major risk factors in ATP III.

4) Impaired fasting glucose

A common metabolic abnormality in the metabolic syndrome is an impaired fasting glucose (glucose 110–125 mg/dL). According to the Framingham Heart Study, the association between elevated plasma glucose and CHD risk is a continuous variable; some investigators thus view impaired fasting glucose to be an independent risk factor.[327,328] However, to other researchers, the strong association between impaired fasting glucose and other risk factors of the metabolic syndrome casts doubt on the independent predictive power of impaired fasting glucose.[329-332] Moreover, at present, impaired fasting glucose cannot be considered a direct target for drug therapy, although weight reduction and increased physical activity will often correct it. Thus, ATP III identifies impaired fasting glucose as one component of the metabolic syndrome that signifies the need for more intensive lifestyle therapies, i.e., weight reduction and increased physical activity. However, its presence does not place a person in the same high-risk category as does overt diabetes; neither does it count as a risk factor to modify the LDL-cholesterol goal.

c. Subclinical atherosclerotic disease

A large body of data indicates that persons with advanced subclinical coronary atherosclerosis are at greater risk for major coronary events than are persons with less severe atherosclerosis. Although the precise relationship between subclinical atherosclerotic disease and CHD risk has not been defined, subclinical disease must be classified as an emerging risk factor. The American Heart Association recently held a conference (Prevention Conference V) to assess the current status of subclinical atherosclerosis as a predictor of major coronary events.[333-336] The major findings of this report represent current understanding of the predictive power of subclinical disease. The conclusions of the Prevention Conference V report are represented in the position of ATP III on subclinical atherosclerotic disease.

1) Ankle-brachial blood pressure index (ABI)

The ABI is a simple, inexpensive, noninvasive test to confirm the clinical suspicion of lower extremity peripheral arterial disease (PAD). It is performed by measuring the systolic blood pressure (by Doppler probe) in brachial, posterior tibial, and dorsalis pedis arteries. An ABI of <0.9, found in either leg, is diagnostic of PAD, and prospective studies indicate that risk for major coronary events is in the range of that of persons with established CHD.[337,338] The test is most likely to be positive in persons over age 50 who have other risk factors. A strong case can be made that a positive ABI essentially constitutes a *diagnosis* of PAD. Consequently the ABI can be considered a diagnostic test to identify persons at high risk for CHD (see Section II.12.a).

2) Tests for myocardial ischemia

Tests available in this category include standardized exercise electrocardiogram (ECG) testing, myocardial perfusion imaging, and stress echocardiography. Exercise ECG testing has been extensively studied. A positive exercise ECG in asymptomatic, middle-aged men with traditional risk factors carries independent predictive power for major coronary events; thus, exercise testing carries the potential to identify middle-aged men who are at higher risk than revealed by the major risk factors. Consequently a positive test could call for more aggressive risk-reduction therapies. The same predictive power apparently does not hold for young adults and middle-aged or older women; a "positive" test is much less predictive of major coronary events. In these groups, the likelihood of inappropriate application of aggressive preventive measures is increased. Myocardial perfusion imaging and stress echocardiography have been less extensively evaluated for their predictive power, although they appear to contain independent prognostic information. Certainly a positive perfusion imaging result obtained in middle-aged men with multiple risk factors and men ≥45 years with a strong family history of CHD is strongly indicative of obstructive coronary atherosclerosis and carries a high risk for acute coronary syndromes. The decision to employ perfusion imaging in appropriately selected persons depends on clinical judgment. The expense of the test and its low yield of positive outcomes makes it unsuitable for routine risk assessment in asymptomatic persons, but does not exclude its clinical utility in selected persons. In ATP III, the presence of myocardial ischemia appropriately identified by stress testing qualifies as a diagnosis of CHD.

3) Tests for atherosclerotic plaque burden

a) Carotid intimal medial thickening

One test in this category is *carotid sonography* used to measure intimal medial thickness (IMT) of the carotid arteries.[336] The extent of carotid atherosclerosis correlates positively with the severity of coronary atherosclerosis. Furthermore, recent studies show that severity of IMT independently correlates with risk for major coronary events.[336,339-341] Thus, measurement of carotid IMT theoretically could be used as an adjunct in CHD risk assessment. For instance, the finding of an elevated carotid IMT (e.g., ≥75th percentile for age and sex) could elevate a person with multiple risk factors to a higher risk category. However, its expense, lack of availability, and difficulties with standardization preclude a current recommendation for its use in routine risk assessment for the purpose of modifying intensity of LDL-lowering therapy. Even so, if carried out under proper conditions, carotid IMT could be used to identify persons at higher risk than that revealed by the major risk factors alone.

b) Coronary calcium

Another indication of subclinical coronary atherosclerosis is coronary calcium as detected by *electron beam computed tomography (EBCT)* or *spiral CT.* Amounts of coronary calcium correlate positively with coronary plaque burden. Therefore, a high coronary calcium score should carry predictive power for major coronary events.[333,336] Several studies indicate that, in persons with multiple risk factors, a concomitantly high coronary calcium score places persons in the range of a CHD risk equivalent.[342-346] A recent report by the American College of Cardiology/American Heart Association (ACC/AHA) acknowledged the potential power of coronary calcium to predict major coronary events.[347,348] At the same time, this report emphasized the limitations of the technique as a tool to diagnose obstructive coronary disease for the purpose of coronary revascularization. Despite these limitations, both the Prevention V report and the ACC/AHA report affirmed that use of EBCT for risk prediction can be an option, provided its use is limited to patients referred by physicians. Under these circumstances, when used appropriately, measurement of coronary calcium could be of value for persons whose absolute risk is greater than that revealed by the major risk factors. Thus, a high coronary calcium score in a patient with multiple risk factors is consistent with a still higher risk state.

In accord with recent reports,[334,347,348] ATP III does not recommend EBCT for indiscriminate screening for coronary calcium in asymptomatic persons, particularly in persons without multiple risk factors. Its predictive power for persons without multiple risk factors has not been determined in prospective studies. Testing is relatively expensive and not widely available. It should be used primarily as an adjunct to modify risk assessment based on the major risk factors. Only in exceptional cases should it evoke further invasive diagnostic tests and interventions. Despite uncertainties as to the predictive power of coronary calcium, ATP III supports the conclusions of AHA's Prevention Conference V

and the ACC/AHA report that high coronary calcium scores signify and confirm increased risk for CHD when persons have multiple risk factors. Therefore, measurement of coronary calcium is an option for advanced risk assessment in appropriately selected persons, provided the test is ordered by a physician who is familiar with the strengths and weaknesses of noninvasive testing. In persons with multiple risk factors, high coronary calcium scores (e.g., ≥75th percentile for age and sex) denotes advanced coronary atherosclerosis and provides a rationale for intensified LDL-lowering therapy. Moreover, measurement of coronary calcium is promising for older persons in whom the traditional risk factors lose some of their predictive power.[349] For example, a high coronary calcium score could be used to tip the balance in favor of a decision to introduce LDL-lowering drugs for primary prevention in older persons.

6. Metabolic syndrome

a. Metabolic syndrome as multiple, interrelated factors that raise risk

This syndrome has become increasingly common in the United States. It is characterized by a constellation of metabolic risk factors in one individual.[350-352] The root causes of the metabolic syndrome are overweight/obesity, physical inactivity, and genetic factors. The metabolic syndrome is closely associated with a generalized metabolic disorder called *insulin resistance,* in which tissue responsiveness to the normal action of insulin is impaired.[353-355] Some individuals are genetically predisposed to insulin resistance; in these persons, acquired factors (excess body fat and physical inactivity) elicit insulin resistance and the metabolic syndrome. Most persons with insulin resistance have abdominal obesity.[356-358] The mechanistic connections between insulin resistance and metabolic risk factors are not fully understood and appear to be complex. Various risk factors have been included in the metabolic syndrome; the following list contains those factors that are generally accepted as being characteristic of this syndrome:

- Abdominal obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance ± glucose intolerance
- Prothrombotic state
- Proinflammatory state

Because of the high degree of association of these risk factors in persons with the metabolic syndrome, it has proven difficult to dissect the individual contributions of each factor to CHD risk. However, there is little doubt that this syndrome taken in aggregate enhances the risk for CHD at any given LDL-cholesterol level. From a population viewpoint, the increasing prevalence of the metabolic syndrome threatens to partially reverse the reduction in CHD risk that has resulted from a decline in serum LDL cholesterol levels in the U.S. population, which has occurred over the past three decades. The metabolic syndrome and its associated risk factors have emerged as a coequal partner to cigarette smoking as contributors to premature CHD.[10,78,79,238,359,360] In addition, the insulin resistance accompanying the metabolic syndrome is one of the underlying causes of type 2 diabetes.[361,362] For these reasons, ATP III places increased emphasis on the metabolic syndrome as a risk enhancer.

There are two general approaches to the treatment of the metabolic syndrome. The first strategy modifies root causes, overweight/obesity and physical inactivity, and their closely associated condition, insulin resistance. Weight reduction[363-365] and increased physical activity[240,366] both lower insulin resistance and indirectly mitigate the metabolic risk factors. The second approach directly treats the metabolic risk factors—atherogenic dyslipidemia, hypertension, the prothrombotic state, and underlying insulin resistance. At present, most success in clinical practice comes from pharmacological modification of the associated risk factors. However, the greatest potential for management of the syndrome lies in reversing its root causes. ATP III promotes this latter approach, which is a major new initiative for persons entering clinical cholesterol management.

Evidence statements: The presence of the metabolic syndrome accentuates the risk accompanying elevated LDL cholesterol (C1). This increase in risk appears to be mediated through multiple risk factors—major and emerging risk factors (C1).

Clinical trials show that modifying three major components of the metabolic syndrome—atherogenic dyslipidemia (B2), hypertension (A2, B1),[160,161] and the prothrombotic state (A2, B1)—will reduce risk for CHD.

Recommendations: Increased emphasis should be placed on therapeutic modification of the metabolic syndrome in persons undergoing LDL-lowering therapy. Primary management of the metabolic syndrome should be to reverse its root causes—overweight/obesity and physical inactivity. In addition, other lipid and nonlipid risk factors associated with the metabolic syndrome should be appropriately treated.

The presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL-cholesterol goals are set with the major risk factors. Primary emphasis nonetheless should be given to modifying the underlying risk factors (overweight/obesity and physical inactivity) and other risk factors associated with the metabolic syndrome.

b. Diagnosis of metabolic syndrome

There are no well-accepted criteria for the diagnosis of the metabolic syndrome. Nonetheless, many persons seen in clinical practice are readily recognized as having multiple metabolic risk factors. Most persons with the metabolic syndrome are overweight or obese; clinical studies have noted a high correlation between abdominal obesity and the risk factors characteristic of the metabolic syndrome.[356,358,367,368] For example, closely associated with abdominal obesity is an elevation of serum triglycerides.[369-371] The elevation can be either borderline high (150–199 mg/dL) or high (≥200 mg/dL). A higher triglyceride level is usually accompanied by lower HDL-cholesterol concentrations.[124,372] HDL-cholesterol levels <40 mg/dL occur commonly in men with insulin resistance.[135] Further, moderate (marginal) reductions of HDL-cholesterol levels are observed commonly in women with the syndrome;[373,374] thus for women, HDL cholesterol <50 mg/dL counts as one indicator in the diagnosis of the metabolic syndrome. A moderately strong association exists between insulin resistance and hypertension.[375-377] Insulin resistance also is associated with high-normal blood pressure.[378,379]

Impaired fasting glucose (110–125 mg/dL) usually is an indicator of insulin resistance and is frequently accompanied by other metabolic risk factors;[380,381] measurement of fasting glucose in overweight and obese persons is a reasonable option.[78,79] A portion of persons with impaired fasting glucose will eventually develop type 2 diabetes,[382,383] which further enhances risk for CHD. Type 2 diabetes is the epitome of the metabolic syndrome. Other components of the metabolic syndrome (insulin resistance, proinflammatory state, and prothrombotic state) cannot be identified by routine clinical evaluation. However, in the presence of abdominal obesity, they often are present. For present purposes, the metabolic syndrome is identified by the presence of three or more of the components listed in Table II.6-1.

Table II.6–1. Clinical Identification of the Metabolic Syndrome*

Risk Factor	Defining Level
Abdominal Obesity	Waist Circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/85 mmHg
Fasting glucose	≥110 mg/dL

* The ATP III panel did not find adequate evidence to recommend routine measurement of insulin resistance (e.g., plasma insulin), proinflammatory state (e.g., high-sensitivity C-reactive protein), or prothrombotic state (e.g., fibrinogen or PAI-1) in the diagnosis of the metabolic syndrome.

† Some male persons can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–39 in). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

c. Metabolic syndrome as a target of therapy

In persons entering clinical management of elevated LDL cholesterol, the full benefit of risk reduction will be lost if the metabolic syndrome is ignored. To achieve maximal benefit from modification of multiple metabolic risk factors, the underlying insulin resistant state must become a target of therapy. The safest, most effective, and preferred means to reduce insulin resistance is weight reduction in overweight and obese persons and increased physical activity. Both weight control[363-365] and exercise[240,366,384,385] reduce insulin resistance and favorably modify the metabolic risk factors. ATP III thus places increased emphasis on the metabolic syndrome and on its favorable modification through changes in life habits.

Drug treatment of several of the individual risk factors of the metabolic syndrome will reduce risk for CHD. The strong trend for benefit of drug treatment of atherogenic dyslipidemia is discussed in Section II.3. Risk reductions by lowering blood pressure with antihypertensive drugs[160,161] and treating the prothrombotic state with aspirin[310] are well established. However, lowering serum glucose with drugs has not yet been documented to reduce risk for CHD. Although drugs are available to reduce insulin resistance, there is no clear evidence yet that they will reduce risk for CHD in persons with the metabolic syndrome.

7. Primary prevention: persons without established CHD

a. Scope of primary prevention

Primary prevention aims to prevent new onset CHD. If prevention is delayed until advanced coronary atherosclerosis has developed, the U.S. public will continue to suffer from a heavy burden of CHD. The essential approach to primary prevention is to reduce risk factors for CHD. Waiting until a diagnosis of CHD is made before beginning risk factor reduction will miss the opportunity to prevent CHD in people whose first presentation is sudden cardiac death or disability.[386-389] One-third of people who experience a myocardial infarction will die within 24 hours and many survivors will have serious morbidity including congestive heart failure, angina, arrhythmias, and an increased risk of sudden death.[389] One-third of all new cardiovascular events occurs in individuals under age 65.[389] These observations argue strongly for primary prevention of CHD.

Elevations of serum LDL cholesterol contribute importantly to the high prevalence of CHD in the United States. International studies find that CHD is uncommon in cultures with low levels of serum cholesterol even when the prevalence of hypertension and cigarette smoking is relatively high.[19,25,390] Migration studies reveal that persons who emigrate from low-risk to high-risk cultures show a rise in LDL-cholesterol levels and assume the risk of the new culture.[391] Mass elevations of serum LDL cholesterol result from the habitual diet in the United States, particularly diets high in saturated fats and cholesterol.[19,241,392,393] When these diets are combined with a relatively heavy burden of other CHD risk factors, a high prevalence of premature CHD results.

b. Clinical strategy in primary prevention effort

NCEP supports two complementary approaches to primary prevention: (1) population strategies and (2) clinical strategies.[1,2,5,6] NCEP encourages dietary and other behavioral interventions for all Americans to reduce the population burden of atherosclerosis. The clinician has the opportunity to bridge the gap between the public health population strategy and clinical primary prevention. The population approach is augmented when physicians reinforce the public health message (see Section V). The clinical approach is needed to identify higher risk persons in whom risk factor modification is more urgently required. It further extends to the identification of relatives of affected persons who also are at higher risk and who need clinical intervention to modify risk factors.

c. Concepts of short-term and long-term prevention

Clinical primary prevention can be categorized into long-term and short-term prevention. Long-term prevention aims to reduce risk for CHD over a lifetime; its goal is to prevent the initiation and progression of coronary atherosclerosis, the underlying cause of CHD. It is directed towards persons who are not in imminent danger of suffering a major coronary event, but instead have a high probability of developing CHD sometime during their lives. Lifetime prevention places priority on modifying adverse life habits that are the underlying causes of risk factors and coronary atherosclerosis.

In some persons, however, when risk factors are categorically abnormal drug therapy is required in addition to life-habit changes to reduce long-term risk.

Short-term prevention is designed to reduce risk for new onset CHD, mostly acute coronary syndromes, over the next few years (e.g., ≤10 years). It is directed towards persons who in all probability already have advanced coronary atherosclerosis and who are at high risk of suffering acute coronary syndromes. Such higher risk persons deserve more intensive intervention. Modification of life habits remains an important component of risk reduction in the short term, but more persons will require the addition of pharmacological therapy to reduce risk factors than in long-term prevention.

d. Role of LDL lowering in short-term and long-term primary prevention

Several general comments can be made about the role of LDL lowering in short-term and long-term prevention before addressing specific issues in these areas. A broad base of evidence indicates that elevations in LDL cholesterol are a direct cause of atherosclerosis. Long-term elevations of LDL cholesterol lead to a progressive accumulation of coronary atherosclerosis, which is essential to development of clinical CHD. Recent clinical trials demonstrate that LDL-lowering therapy reduces CHD risk in both primary and secondary prevention. In fact, LDL lowering reduces risk even when LDL-cholesterol levels are not categorically high. For this reason, LDL-lowering therapy represents a powerful modality for reducing both short-term and long-term risk.

Persons at higher risk in the short term (i.e., ≤10 years) deserve highest priority in clinical intervention. Identification of higher risk persons thus becomes a critical issue. This identification is based largely on algorithms that take into account the interaction of multiple risk factors that raises CHD risk multiplicatively. These short-term risk estimates are less reliable for selection of candidates for long-term prevention in clinical practice. Long-term prevention begins with a fundamental principle: all categorical risk factors should be managed clinically regardless of projected short-term risk. All of the major risk factors for CHD—cigarette smoking, hypertension, elevated LDL cholesterol, and diabetes—can produce CHD or other cardiovascular disease even in the absence of other risk factors. Each deserves clinical intervention. In the case of LDL cholesterol, a categorical elevation for ATP III is defined as a level ≥160 mg/dL. Many persons with persistent levels of LDL cholesterol in this range will ultimately require LDL-lowering drugs to reduce risk, although therapeutic lifestyle changes are first-line management. For persons with LDL-cholesterol levels ≥160 mg/dL, categorization of absolute risk can help guide the type and intensity of therapy. Furthermore, some persons with lower levels of LDL cholesterol, e.g., 130–159 mg/dL, will nonetheless have a short-term risk high enough to justify LDL-lowering drugs because of other risk factors. Absolute risk assessment will assist in identification of the latter persons.

e. Risk assessment in primary prevention

In accord with the preceding comments, clinical risk assessment has two goals: to identify persons who are at risk for accelerated atherogenesis, and to identify those persons who are at higher risk for experiencing an acute coronary syndrome because of established advanced atherosclerosis. Long-term prevention in clinical practice is designed for the former, whereas short-term prevention is intended for the latter. Short-term risk reduction (i.e., prevention of coronary plaque rupture and acute coronary syndromes) depends almost exclusively on absolute-risk assessment for its selection of persons for intense clinical intervention. For short-term prevention, absolute risk can be estimated by the summed interaction of multiple coronary risk factors.

NCEP originally introduced a simple system of risk assessment that employed counting of categorical risk factors (Table II.4–2). Treatment goals for LDL cholesterol were set according to the number of risk factors. This system represented a blending of the concepts of relative and absolute risk in an effort to effectively institute both long-term and short-term prevention. The major intervention in NCEP recommendations has been lifestyle changes; LDL-lowering drugs were reserved for persons with categorical elevations of LDL cholesterol who were projected to be at highest risk. After release of ATP II, several major clinical trials reported results showing the efficacy and safety of LDL-lowering drugs for primary prevention (as well as for secondary prevention). These reports opened the door to wider use of LDL-lowering drugs, both for short-term and long-term prevention. In particular, there is a growing consensus that higher risk persons

should not be denied the proven short-term benefits of LDL-lowering drugs, even when LDL-cholesterol levels are <160 mg/dL. Consequently, the selection of persons for short-term prevention to reduce plaque rupture and acute coronary syndromes has assumed increased importance. Moreover, there has been a growing view that a more quantitative assessment of short-term risk is required for the selection of persons who will benefit most from intensive risk-reduction intervention.

The Framingham Heart Study provides an algorithm for assessing risk for CHD in the short term (≤10 years).[10] This algorithm, which is based on robust risk factors, has been adopted by European cardiovascular societies for their treatment guidelines,[394,395] the British cardiovascular societies[396-398] and the American Heart Association.[399] In 1999, the National Heart, Lung, and Blood Institute sponsored a workshop to evaluate the applicability of Framingham risk scores to other population groups in the United States.[400] Framingham projections for "hard" CHD (myocardial infarction and CHD deaths) were found to be similar to those found in other prospective studies in both Caucasian and African American populations in the United States. Comparisons also showed that Framingham scoring led to some overestimation of absolute risk in certain population groups, e.g., Japanese men in Hawaii (Honolulu Heart Program) and Hispanic persons in Puerto Rico.[400] Nonetheless the broad "transportability" of Framingham risk scores within the U.S. population makes it possible for ATP III to employ the Framingham algorithm for quantitative risk assessment to assist in matching intensity of therapy with absolute risk. It must be noted, however, that other published risk assessment algorithms are available.[401] All algorithms do not contain the same factors, nor are risk predictions entirely congruent. Moreover, Framingham scoring itself has been undergoing modification over the past few years. Therefore, absolute risk estimation must be viewed as an evolving science. This is particularly the case as emerging risk factors and measures of subclinical atherosclerosis are added to risk assessment algorithms.

The ATP III panel was faced with the need to reconcile its previous method of counting risk factors with the developing field of integrated, "global" risk assessment. There are advantages and disadvantages to each approach. For example, risk factor counting provides continuity with previous ATP guidelines; it allows for a history of detected risk factors to be included in risk assessment; it includes family history of premature CHD; and it provides a focus on the individual risk factors, each of which requires clinical intervention. However, risk factor counting alone also has disadvantages: it does not provide a quantitative estimate of absolute risk in the short term; it does not allow for variability in risk factor level or intensity (i.e., it uses only categorical risk factors); and it may underestimate the progressive impact of advancing age on absolute risk in older persons. Integrated models of risk estimation (e.g., Framingham risk scoring) counter several of these disadvantages. For instance, they give a more quantitative absolute risk prediction for short-term risk; they account for variability in risk factor intensity, including the progressive impact of advancing age on risk; and they can include corrections for the interactions of risk factors. Even so, there are disadvantages or potential disadvantages to quantitative models for risk estimation: they introduce an approach that has not been widely field tested for practicality in clinical practice; they do not account for variability of risk factor level from one clinic visit to another (and no historical information on variable risk factors is included); they require extra steps in risk assessment (either manual or computer-based assessment); they tend to focus primary attention on short-term risk (to the exclusion of long-term risk); their transportability to all populations is uncertain; and there are remaining uncertainties due to competing and evolving risk-assessment models. All of these factors were taken into account in the ATP III choice of risk assessment methods.

The final method chosen attempts to capitalize on the advantages of both approaches. Risk factor counting is retained for initial assessment, but Framingham risk scoring, updated for ATP III (see Section III), is layered over risk factor counting to improve risk estimation for refining decisions about goals, intensity, and types of LDL-lowering therapy in persons with multiple risk factors. In the final analysis, however, ATP III risk assessment allows physicians to begin with either approach; ultimately the two give similar results. The method of risk assessment therefore depends on physician preference. These methods are described in detail in Section III.

f. Primary prevention with lifestyle changes

1) *Basis for lifestyle recommendations for primary prevention*

A broad base of evidence supports recommendations for lifestyle changes for LDL-lowering therapy in primary prevention.

2) *Dietary clinical trials of cholesterol lowering*

A sizable number of clinical trials have been carried out to test whether lowering serum cholesterol levels with dietary modification will reduce risk for CHD. Some of these were primary prevention trials,[187,402-405] and others were secondary prevention trials.[406-408] None of these trials provided convincing proof of the efficacy of serum cholesterol lowering by dietary means to reduce CHD risk. Most of the trials, however, showed positive trends. In a meta-analysis of dietary trials, Gordon[45,409,410] found that dietary lowering of serum cholesterol produces as much CHD risk reduction as do drugs, commensurate with their respective degree of cholesterol lowering.

3) *Linkage of public health approach and clinical approach in primary prevention*

A strong case exists for the efficacy and safety of primary prevention through lifestyle changes. Primary prevention efforts extend to both public health and clinical arenas. The essential changes in life habits include smoking avoidance or cessation, modifying intakes of foods and nutrients, weight control, and physical activity. Evidence to support each of these changes has been presented in the NCEP Population Report[5,6] U.S. Surgeon General's Reports on Smoking[186] and on Physical Activity;[238] the Obesity Clinical Guidelines Report,[78,79] and Dietary Guidelines for Americans (2000).[241] ATP III affirms the validity of lifestyle changes as first-line therapy for primary prevention. It places priority on LDL-lowering modifications because of the identification of LDL cholesterol as the primary target of therapy; however, ATP III also urges the use of a broad approach to lifestyle changes for CHD risk reduction in primary prevention.

g. Effectiveness of LDL-lowering drugs in primary prevention

Clinical trials of cholesterol-lowering drugs support the efficacy of clinical primary prevention in higher risk persons. In the era before statin drugs, several primary prevention trials of cholesterol lowering were carried out with drug intervention.[44] Landmark trials among these were the World Health Organization clofibrate trial,[149] the Helsinki Heart Study gemfibrozil trial,[139,411,412] and the Lipid Research Clinics cholestyramine trial.[12,13] All of these trials of lipid-lowering therapy reduced major coronary events. However, they were underpowered to address the issue of total mortality; hence, in the minds of many, the benefits of lipid modification in primary prevention remained uncertain.[413-415] The availability of more efficacious cholesterol-lowering drugs (statins) made it possible to definitively test whether LDL lowering would reduce CHD risk. Two major primary prevention trials with statins were the West of Scotland Coronary Prevention Study (WOSCOPS)[416] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[207]. Their results are summarized in Table II.7–1. In both trials, statin therapy significantly reduced relative risk for major coronary events. WOSCOPS also showed a very strong trend towards a

Table II.7–1. Major Primary Prevention Trials with Statins

Study	Persons	Duration	Statin Drug (dose/d)	Baseline LDL-C (mg/dL)	LDL-C Change	Major Coronary Events	Revascularization	Coronary Mortality	Total Mortality
WOSCOPS	6595	4.9 yrs	Pravastatin 40 mg	192	-26%*	-31%*	-37%*	-33%*	-22%*
AFCAPS/TexCAPS	6605	5 yrs	Lovastatin 20/40 mg	150	-25%*	-37%*	-33%*	NS	NS

* Changes significant at $p<0.05$ or lower.

reduction in total mortality. In AFCAPS/TexCAPS, the numbers of deaths in both placebo and treatment groups were so small that no conclusions could be drawn about effects of cholesterol-lowering therapy on total mortality; however, no significant adverse effects of statin therapy were detected.

WOSCOPS and AFCAPS/TexCAPS have important differences that reveal the potential spectrum of use of drugs for primary prevention. WOSCOPS participants, on average, had high LDL-cholesterol levels at baseline, and they often had multiple risk factors. AFCAPS/TexCAPS participants, in contrast, had only borderline high LDL-cholesterol levels and fewer other risk factors, except for relatively low HDL-cholesterol levels. Because of higher LDL cholesterol and more risk factors, WOSCOPS participants had a relatively high absolute risk. AFCAPS/TexCAPS is important because it showed that LDL-lowering therapy in persons with only borderline-high LDL-cholesterol levels produces a large reduction in relative risk. Nevertheless, absolute risk reduction was lower than in WOSCOPS participants, so that more persons had to be treated to receive the benefits of treatment. The implications of these two studies for use of LDL-lowering drugs in primary prevention are considered briefly below.

h. Selection of persons for short-term risk reduction with LDL-lowering drugs

The major reason for using LDL-lowering drugs in short-term, primary prevention is to reduce the likelihood of major coronary events in persons who presumably have advanced coronary atherosclerosis. Primary prevention trials with LDL-lowering drugs provide the rationale for this approach. The most robust primary prevention trial for evaluating benefits of LDL-lowering therapy was WOSCOPS. Its participants generally had elevated LDL cholesterol along with other CHD risk factors. In the WOSCOPS placebo group, 10-year risk for major coronary events (myocardial infarction and CHD death) was approximately 15 percent. Statin therapy reduced this risk by about one-third (Table II.7–1). In AFCAPS/TexCAPS, the estimated 10-year risk for major coronary events in the placebo group was 10.9 percent, but almost half of these events were unstable angina; risk for hard CHD (myocardial infarction + CHD death) was only about 7 percent. Thus, absolute risk in WOSCOPS participants was approximately twice that of AFCAPS/TexCAPS participants. Statin therapy in AFCAPS/TexCAPS produced reductions in relative risk similar to those in WOSCOPS; nonetheless, because of lower absolute risk in AFCAPS/TexCAPS, the number needed to treat (NNT) for every event prevented was higher than in WOSCOPS.

In these two primary prevention studies, statin therapy proved to be remarkably safe as well as efficacious. Since safety does not appear to be an issue for short-term risk reduction in primary prevention with LDL-lowering drugs, the determining factor for the lower risk cutpoint for drug recommendation will be cost-effectiveness (see Section II.14). As noted in Section II.14, the lower cutpoint for selection of drug therapy at current prices of LDL-lowering drugs is a risk for myocardial infarction and coronary death of about 1 percent per year (or 10 percent per 10 years). By this criterion many persons entering AFCAPS/TexCAPS were below accepted cost-effectiveness for short-term risk reduction with statins.

It must be emphasized that the ATP III clinical guidelines do not advocate the attainment of LDL goals exclusively through drug therapy. The aim of therapy is to achieve the LDL goals that are set according to absolute risk criteria. ATP III recommendations call for achieving the goals of therapy by the safest and most cost-effective means. Use of dietary therapy to attain the targets of therapy is emphasized, and if drugs are required, cost-effective agents should be used in the lowest doses needed to achieve the recommended goals of therapy.

i. Selection of older persons for short-term, primary prevention

Approximately two-thirds of first major coronary events occur in persons ≥65 years. Many asymptomatic older persons have advanced coronary atherosclerosis. Recent clinical trials have revealed that aggressive LDL-lowering therapy is effective in reducing risk for CHD (see Table II.2–3). Therefore, the prospects for reducing clinical CHD in the United States by intensive LDL lowering are good. To maximize this benefit, LDL-lowering drugs will be needed for many persons at higher risk. However, to fully implement widespread use of LDL-lowering drugs in older populations, several major problems will have to be overcome. For example, the most effective LDL-lowering drugs (statins) are often expensive; at current prices, statin therapy can cost up to $500–$1,500 per year.

At present, Medicare does not pay for prescription drugs, and many older Americans do not have other private insurance to cover this high cost. Moreover, techniques to assess absolute risk in older persons are less reliable than for middle-aged persons. In particular, serum cholesterol is less robust as a predictor of CHD events in the elderly than in the middle aged.[417] Measurements of subclinical atherosclerosis are promising,[418,419] but currently are not widely available, nor have evidence-based guidelines been produced for their use (see Section II.5.c). Thus, selection of older persons for intensive LDL-lowering therapy with drugs requires a considerable degree of clinical judgment and may be less open to a specific guideline. Nonetheless, several factors can be taken into account when selecting older persons for intensive LDL-lowering therapy, particularly for drug therapy.

Framingham risk scoring remains the primary means of identifying older persons at higher risk. Even so, one factor that may add perspective in the selection of older persons for LDL-lowering drugs at different levels of risk projected from risk factors is an estimate of the number of persons needed to treat (NNT) to achieve benefit. Table II.7–2 gives an estimate of the benefit of statin therapy in older persons over a 15-year period at different levels of projected 10-year risk, assuming that therapy is applied continuously between ages 65 and 80. The assumption is also made that statin therapy reduces risk for all CHD categories by approximately one-third and that for older persons, CHD deaths account for 50 percent of all hard CHD events. No published data provide the ratio of CHD deaths/hard CHD events in older persons, but considering the high mortality in this large group, an estimate of 50 percent appears reasonable.

Table II.7–2. Number Needed to Treat (NNT) with Statin Therapy for 15 Years to Prevent CHD Events by Age 80 Starting at Age 65*[10]

10-Year Risk for Hard CHD†	NNT to Prevent CHD Events (15 Years of Drug Therapy)		
	CHD Death	Hard CHD†	Total CHD‡
10%	42	21	10
20%	20	10	5
30%	13	7	3
40%	10	5	1–2

* The results in this table assume that statin therapy reduces relative risk for all CHD events by one-third (see Table II.2–3).
† Hard CHD includes myocardial infarction + CHD death.
‡ Total CHD includes myocardial infarction, CHD death, unstable angina, and coronary procedures (angioplasty and coronary bypass surgery).

Factors other than the 10-year risk score based on major risk factors may further aid in selection of older persons for intensive LDL-lowering therapy. Since the relative risk accompanying some risk factors declines with advancing age, measures of subclinical atherosclerosis may assist in the identification of older persons who are at high absolute risk and who should benefit from more intensive therapy (see Section II.5.c). For example, a positive ankle-brachial blood pressure index places an older person in a high-risk category (see Section II.5.c.1), as does identification of myocardial ischemia (Section II.5.c.2). The same is true for older persons with advanced subclinical atherosclerosis identified by increased carotid artery thickening or coronary calcium (e.g., ≥75th percentile for age or sex) (see Section II.5.c.3). Thus, use of noninvasive measures of myocardial ischemia or subclinical atherosclerosis may be helpful in the selection of older persons who are good candidates for intensive LDL-lowering therapy including drug therapy. Beyond these approaches to risk assessment, however, many other medical and social factors must be taken into account in the selection of older persons for aggressive short-term risk reduction. These are discussed in more detail in Section VIII.3.

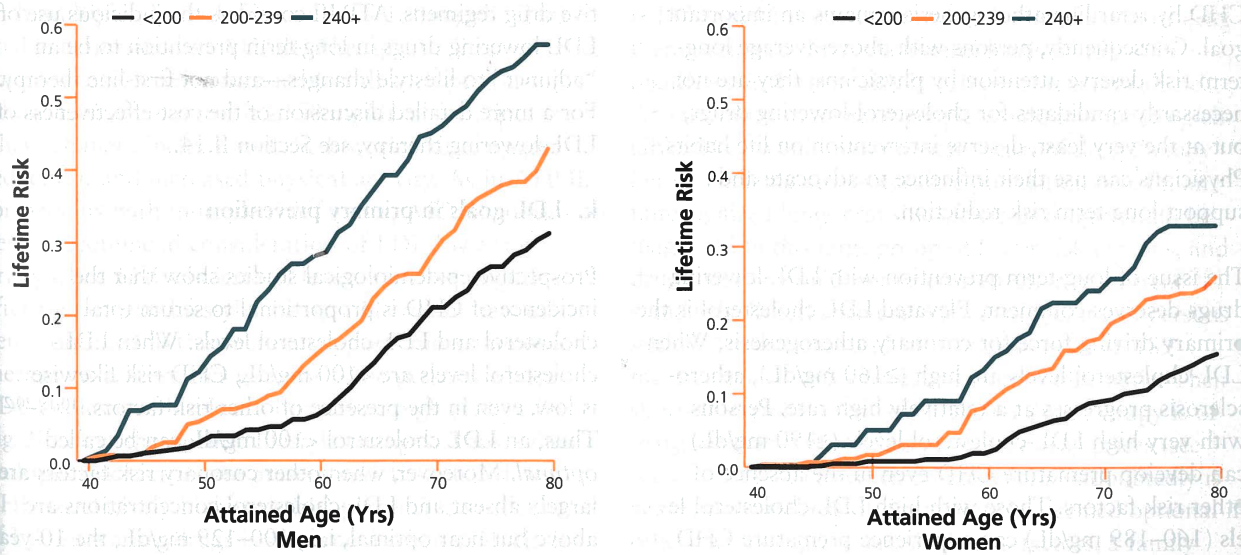
j. Selection of persons for long-term primary prevention in the clinical setting

The essential reason for using clinical resources for long-term primary prevention of CHD is to slow the development of coronary atherosclerosis. Long-term prevention in the clinical setting thus represents an extension of the public health approach. Unless coronary atherosclerosis is prevented (or greatly reduced), the total burden of CHD in society will not be substantially reduced. The lion's share of the effort to prevent coronary atherosclerosis falls to the population (public health) approach; nonetheless, modification of risk factors in persons with a high lifetime risk requires attention by health professionals. A considered judgment is needed for how best to manage such persons. The physician is obliged to identify underlying risk factors (atherogenic diet, overweight/obesity, and physical inactivity) and to introduce risk reduction therapies for them. For the major risk factors, smoking cessation intervention is indicated for cigarette smokers, blood pressure lowering is required for persons with hypertension, and elevated LDL cholesterol should be

Table II.7–3. Short-Term and Lifetime Risk of CHD by Cholesterol Levels Obtained at Various Ages (modified from Lloyd-Jones et al.[17])

	Total Cholesterol Level (mg/dL)					
	Men			Women		
	<200	200–239	240+	<200	200–239	240+
Age 40						
10-year risk	3%	5%	12%	1%	2%	5%
40-year risk	31%	43%	57%	15%	26%	33%
Age 50						
10-year risk	8%	10%	15%	2%	4%	8%
40-year risk	40%	42%	63%	19%	30%	39%
Age 60						
10-year risk	16%	15%	21%	5%	8%	11%
Lifetime risk	34%	41%	51%	20%	24%	36%
Age 70						
10-year risk	18%	22%	28%	5%	7%	13%
Lifetime risk	27%	36%	42%	14%	20%	29%
Age 80						
10-year risk	14%	23%	29%	14%	16%	17%
Lifetime risk	17%	23%	34%	17%	18%	21%

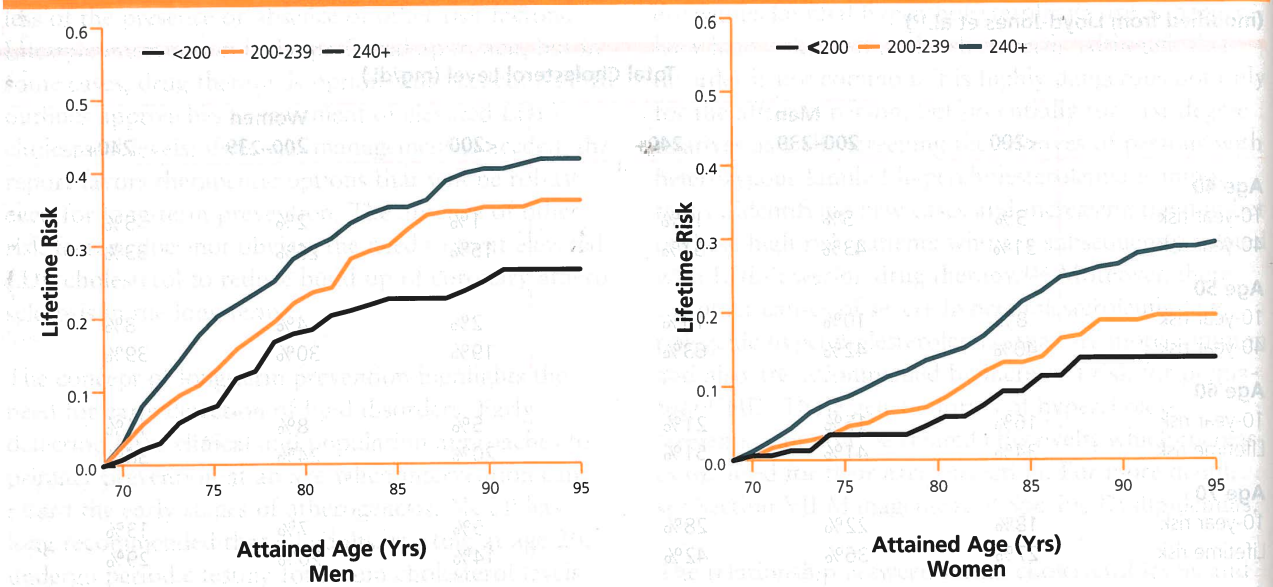
Figure II.7–1. Lifetime Risk of CHD by Total Cholesterol Level for Men (left) and Women (right) at Age 40 Years (derived from Lloyd-Jones et al.[17])



term risk, and it deserves clinical intervention, albeit not necessarily with LDL-lowering drugs.

The major impediment to long-term primary prevention in clinical practice is the cost of therapy. Costs are incurred in all aspects of clinical intervention, e.g., physician time, dietary therapy, drugs, and monitoring. At present, the cost of drugs appears to predominate. This fact has led some guideline committees in other countries to recommend restricting use of LDL-lowering drugs to persons at high short-term risk.[394-398] This restriction is considered necessary because of financial

Figure II.7–2. Lifetime Risk of CHD by Total Cholesterol Level for Men (left) and Women (right) at Age 70 Years



constraints that require a conservative allocation of national medical resources. Certainly persons at higher risk in the short term (≤10 years) deserve priority in intervention including use of LDL-lowering drugs. Still, the advantages of preventing coronary atherosclerosis in the first place cannot be ignored. Lifetime prevention of CHD by retarding atherogenesis remains an important goal. Consequently, persons with above-average long-term risk deserve attention by physicians; they are not necessarily candidates for cholesterol-lowering drugs, but at the very least, deserve intervention on life habits. Physicians can use their influence to advocate and support long-term risk reduction.

The issue of long-term prevention with LDL-lowering drugs deserves comment. Elevated LDL cholesterol is the primary driving force for coronary atherogenesis. When LDL-cholesterol levels are high (≥160 mg/dL), atherosclerosis progresses at a relatively high rate. Persons with very high LDL-cholesterol levels (≥190 mg/dL) can develop premature CHD even in the absence of other risk factors. Those with high LDL-cholesterol levels (160–189 mg/dL) can experience premature CHD when other risk factors are present, even when absolute risk at a younger age is <10 percent per 10 years. There is little doubt that LDL-lowering drugs will curtail atherogenesis in these persons. Therefore, use of LDL-lowering drugs in such persons can be justified to achieve the benefits of long-term risk reduction even when drugs are not considered "cost-effective" by conventional analysis. As patents on initial statins expire and competition increases, it is highly likely that costs of LDL-lowering drugs will decline substantially. Nonetheless, ATP III emphasizes that its goals for LDL cholesterol should be achieved by the most cost-effective means, i.e., by use of maximal dietary therapy before drugs and by choosing the most cost-effective drug regimens. ATP III considers the judicious use of LDL-lowering drugs in long-term prevention to be an "adjunct" to lifestyle changes—and not first-line therapy. For a more detailed discussion of the cost-effectiveness of LDL-lowering therapy, see Section II.14.

k. LDL goals in primary prevention

Prospective epidemiological studies show that the incidence of CHD is proportional to serum total cholesterol and LDL-cholesterol levels. When LDL-cholesterol levels are <100 mg/dL, CHD risk likewise is low, even in the presence of other risk factors. [10,19,20,25] Thus, an LDL cholesterol <100 mg/dL can be called *optimal*. Moreover, when other coronary risk factors are largely absent and LDL-cholesterol concentrations are above but near optimal, i.e., 100–129 mg/dL, the 10-year risk for CHD is relatively low[11,429] (see Table II.7–4).

Despite the low risk for CHD accompanying LDL-cholesterol levels that are optimal (<100 mg/dL) or above but near optimal (100–129 mg/dL), the intensity of clinical intervention required to achieve such levels for everyone in the population would financially over-

Table II.7–4. 10-Year Risk for CHD in the Framingham Population for Low Risk and Lowest Risk Persons with LDL Cholesterol Levels 100–129 mg/dL (modified from Wilson et al.[10])

Age Group (Years)	Average Risk*		Low Risk†		Lowest Risk‡	
	Men	Women	Men	Women	Men	Women
30–39	3%	<1%	1%	0%	0%	0%
40–49	6%	1.5%	2%	1%	1%	0%
50–59	11%	5%	3%	1%	2%	1%
60–69	20%	8%	4%	2%	2%	1%
70–74	25%	11%	6%	3%	3%	1%

* Average 10-year risk for hard CHD (myocardial infarction and CHD death) in the Framingham population regardless of LDL-cholesterol levels.
† Low risk level = 10-year absolute risk for hard CHD (myocardial infarction and CHD death) in a subject with LDL cholesterol 100–129 mg/dL, blood pressure <130/<85 mmHg, no treatment for hypertension, HDL cholesterol 45–59 mg/dL, nondiabetic and nonsmoker.
‡ Lowest risk level = 10-year absolute risk for hard CHD in a subject with LDL cholesterol 100–129 mg/dL, blood pressure <120/<80 mmHg, no treatment for hypertension, HDL cholesterol ≥60 mg/dL, nondiabetic and nonsmoker.

load the health care system. Drug usage would rise enormously. Selection of persons for clinical intervention depends on the principle of adjusting intensity of therapy to absolute risk. Persons at higher risk require more intensive therapy to attain the goal of a lower risk LDL level. In ATP III the decision was made to set the primary LDL-cholesterol goals according to the number of major risk factors, as was done in ATP II.

In ATP II,[1,2] the LDL-cholesterol goal for persons with multiple (2+) risk factors was <130 mg/dL. This goal is maintained in ATP III. Therapeutic lifestyle changes can be recommended for all such persons whose LDL cholesterol is ≥130 mg/dL at baseline. These changes include an LDL-lowering diet, weight reduction, and increased physical activity. As in ATP II, for persons with multiple risk factors, ATP III continues to recommend consideration of LDL-lowering drugs when LDL-cholesterol levels are ≥160 mg/dL after therapeutic lifestyle changes. However, new evidence outlined in this section supports more intensive therapy to achieve this goal for some persons whose LDL-cholesterol levels are borderline high (130–159 mg/dL) after therapeutic lifestyle changes. Thus, when multiple risk factors are present and 10-year risk for CHD is relatively high (i.e., ≥10 percent), consideration of LDL-lowering drugs is warranted when LDL cholesterol is ≥130 mg/dL after lifestyle changes. Not only is consideration justified by clinical trials that showed that drug therapy is efficacious, but it was found to be cost-effective as well (see Section II.14.f). Indeed, for those at highest 10-year risk (i.e., >20 percent), an optimal LDL cholesterol is a suitable target goal. On the other hand, when 10-year risk is low to moderate (<10 percent), restricting LDL-lowering drugs to those with LDL cholesterol ≥160 mg/dL still seems appropriate on grounds of both efficacy and cost-effectiveness.

When 0–1 risk factor is present, LDL-lowering therapy need not be as intense because absolute risk is not as high as when multiple risk factors are present. Most persons with 0–1 risk factor have a 10-year risk for CHD <10 percent. In such persons, an LDL-cholesterol goal of <160 mg/dL is allowable. Although a lower level (<130 mg/dL) is nearer to optimal, introduction of drug therapy to treat LDL-cholesterol levels of 130–159 mg/dL when 10-year risk is <10 percent is unrealistic. An enormous number of people would then be drug-eligible. They would require many years of drug therapy before realizing any discernible population benefit; any unrecognized long-term side effects of drugs would be magnified in this large group of lower risk persons; and drug therapy would not be cost-effective by current standards. Whether to consider drug therapy in persons with 0–1 risk factor and LDL cholesterol 160–189 mg/dL after lifestyle changes is more problematic. Their short-term risk is relatively low, and drug therapy is of marginal cost-effectiveness at current drug prices (see Section II.14.f). However, atherogenesis undoubtedly is accelerated, and use of drugs must be deemed optional if other factors (e.g., severe single-risk factors, a family history of premature CHD, life-habit risk factors, or emerging risk factors) are present beyond the count of major risk factors. Finally, when LDL cholesterol is ≥190 mg/dL after lifestyle changes, drug therapy should be considered even in persons with 0–1 risk factor because of accelerated atherogenesis and high long-term risk.

Evidence statements: A strong relationship exists between LDL-cholesterol levels and CHD risk (C1). An elevated serum total cholesterol contributes to coronary atherosclerosis throughout life; serum total cholesterol levels measured in young adulthood correlate with CHD rates later in life and over a lifetime (C1). For persons without other CHD risk factors, risk for CHD is relatively low when LDL-cholesterol levels are <130 mg/dL (C1). Moreover, for persons with higher LDL-cholesterol levels (≥130 mg/dL), clinical trials document the efficacy of LDL lowering to reduce risk for CHD in primary prevention (A1, B1), particularly when LDL-cholesterol levels are reduced to <130 mg/dL (A1).

Recommendation: LDL-lowering therapy should play an important role in primary prevention of CHD in persons at increased risk. For persons at increased risk because of the presence of multiple risk factors, the LDL-cholesterol goal should be <130 mg/dL. Therapeutic lifestyle changes should be initiated in all such persons. Persons with multiple risk factors whose short-term (10-year) risk is low to moderate (<10 percent) generally should not receive LDL-lowering drugs when LDL-cholesterol concentrations are only borderline high (130–159 mg/dL), but drugs should be considered when LDL levels are high (≥160 mg/dL). For higher risk persons with multiple risk factors (10-year risk 10–20 percent), consideration should be given to drug therapy when the LDL goal (<130 mg/dL) cannot be achieved by lifestyle therapies. Finally, multiple-risk-factor persons at highest risk (10-year risk >20 percent) need to attain even lower LDL-cholesterol levels (LDL goal <100 mg/dL), and consideration should be given to starting drug therapy simultaneously with therapeutic lifestyle changes when LDL-cholesterol levels are ≥130 mg/dL.

Recommendation: For persons who are otherwise at lower risk (0–1 risk factor), an effort should be made to lower LDL-cholesterol levels to <160 mg/dL. In such persons, lifestyle changes should be emphasized when the LDL-cholesterol level is in the range of 130–159 mg/dL to minimize the risk of any marginal (subcategorical) risk factors. Drug therapy at these LDL levels generally should be avoided, because of lack of long-term data on safety and because of relatively low cost-effectiveness ratios. In persons with 0–1 risk factor, if LDL-cholesterol levels cannot be reduced to <160 mg/dL by therapeutic lifestyle changes, LDL-lowering drugs can be viewed as optional when levels are in the range of 160–189 mg/dL, and should be strongly considered when levels persist at ≥190 mg/dL. Physicans should opt for drug therapy at former levels (160–189 mg/dL) when persons appear to have risk that is greater than that revealed by 0–1 standard risk factor, i.e., because of a severe single-risk factor, a family history of premature CHD, or the presence of life-habit or emerging risk factors.

Recommendation: Routine cholesterol testing should begin in young adulthood (≥20 years of age). In young adults, above-optimal LDL-cholesterol levels deserve attention. When LDL-cholesterol concentrations range from 100–129 mg/dL, young adults should be encouraged to modify life habits to minimize long-term risk. In those with borderline high LDL cholesterol (130–159 mg/dL), clinical attention through therapeutic lifestyle changes is needed both to lower LDL cholesterol and to minimize other risk factors. If LDL cholesterol is high (160–189 mg/dL), more intensive clinical intervention should be initiated, with emphasis on therapeutic lifestyle changes. However, if LDL cholesterol remains elevated despite therapeutic lifestyle changes, particularly when LDL cholesterol is ≥190 mg/dL, consideration should be given to long-term management with LDL-lowering drugs.

8. Secondary prevention: persons with CHD

a. Secondary prevention of recurrent CHD

Persons with established CHD are at very high risk for recurrent CHD. A growing body of evidence indicates that LDL-lowering therapy reduces recurrent coronary events in persons with existing CHD. The results of earlier secondary prevention trials, which were the basis of ATP II recommendations, are summarized in Table II.8–1. As shown, even before introduction of statins, cholesterol-lowering therapy was found to reduce CHD events without evidence of an increase in noncardiovascular mortality.[14,430] Subsequent secondary prevention trials with statins documented a reduction in cardiovascular morbidity and mortality and total mortality. These latter trials included those with both angiographic outcomes[46,158,431-434] and clinical endpoints[206,435,436]. In several of the angiographic trials, a significant decline in the incidence of clinical CHD events was observed in the treated group in a period of only two years (Table II.2–2). This finding makes it probable that the instability of plaques (which leads to fissuring, thrombosis, and intramural hemorrhage) is reduced as well.[437-441] The three major secondary prevention trials with statins were the Scandinavian Simvastatin Survival Study (4S),[435] Cholesterol and Recurrent Events (CARE) Study,[436] and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study.[206] Results of these trials are summarized in Table II.8–2. All three showed reductions in recurrent myocardial infarction and coronary death, coronary artery procedures, and stroke. Two of the trials reported a reduction in total mortality with statin therapy. Thus, secondary prevention trials provide strong evidence for the benefit of cholesterol-lowering therapy in persons with established CHD.

Table II.8–1. Earlier Secondary Prevention Trials: Morbidity and Mortality Results*†

Event	Proportion of Deaths	Relative Risk	Confidence Interval
Nonfatal myocardial infarction	—	0.74	0.66–0.84
Fatal myocardial infarction	73%	0.86	0.77–0.96
Cardiovascular deaths	90%	0.89	0.79–1.00
Cancer deaths	5%	0.89	0.59–1.39
Other deaths	4%	1.14	0.71–1.82
All deaths	100%	0.91	0.81–1.01

* Meta-analysis by Rossouw based on Rossouw et al.;[14] Rossouw[442].
† Trials include Medical Research Council's low-fat diet trial,[407] Medical Research Council's soya-bean oil trial,[443] Scottish Society of Physician's clofibrate trial,[151] Stockholm Ischaemic Heart Disease Secondary Prevention Study,[152] Coronary Drug Project's clofibrate trial,[141,444] Coronary Drug Project's niacin trial,[141,444] and Program on the Surgical Control of Hyperlipidemias[445].

Recent statin trials also reveal the impact of LDL lowering on selected populations and on additional clinical endpoints. LDL lowering has been shown to produce marked benefit regardless of gender, age, and the presence of diabetes, smoking, and hypertension.[203,205,436,446-449] Furthermore, in CHD patients, LDL lowering decreases stroke rates,[206,435,436,450,451] improves angina and myocardial perfusion,[448,452-455] and decreases the need for subsequent revascularization.[206,434-436,456]

Table II.8–2. Major Secondary Prevention Trials with Statins: Morbidity and Mortality Results

Study	Persons	Duration	Drug (dose/d)	Baseline LDL-C (mg/dL)	LDL-C Change	Major Coronary Events	Revascularization	Coronary Mortality	Total Mortality	Stroke
4S[435]	4444	5.4 yrs	Simvastatin 10/40 mg	188	-35%*	-35%*	-37%*	-42%*	-30%*	-27%*
CARE[436]	4159	5 yrs	Pravastatin 40 mg	139	-27%*	-25%*	-27%*	-24%*	-9%	-31%*
LIPID[206]	9014	5 yrs	Pravastatin 40 mg	150	-25%*	-29%*	-24%*	-24%*	-23%*	-19%*

* Statistically significant changes at p<0.05 or lower.

ATP II[1,2] identified the LDL-cholesterol goal for secondary prevention to be a level ≤100 mg/dL. Recent clinical trials provide an opportunity for reexamination of this goal. Epidemiological data strongly suggest that the prevalence of CHD is lowest when the LDL-cholesterol level is <100 mg/dL. Large studies and meta-analyses have revealed that CHD rates decrease with declining cholesterol levels down to a total cholesterol of 150 mg/dL, corresponding to an LDL cholesterol of about 100 mg/dL.[11,23,24,457] Epidemiological data demonstrate a continuous (log-linear) relationship between LDL cholesterol (and total cholesterol) and CHD risk.[23,24] The log-linear relationship holds to levels of LDL cholesterol below 100 mg/dL.[458] Factors that increase risk (e.g., presence of CHD) shift the curvilinear relationship, increasing the risk impact of LDL cholesterol at lower ranges.[459] Models based upon epidemiological data support the concept that LDL-lowering treatment at baseline total cholesterol levels >200 mg/dL (comparable to baseline LDL of approximately 130 mg/dL) will lower mortality and morbidity.[460] Finally, Law et al.[23,24] reported that results of epidemiological studies and clinical trials are highly congruent, providing additional support for the applicability of epidemiological data for setting LDL-cholesterol goals in secondary prevention.

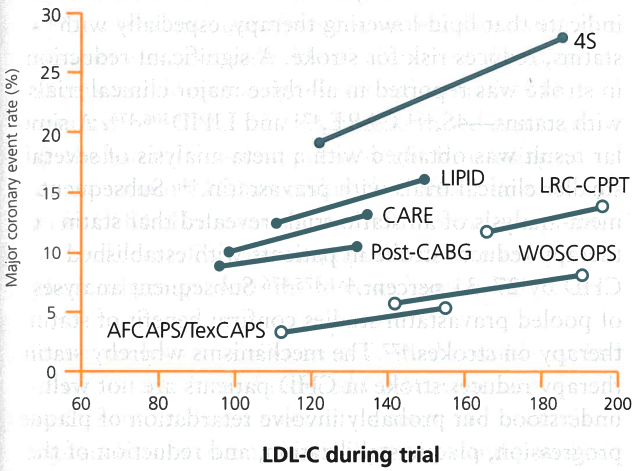
Angiographic studies on the whole are consistent with maximal CHD reduction in secondary prevention occurring at LDL levels <100 mg/dL. Three studies are particularly noteworthy: POSCH,[445,461] FATS,[158] and Post-CABG[434]. POSCH (using surgery) and FATS (using nicotinic acid and a statin or sequestrant) achieved LDL levels near 100 mg/dL and showed favorable changes in coronary lesions. The Post-CABG trial tested the concept that a lower LDL is better by examining the benefits of moderate versus aggressive LDL lowering on progression of atherosclerosis in saphenous vein grafts. Using a statin and sequestrant if needed, the moderate treatment group was treated to maintain LDL levels between 130–140 mg/dL, and the aggressive treatment group was titrated to a target LDL of <95 mg/dL. The aggressively treated group had less progression, fewer new lesions, and needed less revascularization.[434,456]

Post-hoc analyses of statin trials clearly show benefit from LDL cholesterol lowering to the range of 100 to 125 mg/dL.[462-465] Not all of the studies confirm that an optimal LDL cholesterol is <100 mg/dL; however, in subgroup analysis the statistical power to reliably define the lower limit of benefit may be lacking. In the 4S trial,[464] lowering of LDL levels gave proportional and continuous but progressively smaller absolute decrements in CHD risk down to an LDL cholesterol of 100 mg/dL. In CARE[436,463] benefit with statin treatment was seen with mean on-therapy LDL-cholesterol levels in the range of 100 mg/dL throughout the study (Figure II.8–1). Although CARE and LIPID could not rule out a threshold relation at LDL cholesterol less than 125 mg/dL, the combined data from epidemiological, angiographic,[43,466-468] and other clinical trials support an LDL-cholesterol goal of <100 mg/dL for secondary prevention.

Recently, clinical trials have examined the effect of treatment to lower LDL cholesterol goals, and earlier treatment of patients. Although no single trial conclusively confirms a specific LDL-cholesterol goal lower than 100 mg/dL, several studies showed a clinical benefit in the treatment group with on-treatment LDL cholesterol from 72 mg/dL to 98 mg/dL (MIRACL,[469] AVERT,[470] MARS,[466] LAARS,[468] Post-CABG,[434] FATS extension,[467] HATS[159]). The totality of this data suggests that further benefit accrues in patients treated to an LDL-cholesterol level below 100 mg/dL. It is not known whether LDL levels markedly below 100 mg/dL versus marginally below 100 mg/dL confer any additional benefit. Trials with clinical endpoints (AVERT, MIRACL) and other endpoints, including vascular function, confirm an early (1 week to 3 months) benefit of statin treatment for patients with atherosclerosis or acute coronary syndromes. In this regard MIRACL is noteworthy, demonstrating that statin treatment initiated in hospital (in patients with non-Q MI or unstable angina) was safe and was associated with a 16 percent relative risk reduction at 16 weeks. Also supporting the concept of early treatment is a recently published, very large observational study from Sweden. In-hospital initiation of statin treatment was associated with an adjusted 25 percent lowering of total mortality at 1 year.[471]

The recent VA-HIT trial,[48] however, revealed that modification of other lipid risk factors could reduce risk for CHD when LDL cholesterol is in the range of 100 to 129 mg/dL (Tables II.8–3a–b). In this trial, persons with low LDL (mean 112 mg/dL) were treated with gemfibrozil for 5 years. Gemfibrozil therapy, which raised HDL and lowered triglyceride, reduced

Figure II.8–1. Relation of CHD Events to LDL Levels in Treatment and Placebo Groups: Statin Trials[472]



the primary endpoint of fatal and non-fatal myocardial infarction by 22 percent without significantly lowering LDL-cholesterol levels. This study thus raises the possibility of efficacy from optional use of non-statin drugs when LDL-cholesterol levels in CHD patients are in the range of 100–129 mg/dL.

Despite the strongly positive result of gemfibrozil therapy in the VA-HIT trial, less striking results have been reported for other fibrate trials in secondary prevention. For example, the clofibrate arm of the early Coronary Drug Project[141] produced no evidence of benefit. Another early secondary prevention trial[151] with clofibrate gave more favorable outcomes, but the reduction in CHD events was not statistically significant. Results from the recent BIP trial with bezafibrate therapy were essentially negative.[153] This secondary prevention study recruited patients with a mean LDL cholesterol >130 mg/dL; in similar CHD patients, both CARE and LIPID trial results were strongly positive with statin therapy. Thus, statin therapy is clearly preferred over fibrates in patients with borderline high or high LDL cholesterol (≥130 mg/dL). Nonetheless, VA-HIT findings support the potential for significant additional risk reduction in patients with low LDL cholesterol (<130 mg/dL). VA-HIT results also support a positive trend for CHD events (although not for all-cause mortality) when all fibrate trials are considered together.[45]

Table II.8–3a. Veterans Affairs HDL Intervention Trial (VA-HIT): Lipids and Lipoproteins

Persons	Drug/Duration	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Triglyceride (mg/dL)	Non-HDL Cholesterol (mg/dL)
2531 men	Gemfibrozil (1200 mg/day) 5.1 years	175*	111*	32*	161*	143*
	% Difference (Treatment minus Control)	-4%	0%	+6%	-31%	-6%

* Baseline levels.

Table II.8–3b. Veterans Affairs HDL Intervention Trial (VA-HIT): Cardiovascular Events: Percent Risk Reduction (95 percent Confidence Intervals)

Non-Fatal Myocardial Infarction + CHD Death	CHD Death	Non-Fatal Myocardial Infarction	Stroke	Revascularization	Total Mortality
22%*	22%	23%†	31%‡	9%	11%
(7 to 35%)	(-2 to 41%)	(4 to 38%)	(2 to 52%)	(-8 to 23%)	(-8 to 27%)

*, †, ‡ Primary endpoint, p = 0.006. Secondary endpoints, p = 0.02 and 0.036, respectively.

Evidence statements: Secondary prevention trials demonstrate that reduction of LDL-cholesterol levels significantly reduces risk for recurrent major coronary events in persons with established CHD (A1). Evidence from endpoint trials with cholesterol-lowering drugs, angiographic trials, and epidemiological studies indicates that maximal CHD reduction occurs when LDL cholesterol is <100 mg/dL (A2, B1, C1).

Recommendation: Persons with established CHD should receive intensive LDL-lowering therapy. The goal of therapy in persons with established CHD should be LDL cholesterol <100 mg/dL.

Evidence statement: Persons with established CHD who have a baseline LDL cholesterol ≥130 mg/dL receive benefit from institution of LDL-cholesterol-lowering drugs (A1).

Recommendation: Persons with established CHD who have a baseline LDL cholesterol ≥130 mg/dL should be started on a cholesterol-lowering drug simultaneously with therapeutic lifestyle changes and control of nonlipid risk factors (therapeutic lifestyle changes alone are unlikely to achieve the LDL-cholesterol goal of <100 mg/dL).

Evidence statements: Persons with established CHD who have a baseline LDL cholesterol of 100–129 mg/dL likely will benefit from reducing LDL cholesterol to <100 mg/dL (A2, B2, C1). These persons also appear to benefit from therapy that modifies atherogenic dyslipidemia (A2, B2).

Recommendation: Several options should be considered for treatment of CHD patients with baseline LDL-cholesterol levels of 100–129 mg/dL. These include use of a cholesterol-lowering drug, maximization of therapeutic lifestyle changes, use of a drug to modify atherogenic dyslipidemia, and intensified control of nonlipid risk factors.

b. Effects of lipid-lowering therapy on stroke

Recent clinical trials in patients with established CHD indicate that lipid-lowering therapy, especially with statins, reduces risk for stroke. A significant reduction in stroke was reported in all three major clinical trials with statins—4S,[454] CARE,[473] and LIPID[206,474]. A similar result was obtained with a meta-analysis of several smaller clinical trials with pravastatin.[446] Subsequent meta-analysis of all statin trials revealed that statin therapy reduces stroke in patients with established CHD by 27–31 percent.[451,475,476] Subsequent analyses of pooled pravastatin studies confirm benefit of statin therapy on strokes.[477] The mechanisms whereby statin therapy reduces stroke in CHD patients are not well understood but probably involve retardation of plaque progression, plaque stabilization, and reduction of the risk for coronary events.[478] Regardless, reduction in stroke is definitely an added benefit of statin therapy in secondary prevention. Besides statin therapy, treatment with gemfibrozil in patients with established CHD in the VA-HIT trial reduced investigator-designated stroke by 25 percent, confirmed stroke by 25 percent, and transient ischemic attacks by 59 percent.[48] In summary, lipid lowering, particularly with statins, reduces risk for stroke in patients with established CHD. The question of whether LDL-lowering therapy in primary prevention also reduces stroke has not been adequately tested, although one meta-analysis[451] showed a strong trend towards benefit.

Evidence statement: In persons with established CHD, LDL-lowering therapy reduces risk for stroke (A1, B1).

Recommendation: For persons with established CHD, LDL-lowering therapy should be carried out to reduce the risk for stroke and for recurrent coronary events.

9. Total mortality considerations and therapeutic safety

Beyond the striking reduction in CHD rates accompanying lowering of LDL cholesterol lies the question of whether cholesterol-lowering therapy will actually extend the life span. At the time of publication of ATP II (1993), the net impact of cholesterol lowering on

mortality was an area of controversy. Previous clinical trials generally had not been designed with sufficient power to address all-cause mortality. In the early 1990s, several meta-analyses found that mortality from all causes was essentially identical in treated and control persons, despite a significant reduction in CHD mortality.[14,414,415,479-482] This finding raised concerns that cholesterol lowering per se might be causing an increase in non-CHD mortality that offset the reduction in CHD. This concern was reinforced by reports that total mortality rates in populations are relatively high in subgroups with the lowest cholesterol levels.

Further analysis of earlier trials yielded possible explanations for a failure of reduced CHD event rates to translate into reduced mortality rates.[45] For example, drugs such as estrogen, dextrothyroxine, and possibly clofibrate, may have had toxicity that obscured the benefit of other drugs. Also, a reduction in all-cause mortality is difficult to detect when total deaths from CHD in clinical trials are relatively low. For instance, all-cause mortality was reduced in secondary prevention trials (where 80 percent of deaths were due to CHD) but were increased in primary prevention trials that included potentially toxic drugs (where only 37 percent of deaths were due to CHD). Finally, the modest degree of cholesterol lowering in most of the earlier trials probably was insufficient to test the hypothesis that treatment reduced total mortality. Analyses of the earlier trials indicated that the crossover point where the reduction in CHD mortality began to outstrip the increase in non-CHD mortality was at an 8–10 percent reduction in serum cholesterol.[455,457]

Since the ATP II report, trials using statins have been reassuring for total mortality considerations. Five large long-term cholesterol-lowering trials using statins, as well as 11 smaller trials of 2–4 years duration, were published between 1993 and 1999.[206,207,416,432,434-436,483-487] In these trials, which encompass more than 17,000 statin treated persons followed for an average of 5 years, statin drugs have consistently produced reductions of 18 percent or more in serum cholesterol levels, and have been remarkably free of adverse effects. Two of the large secondary prevention trials, 4S[435] and LIPID,[206] demonstrated significant reductions in mortality by themselves, and several others showed clear trends in the same direction. Meta-analysis of these trials shows an overall 29 percent reduction in CHD mortality ($p<0.001$) and an 11 percent reduction in non-CHD mortality ($p=0.06$). All-cause mortality was reduced by 22 percent ($p<0.001$). Finally, a global meta-analysis incorporating 40 trials using statins, fibrates, sequestrants (or partial ileal bypass surgery), nicotinic acid, and/or diet to lower cholesterol now shows a 12 percent reduction in all-cause mortality ($p<0.001$) (Table II.9–1). The results in Table II.9–1 constitute a refinement of a recent meta-analysis reported by Gordon.[45] Results were prepared for ATP III by panel members D. Gordon and M.A. Proschan.

Beyond the recent clinical trials showing a reduction in total mortality from LDL-lowering therapy, questions remain about short-term and long-term safety of specific LDL-lowering modalities. The dispute about the safety of lowering of LDL per se has been resolved, at least for the short term; net benefits in high-risk

Table II.9–1. Meta-Analysis of Mortality in Cholesterol-Lowering Trials by Treatment Modality

Treatment Modality	Number of Trials	Number (Treatment/ Control)	% Change Cholesterol	Mortality	
				Deaths	OR (p)
Statins	17	18494/18449	20%	1107/1381	.78 (<.001)
Fibrates	7	10654/12999	9%	859/1277	1.03 (.58)
		CHD Mortality for Fibrates ➜		495/884	.93 (.24)
		Non-CHD Mortality for Fibrates ➜		364/393	1.19 (.02)
Sequestrants	5	3562/3530	12%	159/191	.81 (.06)
Other*	14	4025/5801	10%	789/1293	.93 (.19)
All trials†	42	36775/37321	15%	2914/3420	.88 (<.001)

* Nicotinic acid, diet, and various combinations of drugs.
† Multi-armed trials (CDP[141], STARS[488]) are counted only once in the totals although their arms can contribute to more than one row.