Practicing evidence-based medicine necessarily depends on the clinician having access to the best evidence available, but in a fast-moving field, keeping up to date with the latest developments is a challenging prospect. In this new volume, leading experts focus on the most important clinical issues associated with the management of lipid disorders, evaluating and interpreting the evidence available to provide the reader with a reliable summary of our current knowledge.

Topics covered include therapeutic strategies for managing hereditary lipid disorders, including familial hypercholesterolemia, both in adults and children, and familial combined hypercholesterolemia. The authors also evaluate the evidence for a link between inflammatory disease and cardiovascular risk, the metabolic syndrome and the interconnections between dyslipidemias and diabetes. They also look at therapeutic challenges such as the management of patients who are statin intolerant, and the control of lipid levels in those suffering renal insufficiency.

Tables highlight important data, evidence from trial results and expert reports, and each section concludes with a series of key points that present a summary of evidence-based recommendations for best practice, graded according to the quality of that evidence.

This book provides the busy clinician with a unique analysis of the data supporting current therapies and will help the reader formulate effective strategies for treating their own patients.
Evidence-based Management of LIPID DISORDERS

Maud N. Vissers
John J. P. Kastelein
Erik S. Stroes
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Foreword

Worldwide, cardiovascular diseases are among the leading causes of death, and atherosclerosis is by far their most common cause. A century has passed since the term ‘atherosclerosis’ was first introduced by F. Marchand in 1904, who suggested that atherosclerosis was responsible for almost all obstructive processes in the arteries. A few years later, the relationship between cholesterol and atherosclerotic plaques was discovered, first by A. Windaus, who detected cholesterol in human atheromatous lesions in 1910, and shortly thereafter, in 1914, by N. Anichkov and S. Chalatow, who discovered the significance and role of cholesterol in atherosclerosis pathogenesis based on their landmark experiments in rabbits. These discoveries heralded a spectacular research effort in the relation between cholesterol and atherosclerosis.

A century of studies on atherosclerosis later, we not only acknowledge the crucial role of LDL-cholesterol in the development of cardiovascular diseases, but we also recognize other players in the field. These risk factors include, but are not restricted to, low HDL-cholesterol levels, high triglyceride levels and the size of the lipoproteins, as well as lifestyle and diseases that impair a healthy lipoprotein balance, such as diabetes, metabolic syndrome, inflammatory diseases, renal insufficiency, and – although not related to lipids – hypertension. Along with these discoveries, several therapeutic strategies have been developed during the last decades. Some of them have been proven to improve lipid levels and to reduce cardiovascular risk, whereas others are still in the investigational phase.

The authors were asked to look systematically at the literature and to evaluate and interpret the available evidence on the selected topics in order to provide the reader with a reliable summary of the current knowledge on the management of lipid disorders. Each chapter concludes with a series of key points that present a summary of evidence-based recommendations for best practice, graded according to the quality of the evidence. For certain topics, however, there are no data from well-designed randomized controlled trials (RCTs), just because it is too early or RCTs are not feasible. As outlined in the first chapter by Dr. Steinberg, RCTs provide by far the most valuable evidence guiding decisions regarding medical intervention, but other relevant evidence must be considered as well. In such cases we have to rely on case reports, descriptive studies or opinions and/or clinical experience of respected authorities.

We are grateful to all the authors for their phenomenal task in putting all the available evidence-based information together. We hope that readers will enjoy all the chapters as much as we did.

Maud N. Vissers PhD
John J.P. Kastelein MD PhD
Erik S. Stroes MD PhD

Amsterdam, May 2010
Contributors

Rob E. Aarnoutse PharmD PhD Hospital Pharmacist, Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Evertine J. Abbink MD PhD Research Physician, Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Martin Adiels MSc PhD Assistant Researcher, Sahlgrenska Center for Metabolism and Cardiovascular Research, Wallenberg Laboratory for Cardiovascular Research and the Department of Molecular and Clinical Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Jane Armitage FFPH FRCP Professor of Clinical Trials and Epidemiology, Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford, Oxford, UK

Benoit J. Arsenault PhD Researcher, Centre de Recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec, Canada

Vincent W. Bloks Research Officer, Center for Liver, Digestive and Metabolic Diseases, Beatrix Children’s Hospital – University Medical Center Groningen, University of Groningen, The Netherlands

Jan Borén MD PhD Professor of Cardiovascular Medicine, Sahlgrenska Center for Metabolism and Cardiovascular Research, Wallenberg Laboratory for Cardiovascular Research and the Department of Molecular and Clinical Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Louise Bowman MD MRCP Clinical Research Fellow, Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford, Oxford, UK

David M. Burger PharmD PhD Hospital Pharmacist - Clinical Pharmacologist, Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Jacqueline de Graaf MD PhD Vascular Specialist, Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Jean-Pierre Després PhD FAHA Director of Research, Cardiology, Centre de Recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec, Canada

Christiane Drechsler MD Fellow, Nephrology and Clinical Research, Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands

Henk-Jan Guchelaar PhD Professor of Clinical Pharmacy and Hospital Pharmacist, Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands
Contributors

Robert A. Hegele MD FRCPC FACP Director, Blackburn Cardiovascular Genetics Laboratory; Scientist, Vascular Biology Research Group, Robarts Research Institute, London, Ontario, Canada

G. Kees Hovingh MD PhD Resident, Internal Medicine and Vascular Medicine, Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Tisha R. Joy MD FRCPC Assistant Professor, Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

John J.P. Kastelein MD PhD Professor of Medicine, Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Folkert Kuipers PhD Professor, Dean of Faculty of Medical Sciences, Center for Liver, Digestive and Metabolic Diseases, Beatrix Children’s Hospital – University Medical Center Groningen, University of Groningen, The Netherlands

Peter J. Lansberg MD PhD Co-ordinator, Durrer Center for Cardiogenetic Research, Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Sarah Lewington MSc DPhil Senior Research Fellow, Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford, Oxford, UK

Ronald P. Mensink PhD MSc Professor of Molecular Nutrition, Department of Human Biology, Maastricht University, Maastricht, The Netherlands

Michael T. Nurmohamed MD PhD Consultant Rheumatologist, Departments of Internal Medicine & Rheumatology, VU University Medical Centre; Department of Rheumatology, Jan van Breemen Institute, Amsterdam, The Netherlands

Sven-Olof Olofsson MD PhD Professor of Medical Biochemistry, Sahlgrenska Center for Metabolism and Cardiovascular Research, Wallenberg Laboratory for Cardiovascular Research and the Department of Molecular and Clinical Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Frans L. Opdam MD Fellow, Vascular Medicine, Section of Vascular Medicine, Department of Endocrinology and Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

Shailendra B. Patel BM ChB DPhil FRCP Professor of Medicine, Medical College of Wisconsin, and the Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin, USA

Jogchum Plat PhD Associate Professor, Human Biology, Department of Human Biology, Maastricht University, Maastricht, The Netherlands

Ton Rabelink MD PhD Professor of Nephrology, Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands
Evidence-based Management of Lipid Disorders

Gerald Salen MD Professor of Medicine, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey, USA

Anton F. Stalenhoef MD PhD FRCP Professor of Medicine, Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Daniel Steinberg MD PhD Professor of Medicine Emeritus, University of California San Diego, La Jolla, California, USA

Erik S. Stroes MD PhD Professor of Medicine, Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Jouke T. Tamsma MD PhD Consultant, Vascular Medicine, Section of Vascular Medicine, Department of Endocrinology and Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

Marja-Riitta Taskinen MD PhD Professor of Medicine, Division of Cardiology, University of Helsinki, Biomedicum, Helsinki, Finland

Serena Tonstad MD PhD Head Physician, Department of Preventive Cardiology, Oslo University Hospital Ullevål, Oslo, Norway; Professor, Clinical Nutrition, Department of Nutrition, University of Oslo, Oslo, Norway

Sotirios Tsimikas MD FACC FAHA FSCAI Professor of Medicine, Division of Cardiology, Vascular Medicine Program, University of California San Diego, La Jolla, California

Hester van Meer MD Paediatrician, Fellow Paediatric Gastroenterology, Center for Liver, Digestive and Metabolic Diseases, Beatrix Children’s Hospital – University Medical Center Groningen, University of Groningen, The Netherlands

Menno Vergeer MD Resident, Internal Medicine and Vascular Medicine, Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Henkjan J. Verkade MD Professor, Paediatric Gastroenterologist and Chair, Department of Paediatrics, Center for Liver, Digestive and Metabolic Diseases, Beatrix Children’s Hospital – University Medical Center Groningen, University of Groningen, The Netherlands

Adie Viljoen MBBS FRCPath Consultant Chemical Pathologist, Lister Hospital, Stevenage, Hertfordshire, UK

Maud N. Vissers PhD Researcher, Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Christoph Wanner MD PhD Professor of Nephrology, Department of Medicine, Division of Nephrology, University Hospital Würzburg, Germany

Anthony S. Wierzbicki DM DPhil FRCPath FAHA Consultant Metabolic Physician & Chemical Pathologist, Guy’s & St Thomas’ Hospitals, London, UK
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We are grateful to all of the contributors for taking on this important task and hope they will be proud to be part of a book which attempts to set out the evidence-based management of lipid disorders.

We would also like to thank Nikki Bramhill and Jonathan Gregory from tfm Publishing Limited for their invaluable assistance.
The process of gathering evidence is a time-consuming task. One of the main reasons for supporting the use of evidence-based medicine, is the rate of change of new practices, and the increasing tendency for specialisation. Medical information is widely available from a variety of sources for clinicians but keeping up-to-date with current literature remains an almost impossible task for many with a busy clinical workload. *Evidence-based Management of Lipid Disorders* has been written to aid this process. The chapters in this book have been written by internationally renowned experts who have applied the principles of evidence-based medicine and taken relevant clinical questions and examined the current evidence for the answers. The authors were asked to quote levels and grades of evidence for each major point, and to provide a summary of key points and their respective evidence levels at the end of each chapter. The levels of evidence and grades of evidence used in this book are shown in Tables 1 and 2 and are widely used in evidence-based medicine.

### Table 1. Levels of evidence.

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from systematic review or meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>Ila</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>Iib</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
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### Table 2. Grades of evidence.

<table>
<thead>
<tr>
<th>Grade of evidence</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>A</td>
<td>At least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia and Ib)</td>
</tr>
<tr>
<td>B</td>
<td>Well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels Ila, Iib, III)</td>
</tr>
<tr>
<td>C</td>
<td>Expert committee reports or opinions and/or clinical experience of respected authorities. This grading indicates that directly applicable clinical studies of good quality are absent (evidence level IV)</td>
</tr>
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</table>
Chapter 1

How much evidence is enough?

Daniel Steinberg MD PhD, Professor of Medicine Emeritus
University of California San Diego, La Jolla, California, USA

Introduction

The title is deliberately vague. One needs to know more. “Enough for what?” If, for example, the issue is whether or not to approve clinical use of a promising new cancer drug even though it may have potentially lethal side effects, the evidence for efficacy had better be all but overwhelming. If, at the other extreme, the only issue is whether or not to pursue further animal research on a promising drug, a few preliminary in vitro studies might be sufficient evidence. Obviously, the bar has to be set at the level appropriate to the specific question under consideration. This chapter discusses the criteria we use in deciding whether or not to accept a given hypothesis as proven and, most important, whether or not to go ahead and recommend its incorporation into medical practice.

Evidence-based medicine

The large-scale, randomized, double-blinded, placebo-controlled clinical trial (RCT) continues to be the gold standard for evaluation of a new medical or surgical intervention. This is as it should be. Everyone will agree that the best way to find out if an intervention really works is to do an RCT, a single-variable experiment that tests the new intervention against a placebo or against an alternative intervention already in use. However, in the minds of many clinicians and investigators, this is the only kind of evidence that counts. The ‘evidence’ in evidence-based medicine has come to be almost synonymous with results from RCTs. Yet evidence-based medicine was originally meant to call for integrating clinical expertise and the best external evidence 1. There was never an intention to confine the relevant evidence to the
results of RCTs. For example, if there is already evidence from animal model studies that a certain inborn error of metabolism responds favourably to a simple dietary intervention, that should be taken into account. If that dietary intervention is totally harmless, and especially if the disease is so rare that a large-scale trial is out of the question, few would argue against testing the treatment in a few selected cases. Over 200 years ago Thomas Bayes formally proposed using what he called a “prior probability”, based on previous trials and/or other relevant lines of evidence, in evaluating the truth of a hypothesis. In the present context the Bayesian view is that you should consider the likelihood of a hypothesis based on all the relevant evidence available to you before you enter into a clinical trial and weight the significance of the results of the current trial accordingly. Now, pooling the results of previous clinical trials with the results of a new clinical trial can and should be done using the Bayesian approach. Unfortunately, there is no easy way to quantify and weigh other kinds of evidence so that they can be taken account of in a mathematically rigorous fashion. For example, let’s assume you have a new antibiotic that has cured septicemia due to a penicillin-resistant S. aureus in 90% of 100 rats treated with it. You carry out a clinical trial in 100 cases of septicemia due to this same organism and find a cure rate of 70%. However, the p value is 0.07. Should the FDA give approval even though the p value is >0.05? Most of us would probably vote for approval, taking into account the remarkable results of the prior animal studies. But what if the cure rate in the clinical trial were only 1.5% with a p value of 0.04? With such a numerically small (even though statistically significant) cure rate, we would probably defer judgment until additional evidence became available.

How much of what we do is based exclusively on RCT data?

Many, perhaps most, of the things we do in clinical medicine do not have the imprimatur of an RCT to back them up. For example, the hypothesis that cigarette smoking causes lung cancer has never been proved by an RCT… and almost certainly never will be. However, the strikingly high morbidity and mortality in cigarette smokers, together with the facts that risk decreases when they quit and that cigarette smoke contains carcinogens, was more than sufficient to justify the current vigorous public health programs to help people stop smoking. Unfortunately, most of the major chronic disease problems that face us have multiple rather than single etiologies and their prevention is not nearly so straightforward. Still, here is an example of a major public health problem in which prevention and treatment is based not on RCT data but ancillary evidence of several different kinds.

When a clinician today prescribes statins or other cholesterol-lowering drugs for hypercholesterolemia, he has strong RCT data to back him up. Yet his confidence that he is doing the right thing is importantly based also – directly or indirectly, knowingly or unknowingly, – on the many additional lines of evidence that have supported the lipid hypothesis over the years. The first large-scale RCT to critically test the lipid hypothesis was the National Institutes of Health Coronary Primary Prevention Trial (CPPT) published in 1984. However, for many years before that some physicians were already recommending dietary and drug regimens for lowering blood cholesterol. They felt justified in doing so because of the lines of evidence coming from several different biomedical disciplines (Table 1).
Table 1. The multiple different kinds of evidence supporting the lipid hypothesis available prior to the large-scale randomized clinical trials.

<table>
<thead>
<tr>
<th>Source of the evidence</th>
<th>Nature of the evidence</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Human pathology</td>
<td>Cholesterol derived from plasma lipoproteins is a consistent and striking feature of atherosclerotic lesions</td>
<td>(5)</td>
</tr>
<tr>
<td>Experimental pathology</td>
<td>Lesions similar to those of human atherosclerosis can be produced in many different animal species by raising the level of cholesterol in their blood to a high enough level and maintaining it for a long enough time</td>
<td>(6)</td>
</tr>
<tr>
<td>Genetic studies</td>
<td>People with dramatically high blood cholesterol levels, as in familial hypercholesterolemia, have dramatically premature coronary heart disease</td>
<td>(7)</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>People with even relatively modest elevations of blood cholesterol levels are at significantly higher risk. This is true across a wide spectrum of blood cholesterol levels and holds on comparison of populations from different countries and also within populations</td>
<td>(8, 9)</td>
</tr>
<tr>
<td>Clinical investigation</td>
<td>Blood cholesterol level is increased when dietary saturated fat intake is increased, as shown by carefully controlled metabolic ward studies</td>
<td>(10, 11)</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Populations with dietary habits that include a high saturated fat intake have higher blood cholesterol levels and a higher coronary heart disease incidence than populations with lower saturated fat intake</td>
<td>(12)</td>
</tr>
<tr>
<td>Geographic epidemiology</td>
<td>The wide differences in blood cholesterol levels and coronary heart disease risk between populations of different countries is largely due to environmental factors (probably diet) rather than genetic factors, as shown, for example, by the Japanese migration studies</td>
<td>(13)</td>
</tr>
<tr>
<td>Pilot clinical trials</td>
<td>Dietary intervention to lower blood cholesterol decreased the risk of coronary heart disease in several studies, small and flawed in some ways, but offering support to the lipid hypothesis</td>
<td>(14-17)</td>
</tr>
</tbody>
</table>
All of these findings were already in hand by the early '70s but there was no truly definitive RCT until the 1984 CPPT. Still most research workers in the relevant fields were already convinced of the causal relationship between blood cholesterol and coronary heart disease. In 1978, Norum surveyed 211 scientists involved in one or another way in atherosclerosis research – epidemiologists, nutritionists, geneticists, clinical investigators. The response rate was a remarkable 90% so the results are representative. He asked: “Do you think there is a connection between plasma cholesterol level and the development of coronary heart disease?” Almost 98% said “Yes”. To the question, “Do you think that our knowledge about diet and coronary heart disease is sufficient to recommend a moderate change in the diet for the population in an affluent society?”, 91% said “Yes”. In other words for years prior to the publication of a large definitive RCT almost 90% of experts in the field already believed that blood cholesterol levels were causally linked to heart attacks.

Nevertheless, most clinicians were unwilling to take hypercholesterolemia seriously and most authorities were unwilling to extrapolate from the lines of evidence listed above and get on with developing intervention guidelines and treatment programs. In retrospect they were too conservative and cholesterol levels below 300mg/dL continued to be considered ‘in the normal range’. How many myocardial infarctions could have been prevented had measures to reduce hypercholesterolemia been actively pursued in the 1970s? But policy makers were unwilling to take action without RCT evidence, the gold standard.

The history of how we have approached the management of hypercholesterolemia over the years is marked by extraordinary conservatism. In fact even after the 1984 Coronary Primary Prevention Trial had provided the RCT data that should have convinced even the skeptics about the causative linkage between hypercholesterolemia and coronary heart disease, there was continuing resistance to implementing appropriate interventions. It was argued that the CPPT study was done in men only and therefore did not justify treatment in women. It was argued that the study was done using a drug (cholestyramine) and therefore did not justify recommendations for diet treatment. It was argued that the study was done in middle-aged men with very high cholesterol levels and therefore did not justify treatment in the very old or in the very young. While the CPPT showed a statistically significant reduction in coronary heart disease morbidity and mortality, all-cause mortality was not reduced. It was argued then that lowering cholesterol levels might be increasing deaths due to other causes. Well, as we all know now, each and every one of these objections to extrapolation from the CPPT was laid to rest by subsequent clinical trials using statins because blood cholesterol was lowered more effectively and therefore the decrease in hard endpoints was greater. There is little doubt that the foot dragging that held back full implementation of cholesterol-lowering programs for years was responsible for many thousands of preventable coronary events.

Today we are being asked to consider another extrapolation: should we consider initiating cholesterol-lowering treatment at an earlier age, say age 30, in patients at only moderately high risk?
The case for earlier intervention

The war against coronary heart disease is going well: statins reduce events by about one third. Yet many are asking: what about the two thirds that go on and have their infarction despite statin treatment? Some have concluded that this 30% salvage rate is the best that can be done with current methods of treatment... that better results will require alternative interventions such as the use of anti-inflammatory agents. But if treatment were started at an earlier age, say 30 rather than 50 or 60, the salvage rate could be considerably higher, possibly as high as 80-90%. The evidence to support this point of view is extensive and persuasive, as reviewed by Steinberg, Glass and Witztum 19. Why do we think we can do better?

Human pathology

The Japanese in 1952 had a mortality rate from coronary heart disease that was about 10% that in the United States 20, 21 and this large difference was not genetically based. Epidemiologic studies have shown that the Japanese who migrate to Hawaii or to San Francisco have higher blood cholesterol levels and a higher incidence of coronary heart disease 13, 22. This occurs within a few generations so the gene pool has not had time to change significantly. There is good reason to believe that the major change in the new environment is diet. Keys reported that the fat content of the diet rose from 10-15% of total calories in Japanese on the home island to about 30% in Japanese migrants to Hawaii and to almost 40% in migrants to Los Angeles 12.

Now the Japanese follow the dietary patterns of their country for their entire lifetime and thus they have their lower cholesterol levels over that lifetime. In contrast, most of our clinical trials only last for 5 years. Even if the drop in blood cholesterol during that 5-year trial is profound enough to bring it down to Japanese levels, the event rate is unlikely to drop to the Japanese event rates. The canonical 5-year trials give us a minimum estimate of the impact of preventive management.

Fatty streak lesions

Fatty streak lesions begin in childhood and are extensive by age 30 23, 24. These fatty streaks themselves are clinically benign. However, they are the precursors of the fibrous plaque and, ultimately, the vulnerable plaque that is the site of fatal thrombosis. We know that the risk factors correlating with the extent of fatty streaks in the young, including hypercholesterolemia, hypertension and obesity, also correlate with coronary heart disease risk in adults 25, 26. So we are dealing with a single disease entity that evolves slowly over many decades. The PDAY study 27 showed that the arterial sites susceptible to fatty streak formation are anatomically the same as those susceptible to plaque formation. It follows that if we intervened early and were able to limit fatty streak formation we would prevent or at least defer the later evolution to the fibrous plaque and the vulnerable plaque. Instead of deferring treatment until middle age, as most clinicians do with patients at only moderate short-term...
risk, why not nip the fatty streak in the bud? Reductio ad absurdum, no one would seriously advocate deferring treatment of diabetes until microvascular disease became clinically evident. We should not be waiting until an age when clinical coronary heart disease is just around the corner.

**Early statin treatment**

There are no serious untoward effects of early statin treatment, even in children. We already treat very high-risk patients in childhood (e.g. patients with familial hypercholesterolemia). It has been shown that it works and that it is safe. In children ages 8 to 18, pravastatin treatment for 2 years did not impair growth or maturation. Starting treatment at an earlier age would entail a longer exposure to drug so both risk/benefit and cost/benefit would have to be taken into account. New guidelines would have to balance the anticipated improvement in prognosis against the risk and cost of treatment.

**A low LDL level from birth**

Having a low LDL level from birth confers much greater protection from coronary heart disease than does a comparable degree of cholesterol-lowering over the 5 years of a clinical trial. This is dramatically demonstrated by recent studies by Cohen, Hobbs and colleagues on a new gene importantly involved in regulation of the LDL receptor. This gene (PCSK9) codes for a protein that plays a major role in regulating cell surface expression of the LDL receptor. Adults with a nonsense mutation in PCSK9 have plasma LDL levels that are 28% lower than that found in those with the normal gene. Now, in the 5-year statin trials a 28% drop in LDL would be associated with a 25-35% drop in risk. In contrast, risk in these subjects with the mutations was reduced by fully 88%. As nicely pointed out by Brown and Goldstein, the implication is that having a low LDL from birth almost triples the magnitude of the effect on risk compared to that seen in a 5-year trial starting in middle age. The findings of Cohen and Hobbs have been confirmed by two groups. They strongly support a mandate to treat earlier. Drugs that regulate the expression and function of PCSK9 are probably in the pipeline. Since PCSK9 works by a different mechanism, such inhibitors would probably have effects additive to those of other drugs.

**Levels of LDL currently considered ‘normal’ or ‘acceptable’**

The levels of LDL currently considered ‘normal’ or ‘acceptable’ are not benign with regard to atherogenesis. The results of the recent JUPITER Trial make that clear. This trial randomized 17,802 apparently healthy men (age 50 or older) and women (age 60 or older) to placebo or to 20mg rosuvastatin daily. An entry hsCRP level of 2.0mg/L was required but other major risk factors were a basis for exclusion. The combined primary endpoint was myocardial infarction, stroke, arterial revascularisation, hospitalisation for unstable angina or cardiovascular death. Initial LDL had to be less than 130mg/dL and the median value for the cohort was 108mg/dL. The study was interrupted after only a little less than 2 years because
of a striking 44% reduction in endpoints in the treated group (hazard ratio 0.56, p<0.00001). LDL was reduced to a median of 50mg/dL. Because subjects with high-risk factors (other than CRP) were excluded, the absolute incidence of endpoints was very low – 0.77 and 1.36 per 100 person-years in the treated and untreated groups, respectively, but the relative risk reduction was as great as that in the groups at much higher risk in other statin trials. The JUPITER results further underscore the need to treat more aggressively and to widen the net both in terms of LDL level and age.

So what should be recommended?

It is already best practice to treat those at very highest risk, e.g. patients with familial hypercholesterolemia, from childhood. Patients with established clinical coronary heart disease or diabetes are also treated aggressively on discovery, at whatever age. On the other hand, according to current guidelines 36, a 40-year-old man with a cholesterol level of 229mg/dL would not qualify for aggressive treatment because his 10-year Framingham risk might be only 5%. However, even though he develops no additional risk factors, over the years his calculated Framingham risk rises progressively and his life-time risk, the probability of his having a major cardiovascular event sooner or later, is 43% 37, 38. At age 40 the extent of atherosclerosis is already quite significant and gets progressively worse over the ensuing decades. It would seem reasonable to recommend that this man and others with a similarly high life-time risk should be treated more aggressively beginning no later than age 30. A recent analysis by the Heart Protection Study Collaborative Group concludes that life-time treatment with 40mg/d of simvastatin at current generic prices would be cost effective in people age 35-85, even in those with risk of a major cardiovascular event as low as 1% per year 39.

However, because there are no RCTs in 30-year-olds, those responsible for developing guidelines are unlikely to make such a proposal. They will more likely tend to be conservative and only make recommendations that bear the imprimatur “evidence-based medicine”. They are more likely to say “Let’s wait for the clinical trial”. But in this instance a clinical trial is not feasible. A clinical trial of drug treatment initiated at age 30 would have to span 25 years or more and would be forbiddingly expensive. It surely isn’t going to happen soon, if ever. If, as we believe, treatment started at 30 would double current salvage rates with statin therapy, each year we delay the ‘treat early’ strategy may be costing thousands of lives. Doing nothing is de facto making a decision. Do we sit on our hands? Or do we invoke the power of the lipid hypothesis and urge those who write the guidelines to think outside the box and consider departing from current practice. There are so many lines of evidence justifying the extrapolation that Bayes himself would no doubt concur and so would most clinicians.

Conclusions

In this chapter we have chosen for analysis the particular case of the management of hypercholesterolemia but similar dilemmas are bound to arise in other areas of medicine. We
should not be rigidly wedded to the RCT as the only arbiter of what is best medical practice. This is obviously the case when an RCT trial is not feasible or is many decades down the road. Even when RCT data are available, decisions about intervention should take into consideration all of the relevant evidence, not just the RCT data.

<table>
<thead>
<tr>
<th>Key points</th>
<th>Evidence level</th>
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<tbody>
<tr>
<td>While the results of a randomized, double-blind clinical trial (RCT) provide by far the most valuable evidence guiding decisions regarding medical intervention, other relevant evidence must be considered as well.</td>
<td>Not applicable</td>
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<tr>
<td>Evidence from clinical observations, basic studies of pathogenesis, animal model studies, epidemiologic correlations, genetic studies, and any other relevant sources should be considered along with the RCT results in deciding whether or not to recommend a new intervention.</td>
<td>Not applicable</td>
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<tr>
<td>In some instances an RCT may not even be feasible and yet a recommendation for intervention may be warranted on the basis of other lines of evidence. This was the case with respect to cigarette smoking and lung cancer. With appropriate attention to risk/benefit ratio, the same may be true of earlier intervention to correct hypercholesterolemia and other risk factors for coronary heart disease.</td>
<td>Not applicable</td>
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References