FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE CARDIOVASCULAR AND
RENAL DRUGS ADVISORY COMMITTEE
(CRDAC)

Wednesday, September 10, 2014
8:31 a.m. to 4:22 p.m.

FDA White Oak Campus
Building 31, The Great Room (Room 1503)
White Oak Conference Center
Silver Spring, Maryland
Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Kristina A. Toliver, PharmD
Division of Advisory Committee and Consultant Management
Office of Executive Programs, CDER, FDA

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Vice Chairman

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Director, C5Research (Cleveland Clinic Coordinating Center for Clinical Research)

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Cardiovascular Therapeutic Area Head
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TEMPORARY MEMBERS (Voting)

Bonnie Arkus, RN
(Acting Consumer Representative)
Hamilton Township, New Jersey
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<td>Ralph B. D’Agostino, Sr., PhD</td>
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<tr>
<td>Professor of Mathematics and Statistics</td>
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<td>Biostatistics and Epidemiology</td>
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<td>Executive Director MA/PhD Program in Biostatistics</td>
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<td>Professor of Biostatistics</td>
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<td>Chair, Department of Internal Medicine</td>
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<td>Wayne State University School of Medicine</td>
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Susan Leighton
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Huntsville, Alabama

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Clyde Yancy, MD, MSc, FACC, FAHA, MACP

Chief, Division of Cardiology
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GUEST SPEAKERS (NON-VOTING)

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Diabetes Lead Care Management Institute and
Community Benefit
Kaiser Permanente

Suzanne Oparil, MD
Distinguished Professor of Medicine
Director, Vascular Biology and Hypertension
Program of the Division of Cardiovascular
Disease, Department of Medicine, University of
Alabama at Birmingham
Panel Member on the Eighth Joint
National Committee (JNC8)
Sidney Smith, Jr., MD, FACC, FAHA, FESC

Professor of Medicine
University of North Carolina, Chapel Hill
Panel Member for the development of the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Professor Sir Nicholas Wald, FRCP, FRS

Professor of Preventive Medicine
Wolfson Institute of Preventive Medicine
Barts and The London School of Medicine and Dentistry
Queen Mary University of London

Salim Yusuf, DPhil, FRCPC, FRSC, OC

Professor of Medicine, McMaster University
Executive Director, Population Health Sciences
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ODE I, OND, CDER, FDA

Ellis Unger, MD
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Office of Drug Evaluation I (ODE I)
Office of New Drugs (OND), CDER, FDA
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PROCEEDINGS
(8:31 a.m.)

Call to Order

Introduction of Committee

DR. LINCOFF: Good morning, everyone. If everyone could please take their seats, we can get started.

I would like to remind everyone to please silence your cell phones, BlackBerrys, and other devices if you've not already done so. I'd also like to identify the FDA press contact for this meeting, Ms. Sandy Walsh. If you're present, please stand.

My name is Michael Lincoff. I'm the chairperson for the Cardiovascular and Renal Drugs Advisory Committee. I'll now call this meeting of the cardiovascular and renal drugs advisory committee to order.

We'll start by going around the table and introducing ourselves. Let's start down at the right.

DR. SCOTT: Good morning, everyone. My name
is Rob Scott. I'm the head of cardiovascular and metabolic development at Amgen. I'm the nonvoting industry representative on the panel.

MS. LEIGHTON: Good morning. I'm Susan Leighton. I'm the patient representative from Huntsville, Alabama.

MS. ARKUS: Good morning. I'm Bonnie Arkus. I'm the consumer representative from Trenton, New Jersey.

DR. FLACK: Good morning. John Flack, a professor of medicine and physiology at Wayne State University.

DR. DAVIS: Barry Davis, professor of biostatistics at University of Texas School of Public Health.

DR. DELEMOS: James DeLemos, cardiologist at UT Southwestern in Dallas.

DR. LI: Jennifer Li. I'm a pediatric cardiologist at Duke University.

DR. SAGER: Philip Sager, cardiologist at Stanford University.

DR. LINCOFF: Mike Lincoff, a cardiologist
at the Cleveland Clinic.

DR. TOLIVER: Kristina Toliver, designated federal officer, CRDAC.

DR. FRIED: Linda Fried, nephrologist, Pittsburgh VA and University of Pittsburgh.

DR. RICH: Stuart Rich, cardiologist, University of Chicago.

DR. LEWIS: Julia Lewis, nephrologist, Vanderbilt.

DR. D'AGOSTINO: Ralph D'Agostino, statistician from Boston University and the Framingham study.

DR. KAUL: Good morning. Sanjay Kaul, cardiologist, Los Angeles.

DR. WILSON: Peter Wilson, endocrinology, preventive cardiology, public health at Emory.

DR. STOCKBRIDGE: Norman Stockbridge. I'm the director of the Division of Cardiovascular and Renal Products at FDA CDER.

DR. UNGER: I'm Ellis Unger. I'm director of Office of Drug Evaluation I in the office of New Drugs in CDER, FDA.
DR. LINCOFF: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that the conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please
refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now we'll have the conflict of interest statement.

Conflict of Interest Statement

DR. TOLIVER: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of the committee are
in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of the potential clinical utility of fixed-combination
prescription drugs composed of an antihypertensive
drug, aspirin, and a statin administered to reduce
the risk of cardiovascular death, nonfatal
myocardial infarction, and nonfatal strokes in
patients with a history of cardiovascular disease.

The committee will be asked to discuss the
patient population that could benefit from such a
product, whether that population would be likely to
take such a drug long term and how this could be
assured. The committee will also be asked to
consider the pros and cons of a treatment that
would not be titrated and in a setting where
monitoring might not be rigorous.

This is a particular matters meeting during
which general issues will be discussed. Based on
the agenda for today's meeting and all financial
interests reported by the committee members and
temporary voting members, no conflict of interest
waivers have been issued in connection with this
meeting.

To ensure transparency, we encourage all
standing committee members and temporary voting
members to disclose any public statements that they
have made concerning the products at issue.

With respect to FDA's invited industry
representative, we would like to disclose that
Dr. Rob Scott is participating in this meeting as a
nonvoting industry representative acting on behalf
of regulated industry. Dr. Scott's role at this
meeting is to represent industry in general and not
any particular company. Dr. Scott is currently
employed by Amgen.

With regard to FDA's invited guest speakers,
the agency has determined that the information to
be provided by these speakers is essential. The
following interests are being made public to allow
the audience to objectively evaluate any
presentation and/or comments made by the speakers.

Dr. Robert James Dudl has acknowledged he is
employed part-time by Kaiser Permanente. Dr. Salim
Yusuf has acknowledged he receives grants from
Cadila Pharmaceuticals, Limited, India, to conduct
duvpill studies.

Dr. Nicholas Wald has acknowledged he is
center lead of the Wolfson Institute of Preventative Medicine Barts, Queen Mary University of London. He is also director and shareholder of Polypill, Ltd. As joint shareholders of Polypill, Ltd, Dr. Wald, his son David Wald, and daughter Karen Wald are working together to develop the polypill.

Dr. Wald is co-investigator on various polypill studies and joint patent holder for the polypill in the United States, Canada, and European Union countries.

He has served as scientific advisor to various groups, including the United Kingdom, New Zealand and Canadian governments, World Health Organization, and the United States Public Health Service on issues relating to preventative medicine, public health, and medical screening.

He has jointly published papers on polypill for the prevention of cardiovascular disease. And in the last 40 years, Dr. Wald has received various speaking fees, including recent fees from the University of Illinois Chicago and the British
Hypertension Society.

As speakers for this meeting, Dr. Dudl, Yusuf, and Wald will not participate in committee deliberations nor will they vote.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firms that could be affected by the committee's discussions. Thank you.

DR. LINCOFF: We will now proceed with the FDA opening remarks from Dr. Norman Stockbridge. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate
Dr. Stockbridge.

FDA Introductory Remarks

DR. STOCKBRIDGE: Good morning, and a very hearty welcome to everybody who's here today for this. All advisory committee meetings take a fair amount of planning and preparation and person hours. This one's been in discussion for years, so we're really very happy to have everybody here for this.

There are a number of issues that are going to need to be discussed here. We had a meeting yesterday where we discussed a two-drug combination. I think the committee is now ready to discuss a four- or five-drug combination, and various things are going to come up in context for that.

One issue is going to be the Combination Rule, which is 21 CFR 300.50, which refers to combination products as two or more drugs in a single dosage form where each component makes a contribution to the claimed effects. But
regulations do not specify what's necessary to establish that the components contribute.

Factors that you'll want to consider are pharmacokinetics. You might be inclined to think that sufficed if you knew the combination didn't affect the bioavailability of the drug, but we've generally worried that pharmacokinetics alone is not sufficient despite common use of agents together.

Another consideration is pharmacodynamics, and we've generally thought it was necessary to have those data, too, noting that we're probably not smart enough to anticipate all possible drug interactions. And the poster child for that, from my perspective, has been data that suggests that aspirin interferes with ACE inhibitors.

The third component is, of course, outcome data, and we've generally said that if the PK and PD seem to be not much affected by use in combination, that we want to see any available outcome data there are with the combination, but there's no real requirement or expectation that
such data be developed.

Another issue is what doses need to be made available. Must you be able to move through a sequence that's intended to manage titratable components and conditions. Historically, we required two-drug antihypertensives to be approved with all reasonable dose combinations to avoid having the presence of the product on the market interfere with the sensible prescribing behavior.

However, it developed that sponsors would simply stop manufacturing dose combinations that they thought weren't in their marketing interest, and there were no repercussions from FDA. So some years ago, I stopped insisting that combination products be made available with all combinations available at the time of approval.

Then there's the point of view that for some of these drugs, you get a substantial fraction of the benefit with a good dose of each component and less incremental benefit associated with subsequent titrations.

Another issue we'll deal with here today is
what the claim of a product might look like here
and what you might need to do in order to establish
such claims. We've approved some combination
products with a substitution claim in which the
label basically said the product was for use in a
patient population that was the intersection of the
populations described in the individual labels, and
the claims constituted the union of the set of
claims for those products.

To support that, we, as I've said, generally
didn't require anything more than PK/PD.

At the other end of the spectrum, there's a
sort of vaccine-like claim here. The drugs are
pretty safe, and maybe a population that's at even
moderate risk -- maybe everybody over some
age -- might be better off on some treatment.

You might think one might need real kind of
public health trials, testing various strategies of
use. And if you thought that, you'd have to face,
I think, possible implications of the Combination
Rule.

What encouraged this meeting from my
perspective was the idea of a sort of intermediate kind of claim in which the patient population was one with a clear indication for treatment. In other words, we wouldn't be necessarily thinking about extending the population beyond what's currently labeled for the products.

If you had a population where you thought you weren't likely to get good follow-up, it seemed sort of obvious on its face to me that such patients would be better off on even suboptimal therapy if you thought titration was optimal, better off on suboptimal therapy than on nothing.

Would you need a trial to show that? I would guess not, but we'll see what other people think here today. Thank you.

DR. LINCOFF: Dr. Temple, would you like to introduce yourself to the room?

DR. TEMPLE: Yes. Bob Temple. Sorry. I was late; on the Beltway. Deputy director, ODE I.

DR. LINCOFF: We will now proceed with the guest presentations from Drs. Wald, Yusuf, Oparil, and Smith.
Guest Presentation -Nicholas Wald

PROF WALD: Good morning, ladies and gentlemen, and thank you for inviting me to today's meeting. Fourteen years ago in 2000, Professor Malcolm Law and I set out in our patent filing the details and concept and formulations of polypill that could, in our judgment at the time, scientific judgment, prevent most heart attacks and strokes in the community.

While secondary prevention is important, our focus was on primary prevention. So this would have a substantially greater effect in preventing these two important diseases. Today, however, I was asked to focus on secondary prevention, which I will do, but in view of the importance of primary prevention, I will touch on it towards the end of my talk.

The polypill itself is actually kind of simply defined as a physical thing, a single pill that will modify two or more causal cardiovascular risk factors simultaneously. I put there, and I know it's been disclosed, the conflicts of interest
statement.

Now, the scientific basis for a polypill involves characterizing the dose response relationships between specific causal risk factors in the disease, and understanding this is really important.

I show here the dose response relationship between usual systolic blood pressure and relative risk of stroke from the Prospective Studies Collaboration published in 2002, and we see here this straight line relationship on a doubling or log scale. And this shows clearly that there's no threshold, the lower the blood pressure, the lower the risk.

I've shown on the right the same data published with an arithmetic vertical scale, which I suspect has led to the belief that there's been a threshold because on this scale, because there's a naught and you can't have a negative rate of disease, it must necessarily flatten.

The straight line log relationship is important because it tells us that there's a
constant proportional change in risk for a given change in the risk factor. So going from 180 to 160 will proportionately give you the same as 140 to 120.

Here this shows you that the effect of the 20 millimeter systolic from these data -- this relates to people age 60 to 69 -- is equivalent to a 56 percent lower risk of stroke or translating it to diastolic; approximately a 10 millimeter diastolic would achieve this 50 or 60 percent reduction in stroke were this obviously to be causal. And there's clearly evidence from randomized trials that this is causal.

So we have this conclusion, proportional reduction in risk for a given change in risk factors independent level of a person's risk factor.

Now, I've shown you the same data there, the 60 to 69 year olds, but I've now added the other age groups plotted on this relative risk rate scale. It goes from 1 to 2, over 250. And it shows that this linear relationship is true at all
levels of risk and at all ages.

So here's the data for ischemic heart disease and blood pressure, and I'm not showing it, but this is similar for cholesterol and ischemic heart disease.

So we can now say that the proportional reduction in risk is also largely independent to the level persons of overall risk. I say largely because the slope of those lines tends to get shallower with increasing age.

Now, let's look at hypothetical risk factor in relation to the risk of disease on a doubling scale, and say we go from a high level of this risk factor to 6. The reduction in risk would go down there from 16 to 8 per thousand, per year in this hypothetical example. If one went from a low level to an even lower level, 5 to 4, go down there, then that would go from 4 to 2. So there's a halving, which is summarized in this bit at the bottom.

But the absolute risk reduction is less at the lower level, and that I believe has led to people think, well, if you've got a low risk
factor, say, blood pressure or cholesterol, it's really less important or unimportant to get it down further. However, this ignores the fact that you could be at high risk and usually will be at high risk for reasons other than the risk factor that you might seek to intervene on.

For example, someone might be up here, say, simply because they're older, and if they reduce this particular risk factor from low to even lower, they go down there. And it goes from 16 to 8, which would be a comparable absolute risk factor. It could even be higher.

So the clinical priorities emerge from this simple analysis is that we need to identify high risk, not high risk factors, and avoid titration because there's no threshold. Titration is actually a mistake, in my view. It's not that by not titrating it's less optimal. It's actually inappropriate.

Let me now move to blood pressure lowering drugs, and this analysis with Professor Law and colleagues shows really quite well -- one thing
which I'm not showing is that the different blood pressure lowering drugs at standard dose have similar effects on lowering blood pressure. But if you look at the standard effect on diastolic 5.5 reduction or about 10 or 11 systolic, but if you go to half standard dose, you don't have the effect on blood pressure. It's only reduced by about 20 percent. So half versus standard is 20 percent loss, not 50.

Now, let's consider combining different blood pressure lowering drugs and comparing it in a moment with doubling the dose. Are there different classes of blood pressure lowering drugs, they have different mechanisms of actions? Do they have independent effects?

This analysis shows trials. Each blob is another randomized trial. And along here, these are trials in which the blood pressure lowering drugs were used individually, two of them, pending combination. And this shows the expected fall in blood pressure is the effect where independent and additive. And this is the observed. And there is
the line of identity. And you see that all the
studies hover around the line of identity,
indicating that they are independent, the different
classes of drug.

Now, let's consider here, for example,
thiazide. Let's imagine that we were going to add
another drug. Then to simplify it, if we added,
the added effect would be that, systolic blood
pressure reduction in this example of 14.

In the thiazide, if you double the dose of
the thiazide, in fact, the meta-analysis of studies
on thiazide show this effect, which happens to be a
19 percent of adding the second drug. And here's
the same data. I'm showing you quickly the other
classes to show it's a consistent effect. The red
bars show the addition of the second drug, the blue
bars, the incremental effect of doubling the dose
of the same class of drug. And lastly, it shows
you overall.

So we see here clearly that adding an extra
drug is better than increasing the dose. And I'm
now showing it here, but for many of these drugs,
the side effects are dose dependent. So one could use by current standards -- I don't like the word "sub-therapeutic" -- or low-dose blood pressure lowering drugs in combination rather than working with one until they become -- people are intolerant to it.

Here's an example of a formulation for secondary prevention, aspirin, three blood pressure lowering drugs, which are shown here, and a statin. And in the particular example here, I've just used simvastatin.

This shows from randomized trials the effect of 40 milligrams of simvastatin would be equivalent to 10 milligrams of atorvastatin, for example, which would lead to a 1.8 millimole per liter reduction in LDL cholesterol of 70 milligrams per deciliter.

The combined effect of three drugs at half standard dose, blood pressure drugs, is about 11 millimeter reduction in diastolic blood pressure. And with aspirin, there are studies in platelet aggregation.
Now, these changes, might they be regarded in some people as being excessive? Well, let's look at people age 60 not on a polypill such as the one I've shown you. If they were to take that, their distribution of LDL cholesterol would be shifted there.

Now, how does that compare with other epidemiological evidence? Well, if we look at the distribution of LDL cholesterol in 20 year olds, and the population is that. So effectively, it's moving LDL cholesterol in a 60-year-old on average to the level that person would have had when he was 20 or she was 20.

Similarly, blood pressure -- and I've chosen here diastolic blood pressure -- not on the polypill, on the polypill, a shift in the whole distribution. And how does that compare with 20 year olds? Very similar.

Now, translating, we've got from drug to risk factor to risk reduction, and these risk reductions come from cohort studies supported -- and I'll show you in a moment.
how -- with evidence from randomized trials.

In terms of blood pressure lowering and LDL cholesterol, there's a remarkable consistency between what you'd expect from epidemiology and what you find in trials. And you see that with the LDL cholesterol reduction that's specified, there would be about a 60 percent reduction in IHD and about 63 percent reduction in blood pressure.

Now, with LDL cholesterol, I have to mention something that really is important, is that this expectation is supported by the randomized trials if you censor the first two years of data. Because if you take a statin, you don't immediately reduce your risk of a heart attack tomorrow. What is remarkable is you achieve almost the full expected effect after two years.

Here's the combined effect. You might say, well, how adding 61, 46, 32 combined, get 86? Now, very quickly, I'll show you because it's not complicated. The best way to consider it is if you had 100 people have a heart attack, 61 would be prevented, 39 remain, 46 percent prevented of
those, 21 remain, 32 percent of those, 14 remain. If 14 remain out of 100, you've prevented 86.

Now, is there an assumption there? Yes, the assumption is that they are independent, but it's not an assumption. There's evidence for it. First of all, there's prior biological reasonableness because the mechanisms are different. In cohort studies, these two risk factors are independent. And in randomized trials, the critical test of this, they are independent.

Here's an example of the randomized trial stratified by the extent of the cholesterol reduction, and you see here that in the trials that achieved greater than 1.5 millimole reduction, on average it was 1.6. We see here 1.6 is about 60 milligrams per deciliter. The observed in trials was 51 percent reduction.

What would one have expected from the epidemiology? Well, 57. So it's really rather quite striking correspondence, and that's only with excluding the first two years of treatment. You don't need to do this with blood pressure because
the effect on lowering blood pressure is rapid.
And the confirmation of the randomized trials
supporting the epidemiologic studies are in this
paper published in 2009.

One of the advantages of a fixed-dose
combination is properly formulated, they can
counteract or compensate for the metabolic effects.
And here's an example where thiazide will tend to
lower potassium, increase glucose and uric acid,
and an ACE inhibitor or an ARB will do the
opposite.

Adherence is an advantage with a combination
product, and here's just one example of several
studies, the UMPIRE study showing that the
adherence was 86 percent rather than 65 with the
separate components. And in this particular study,
there were small benefits and a further reduction
in systolic blood pressure and in LDL cholesterol.

Monitoring. I've already dealt with
titration as being not only unnecessary but in my
view inappropriate. Should one monitor with
electrolytes, renal, and liver function tests? My
own view is that there's no evidence of their value, in fact. They may cause more harm by removing effective treatment from people who need to benefit from it rather than avoiding some hazard of the treatment. And in general, the view should be to avoid doing something unless there's evidence that whatever you're doing is useful.

Secondary prevention polypill, is there any great advantage over taking the components? Essentially, it's the same. So pharmacologically, there's no particular advantage other than you've fixed it and put it into one. But it's more convenient, and three, it improves adherence.

So clinically, a secondary prevention polypill is an option if it's judged the benefits of two and three outweigh the benefits of tailoring treatment by changing the drug or changing the dose.

Now, in the tail end of this, I do want to point out that if a first heart attack or stroke is prevented, there isn't a second one to prevent. I have been in this debate before in the prevention
of neural tube defects where a study that I was
associated with showed that folic acid could
prevent actually a similar proportion to this,
about three-quarters of neural tube defects.

Shortly after, not in America, thank
goodness, not at CDC or FDA, but in Europe several
people said, well, if you prevent a second neural
tube defect, how do you know you'll prevent a
first?

Well, there are very few preventive measures
where if you can prevent a second you won't prevent
a first. We're not going to make seat belts
compulsory only after you've had your first major
road traffic accident.

So if a first is prevented, there's no
second to prevent. So the public health priority
should be primary prevention. Here's a possible
formulation with this calcium channel blocker
instead of the beta blocker and no aspirin for the
time being. That may change in light of evidence
on the prevention of cancer.

We have this picture with aspirin in it.
Well, let's say we take aspirin out. The combined effect, aspirin the point estimate on IHD, is about 30 percent. Well, if you remove the aspirin, the combined effect is 79 percent. It's only 7 percent less, not 32, because the other components pick up what is there to prevent. So this is an interesting example of pharmacological auto compensation that you get from a combination product.

So there's the summary. The results of a crossover trial that we did -- or my son did, David Wald. The end of the placebo period, this was the LDL cholesterol. The expected reduction from what I've shown you in LDL was going from 3.7 to 2.3 millimoles per liter, and the observed was almost spot on.

Now, I haven't shown it on there, but the confidence intervals on these estimates are .1 of a millimole or 4 milligrams per deciliter. So saying this is too small is ridiculous. It's small by comparison with parallel group designs, but crossover studies have the opportunity of giving
considerable power with smaller numbers.

Here's the systolic blood pressure in the same way, the expected, and there's the observed, a 12 percent reduction. It's actually quite useful, I think. It's relatively new to even consider. We think of percentage reduction in cholesterol. One could also begin to think of that in terms of blood pressure.

We often talk about what's your 10-year risk of a disease. My own view is one's got to, A, think of lifetime risk, but then give information not on the risk but the benefit of the intervention that would be offered. Because if you identified a high risk, like high risk of dementia, and there's was no means of preventing it, you're lost. So it's prevention that has to be specified.

Thirty-three percent of 50 year olds who would take a polypill would benefit. Why would the others not? Because they die of something else first. And they would gain eight years of life on average without a heart attack or stroke.

Who should take this? This gives you the
story. This is the relative risk of a heart attack or stroke by age. Across from 25 to 80, there are 180-fold risk difference.

I'll now show you a slide I showed before, but on the same scale, which is systolic blood pressure in 60 to 69 year olds, that's an 8-fold risk between the 10th and 90th centile. Age dominates in terms of predicting risk.

Let's say we used age, and we simply said age 50. Well, that would identify 92 percent of all first heart attacks and strokes that would occur because 8 percent occur in younger people. It would also identify 22 percent of the population who would not have a heart attack or stroke who would effectively be taking it unnecessarily, but you couldn't tell that in advance.

Let's say we used an age cutoff of 60. You'd pick up less, 79 percent, but the effective false positive rate would reduce to 14 percent. If you went to age 70, you'd pick up just over half of these events, but the false positive rate, 8 percent.
Now, what I really want to just end on is you may say I'm just using age. What if you used a risk score like Framingham? And I've here set -- if you look at the right side of this. These were the false positive rates on age and setting them the same.

So for a given proportion of the population who effectively would be taking this unnecessarily, adding annual physical examinations with all that's involved in a scoring system such as Framingham would, in the first instance with a 22 percent corresponding to this, add three percentage points to detection from 92 to 95.

So the issue here is the complexity of the examination for this marginal return. And quite interestingly, if you choose 14 percent, you lower the false positive rate. The marginal gain is greater. If you go to 8 percent, the last comparison, you actually get 16 percent extra events identified. And that's because you're moving further into the tail, and there's more opportunity for other tests to get it. But clearly
with Framingham, you're not fixing the age. You're basing it upon the risk score.

So in conclusion, I think what I sense is an approach -- and this is what in a way I'm putting to you as an advisory committee -- is in terms of the regulatory pathway for primary and secondary prevention, not to lose sight of primary prevention even though the focus here is secondary.

Now, should one adopt a stepwise approach, consider licensing secondary prevention polypill and then primary, or what about a concurrent approach? Consider collecting the evidence needed, the reasonable evidence needed, to consider licensing both at the same time. They might involve different arguments, different sets of data.

I would suggest this is sensible because why deny the public health benefit to our population in primary prevention because we're waiting for a process that is simply providing a single pill for secondary prevention in people who are going to get medical care anyway, and the marginal advantage is
simply the one I mentioned, is convenience and
probably better adherence to?

But it's not a big difference. The primary
prevention approach with age would be a dramatic
difference and would, in my view, if adopted and
implemented widely, lead to a substantial reduction
in heart attacks and strokes in America. Thank you.

(Applause.)

DR. LINCOFF: Dr. Yusuf.

**Guest Presentation – Salim Yusuf**

DR. YUSUF: Good morning, ladies and gentlemen. Since we didn't see the slides of other people, there will be some overlap as we go on when I reviewed the book, so please excuse us for that.

The first thing I want to say is to identify four emerging concepts in cardiovascular disease prevention. The first is a fact that we all know, that cardiovascular disease causes about one-third of deaths in adults. Pause and think what it means. It means it's an epidemic, and we don't
at a time. We tackle it on a population basis.
That's the way we've always tackled epidemics.

Yet, because of the historical nature in
which cardiovascular disease prevention and
treatment has emerged, we're still firmly bound in
a clinical mold, and I must say, I'm a clinician.

Second is lifestyle measures are important,
but they alone have not been successful except for
tobacco control policies, and we are making headway
there.

The third is that only 10 to 15 percent of
cardiovascular disease events comes from those who
already have cardiovascular disease. So if we
would even eliminate the majority of these events
in people by treating people with existing vascular
disease, we're not still going to touch the
majority of this epidemic.

So some form of primary prevention is
essential, and Nick Wald spoke about the risk
approach, and there are different ways of coming up
with that. But I think a primary prevention is
essential based on some measure of risk.
We know from a ton of studies that statins, ACE inhibitors, beta blockers, diuretics are proven and safe in both primary prevention and secondary prevention. And aspirin certainly in secondary prevention is not controversial.

We published this in the Lancet as a theoretical exercise when I was given the opportunity to write an editorial accompanying the heart protection study. And it's very simple. If you gave nothing and you said somebody after a heart attack had a two-year event rate of 8 percent after the first 30 days, and you gave aspirin and you reduced it by a quarter, 8 would go down to 6.

You gave a beta blocker. Your 6 could go down to 4 and a half percent. You gave a statin that lowered LDL by 1 millimole or 40 milligrams per deciliter, it would be reduced by a third, so 4 and a half would go down to 3. And if you gave an ACE inhibitor like in the HOPE or the EUROPA study, it would go down by a further quarter, so that it will go down to 2.3.

So 8 comes down to 2 and a half, which is
about a 75 percent risk reduction.

Now, this curiously matches the much more careful and thorough analysis that Nick Wald and Malcolm Law did so that there's an intuitive validity to the assumption that if we were able to use all four medications in the right kind of person and they'd adhere to it, we'd get a substantial benefit.

Now, all of my numbers are what was observed in the trials, so already non-adherence is incorporated into this.

Now, despite the enormous amount of information and all guidelines saying that aspirin, beta blockers, ACE inhibitors, and statins should be used in secondary prevention, it simply isn't worldwide. And you will see that this is the use overall in urban societies, rural societies, in 17 countries, 620 communities. Same thing with beta blockers, less than 20 percent; ARBs, also about 20 percent, and statins is about 15 percent.

Now, we are in a high-income country, and these are data from Canada, Sweden. And you will
see that even in Canada, where actually the rates
of use of drugs are slightly higher than the U.S.,
aspirin is only used for 40 percent of people with
vascular disease in the community, beta blockers
40 percent, ACE inhibitors a little more, and
statins a little more. And if you look at
combination therapy, that is all four, it's less
than 20 percent in Canada and Sweden.

In the U.S., the data are no different, and
you will see in those with a history of myocardial
infarction on the left and history of stroke on the
right, 52 percent of the people are not taking any
one of anti-platelet statins or blood pressure
lowering drugs.

You will about 30 percent of people are
taking nothing at all. Thirty percent are taking
nothing at all in the U.S. And only about 35
percent are taking all four medications here, and
about 30 percent are taking medications here.

Now, we can leave things as they are and say
despite the evidence, we can start yelling at
people and writing guidelines, but it's not
working. So we've got to do something that will improve it. And these aren't necessarily your inner city or poor people. This is average Joe Blow on Main Street, USA.

Now, hypertension control, these are data that we published in JAMA from the PURE study in 17 countries. Look at high-income countries. That's Canada and Sweden, and you'll see, only 20 percent have hypertension control. And it's obviously lower in other parts of the world. And the U.S. is generally in that ballpark.

Now, the U.N. General Assembly had a major declaration about two years ago that set a global target of reducing cardiovascular disease by 25 percent by 2025. It is actually both a modest goal and an ambitious goal because the goal is, well, if we can reduce it by a quarter, that's a big deal. Actually, even 25 percent is hard to achieve.

In that, one of the goals is to improve access to essential medications by 80 percent and use in 50 percent. Now, the 80 percent access
likely occurs in the United States, but the
50 percent use, we're far from it of people using
all four in the United States. So we haven't even
achieved in the richest country in the world what
the U.N. is saying the whole world should achieve.

So this can only be achieved by new ways of
thinking and new ways of delivering proven
medications. And what Dr. Stockbridge raised is
something we can think of in the framework of
vaccine is something that's worth thinking about.

So what are the barriers to effective
prevention? First is the lack of expertise or
interest, both are equal, in prevention. A very
famous cardiologist from the Mayo Clinic once
remarked to me, "Prevention is boring. It's
important but it's boring."

So we had to think of how can we get
prevention to be done by people willing to do
things systematically and don't think. Titration
is thinking, but thinking gets in the way of doing
the right thing. So if we know -- like when the
health worker inoculates somebody, they don't
think. They just do it.

So we have to go to the Nike ad, "Just do it." And we have to get non-physicians to do it because honestly, physicians are not interested and they don't have the time.

Now, let me tell you my experience. I did the HOPE trial. I was the PI. Now, we had three steps in titration, 2 and a half, 5, and 10. I'll tell you why most of my patients don't get to 10. I discharge them from the hospital on 2 and a half. I see them at 30 days at the standard visit and pushed them up to 5.

The next time I'm allowed to see them given the fee schedule in Canada, which probably relatively is not that different from the U.S., is a year later. If I see them earlier, I get $18. Eighteen dollars doesn't cover my overheads. So I therefore have to write a letter to the GP and say, "Would you mind just titrating it up?" Ninety percent of the people when they come back in a year are still on 5.

So titration actually gets in the way of
actually doing the right thing, and this is me who
at least knows ACE inhibitors. In other people's
case, it's worse.

Second is drugs are not available. That's
not an issue in the rich countries. Not affordable
is true for a certain segment of the population,
and even the richest country in the world can
sometimes face bankruptcy. So you want to save a
few pennies so that you can use the money for other
things.

But more importantly, it's not prescribed.
The regimen may be too complex. One
drug -- imagine four drugs, each drug being
titrated. So that's going to be a challenge even
as a clinician.

Lack of access, of cost to healthcare.
Remember, each step in titration is a visit to the
doctor. It's a fee paid to the doctor. It's time
off from work if you're working. It's parking fees
at least in Canada, maybe here. It's driving. All
that adds to the cost.

So titration now is a barrier. So we need
to think of if we have simple safe drugs, how can we quickly get them to a reasonably effective dose? So we need a health systems approach that simplifies things. The polypill is part of the delivery strategy under these circumstances. It's not a new drug.

I know this kind of decision has been faced in the TB area and the antiretroviral area, and they've not had a problem with coming to what I'd say is the right conclusion.

So what is the polypill? The polypill is, as Nick Wald said, a couple of risk factors being modified. Statins, we all agree, it's better to use blood pressure lowering drugs than push the dose up, but if you can do both, I have no objection. Aspirin certainly is secondary prevention.

Who should get it? We could compartmentalize it into three. Right now in those with existing vascular disease, there's a consensus. They need all these drugs. So why don't we put it into a single pill and give it to
people? That should be a no-brainer.

The second is we do have to move into prevention, and right now, there are various forms of guidelines for hypertension or diabetes or high lipids. And we do want to use drugs in them. And in high blood pressure people, not only do you lower blood pressure, but there are data like the ASCOT-LLA study that lowering lipids will help. Same thing in diabetics, lowering blood pressure will help and statins help. So surely, an extension from A to B is very much within our conceptual framework.

The bold step, which is controversial, is the last one. That is, just use age as the only risk factor. I don't know whether we are there yet, but I think this is the right approach. And I know this may be the hardest one for people to come to consensus, but I don't think it is wrong. Whether this panel or another panel is ready to go to C right now, I don't know, but certainly, they should be willing to go to A, perhaps to B.

There are five different polypills I am
aware of under development. There are clinical
data on the polycap, the Red Heart pill, Trinomia.
And the polycap is marketed in India and in two
African countries. It is in front of the
Argentinian ANMAT.

The Red Heart pill, excellent work by
Anthony Rogers and the George Institute group.
Trinomia has been remarkable because they've got
approvals in 11 countries, including many European
countries for a substitution indication without
much clinical data, just on PK/PD. And in Iran,
there is a polypill, but I don't know too much
about it. And I believe there is one in the U.S.,
and then there is the one that Professor Wald and
his colleagues have worked on.

I'll briefly tell you about three programs,
ours in the TIPS program, the work done by the
George Institute and a couple of study slides on
the FOCUS study, which is the work that Valentin
Fuster's group has been doing with the Trinomia.

So we studied a five combination polycap
because it's a capsule, and it has anti-platelet
agents, low-dose simvastatin initially. The reason is we did the study in India. In India, there was a lot of concern about myopathy. And as you know in Asia, there is concern about statins and muscle problems; ACE inhibitors at half standard, beta blockers at half standard and diuretics.

Then later on in TIPS 2, we went on to studying it with doubling the dose, so you got to standard. And these have been published, and we have two formulations with and without aspirin. The without aspirin formulation is being tested in primary prevention trials right now.

The first thing is it's tolerated. This was a partial factorial reciprocal design, and you will see this is one drug. It could be aspirin, simvastatin, or thiazide alone. This is two drugs. This is three drugs. This is four drugs. This is five drugs.

These are the rates of discontinuation over three months, but the red part, or the crimson part, is specific discontinuation for side effects. The others, the blue, is the patient saying I'm in
a trial. I'm really not interested. This thing is not going to do me any good. So the majority of discontinuation, which is something we see trial after trial, is for non-specific reasons.

If you look at this red bar, it's more or less the same right across, and certainly the polycap with 5 is no higher than with aspirin alone or simvastatin or thiazide, and this experience is repeated with many drugs. Again, the blood pressure lowering, this is systolic and diastolic. With one blood pressure lowering drug at half dose, about 2 and a half millimeters, double that, 7 here. And the half standard dose is 7 and a half. And when we tested the full standard dose, it's 10 by 7.

There is a certain amount of non-adherence in these trials, and this is the post non-adherence data rather than modeling it without non-adherence taken into account.

I must publicly disclose -- and it's there in the paper -- that in this study, the TIPS 2 study, we had a little bit of mishap in the
randomization, and we only discovered it at the end of the study, which is there was a factorial design with potassium as well.

The reason we put potassium is we had data from our epidemiological studies that potassium was reducing clinical events. We published some of that in the New England Journal last month. And we were hoping that if we went to a big study, we could factor in potassium as just like you know we love to do factorial designs. Like with the HOPE study, we did Vitamin E. So this was going to be a cheap way of trying to find out if potassium would have an independent effect.

As far as I know, supplementing potassium has no effect on statins. It may have an effect on blood pressure. But when you look at the data, it's very little. So I think this 10 is more or less fits in with what Professor Wald has said, 10 versus 7, the incremental. So you do get something more, but it's not hugely more.

The same thing with statins, this is simvastatin 20 by itself. This is within the
polycap. We saw some attenuation, but it's still important. And if people are taking nothing and you can get them to reduce their LDL by 30 or 35 milligrams per deciliter along with a blood pressure lowering drug, that's pretty useful. The full dose was larger than that, significantly so. And, sure, the 40 milligram simvastatin would be more effective than the 20, and we know it.

This is a subgroup analysis where we looked at no blood pressure agent versus the polycap in single and double, and you will see the proportion of people with blood pressure control, not surprisingly, increases with one blood pressure agent versus zero, 2, 3. And you can see this flattening out here, and this is the polycap. And this is the standard dose.

Why would you deny people having the benefits of greater blood pressure lowering in a simple way? And you can see it's half standard dose. It's pretty effective.

These are the theoretical modeling based on an extrapolation on Nick Wald and Malcolm Law's
work, and you see at the full dose, you get a 70 to
80 percent risk reduction using these three drugs
in ischemic heart disease and about the same on
strokes. And this is looking at it a different way
based on our trial data.

But what is more important is this. There's
been a debate in the prevention community, are you
pillifying everybody or a medicalizing thing? And
the answer is, well, let's save lives. Let's not
get into dogmatic principles. Surely, for the sake
of an argument, why would we stop saving lives?

So my view is let's do both. And we've
always said let's first try lifestyle modification.
If it doesn't work, we add a pill, and we add it at
low-dose, then the full dose. My God, we made it
complex. Let's say let's do both simultaneously.
And this shows you the modeling of doing both.

So if we had 50 percent adherence to
lifestyle and 75 percent adherence to the polypill,
you'd get about a 70 percent risk reduction. If
you were brilliant and you got 90 percent adherence
to lifestyle and 75 percent adherence to the
polypill, you nearly eliminate the disease. So it's time to stop arguing on a sort of ideological platform and to move on to just saving lives.

The UMPIRE result trial will be gone on in greater detail by Anthony Rogers, and essentially, it was a fixed-dose strategy. It was giving the same drugs individually, and these are the endpoints. And I'll skip this except to say that half the people came from India and half the people came from Western Europe. So the U.S. is no smarter than Western Europe, so let us say Western Europe practices are applicable to the U.S.

The other key point is it is the longest -- the studies done from the George Institute, many of them are the longest exposures to polypill that is published, and so the mean follow-up was about 18 months.

They had two versions. Essentially, they're the same except for one was simvastatin 40 and the other one is atorvastatin 40. And the other thing was in the fixed-drug group, they would dispense the drug free of charge. In the usual care group
for a variety of practical reasons, the people were requested to pay the local payments. About half the people were exempt. And when you look at the results in the people who were exempt, the results are identical as the people who had to pay for it.

I will skip this for a minute -- no, I won't. I want to show you this at the bottom. You will see in this trial, because most of the people had cardiovascular disease, most of them were taking some medicines, which is not what happens in a population. And you will see all indicated medications was used in 60 percent.

So this is switching people on medications that you would consider is more or less optimal, at least in numbers. And these are the effects on the primary endpoint and improvement in adherence by 33 percent. Systolic blood pressure actually is lower. So the same number of drugs but better adherence leads to greater systolic blood pressure lowering. And LDL is also significantly lower.

This is an interesting slide, and there is a thing missing that should say no drugs at baseline,
one drug. This is two, and this is three. The first thing you'll note is in all four graphs, the initial use of the full combination is greater in the fixed dose. So this gets over physician inertia. So remember the physicians participating in this trial knew they had to use all four drugs, yet this is reflecting physician inertia.

The second is obviously at zero, 1 and 2, they're more or less the same. This contrast, you will see, is maintained for two years or so. And even in those who were receiving everything at the start, there is a benefit simply because the physician didn't have to think, and therefore, all the medications were given. This is a big indictment of physicians' thinking. We don't think, and when we think, we think wrong.

Here are the data --

DR. LINCOFF: Dr. Yusuf, just time constraints, please, if you could wrap up in five minutes.

DR. YUSUF: Five minutes? Yes, thank you.

DR. LINCOFF: It's close to 9:30.
DR. YUSUF: Okay. The other thing to remember is that the result, that's positive on adherence in both those with established risk factors and those that don't. And we covered that, but also the consistency of results in Europe and in India.

I'll skip these because I have a feeling Anthony Rogers will cover them. And the other point I want to say is lifestyle factors were not changed in one direction or the other in these trials.

I want to briefly tell you about the FOCUS trial before I conclude. This is the one that was just published from the Trinomia compound that Valentin Fuster heads the program. This is 700 people, half in Spain and Italy and half in South America. And 350 were randomized to the polypill group, and 350 to the standard formulation. And you will see in this, the people in the standard formulation, the drugs were provided free as was the fixed dose. So there is no differential in drug cost.
So it's just what the polypill does. And you will see adherence is improved in the polypill group compared to the control group, and this is using the Morisky-Green scale, and using 20, which is near perfect.

What are the barriers to the polypill? The first is commercially, this is not attractive. We've tried to get four big pharmas interested, and after extensive discussion, the medical people say this is great, but the commercial people have turned it down.

A big challenge is the regulatory pathways, and the only countries -- but Europe is coming onboard -- and the reluctance of some physicians to accept in cardiovascular disease a combination pill. But the combination approaches are widely accepted in cancer where treatment is by protocol and people have started to do well. It's widely acceptable in HIV and in TB, but attitudes are changing. There is a misplaced opinion that the polypill is second-rate medicine. I would argue that it's first-rate medicine because it takes out
a number of barriers out of the way.

So the benefits are adherence, potentially lower cost, improved access, and non-physicians can be the ones dealing with this. And in some countries like Malaysia, pharmacists are allowed to prescribe a number of medications for prevention without a doctor's prescription, and that may be the way we have to go even in wealthy countries like Canada and the U.S. And we reverse it and say let's do prudent lifestyle simultaneously.

There are four trials of clinical outcomes underway. We're doing three. We have a big study of 12,700 people in -- it's a factorial design in moderately high risk people. It'll have six years of follow-up. The results will be available in early 2016.

We're doing one of the polypill itself versus control in high risk primary prevention, and 90 percent have hypertension, 40 percent has dysglycemia. This is funded by the Canadian government and Aastra. This is funded by the Wellcome Trust and Cadila.
We moved into HOPE 4, which is a strategy trial, and we have funding for a community-based screening of high-risk individuals which can include those with cardiovascular disease. But the entire process is primarily run by non-physician health workers with physicians advising long distance. We have funding for the pilot, and there is a big study underway.

So in conclusion, the polypill really is an efficient way to improve adherence of both physicians and patients to proven and effective drugs. It's safe and well tolerated. Its effect on risk factors is at least as large as giving each of the components separately.

In theory, it should lead to substantial risk reductions, and one would expect that from the individual effects of the drug. I believe the polypill should be an integral part of the healthcare system -- and the word is "system" -- for cardiovascular disease prevention in countries at all economic levels, not just the poor countries or the middle income countries, but
would also include any sensible country. So thank you.

(Applause.)

DR. LINCOFF: Thank you.

Dr. Oparil.

Guest Presentation - Suzanne Oparil

DR. OPARIL: A little change of pace. I was asked to comment on what JNC 8 had to say about drug titration for the treatment of high blood pressure. The short answer is nothing because we didn't get that far, but there are some very pertinent findings that we made. I was co-chair of this group.

First of all, we dealt with hypertension or high blood pressure as a solitary risk factor. We looked only at studies that you could only get into if you had high blood pressure, and we focused on randomized controlled trials as the highest level of evidence of blood pressure treatment only in people who were hypertensive, not high-risk people who happened to have a little bit of blood pressure on the high side. So three levels of evidence high
based on well-designed and well-conducted RCTs,
moderate RCTs with some flaws and good
observational studies, and then low evidence,
observational plus RCTs with limitations. Then we
developed on that basis evidence statements, which
were extensive and then recommendations of these
various levels.

We sought for high, strong recommendations,
and we were not able to do that in many cases. So
we focused -- because of limitation on resources,
we really had to focus on what the committee
thought were the most important questions in
hypertension. And we ended up with three of them:
Does treating blood pressure at specific thresholds
improve health outcomes? Does treating blood
pressure to specific goals improve health outcomes?
And then does it matter what drug or drug class you
use?

For the first question, we collapsed the
threshold and goal question, and we found some
major clinical trials that did address this. They
were older trials, SHEP, Syst-Eur and HYVET. All
looked at older people over age 60, or in the case of HYVET, over age 80. And the finding was that getting the systolic blood pressure to a goal of less than 150 improved all of these outcomes, stroke, cardiovascular disease and in the case of HYVET, mortality.

These two other studies, JATOS and VALISH, that looked at a systolic goal of less than 140, smaller studies, shorter duration of follow-up, did not show cardiovascular disease benefit.

Also, there were many trials in the old-old days when we thought that diastolic blood pressure was more important than systolic. They all looked at a goal of less than 90 millimeters of mercury and demonstrated consistent benefit with respect to cardiovascular disease outcomes.

So based on this, our first recommendation -- and this was grade A evidence based on these RCTs -- we said that for people over age 60, the threshold and goal should be a systolic blood pressure of 150, a diastolic blood pressure of 90. There was some concern about this. That's
what the evidence shows, but there's not all the RCT evidence that you would like to have is available.

So there was a corollary recommendation endorsed by some members of the committee and published separately in the Annals of Internal Medicine, saying that for people over age 60, if you treat with drug and the blood pressure goes to a level of less than 140, and there are no adverse effects on either health or quality of life, you don't need to back off on treatment. This was expert opinion; couldn't really find evidence for this.

Then to go on strictly swiftly through these other recommendations, the goal for diastolic blood pressure was a strong recommendation for people over age 30, weak for younger people ages 18 to 29 because there's just no evidence. They're excluded from most of the trials.

Despite that, based on expert opinion, we adopted a threshold and goal of less than 90 for younger people. And for people less than age 60,
we stuck to the traditional systolic blood pressure
goal of 140 simply because it was tradition, and we
found no evidence to contraindicate it. Again,
expert opinion.

Coming to the question of what drug or drug
class improves outcomes compared to any other, we
looked at randomized controlled trials that
compared treatment with different drug classes, and
we found very little difference. When we looked at
everything that we could find in a randomized
controlled trial of good quality, we found that
there seemed to be no difference between the
thiazide-type diuretic, calcium channel blocker,
ACE or ARB.

So it was a moderate recommendation,
grade B, to start with one of these drug classes if
one is going to start with monotherapy.

This says non-black because we found data
from the ALLHAT trial, which is the only trial that
had any substantial number of black participants,
that Afro-Caribbeans or African Americans did not
do as well on the ACE inhibitor lisinopril as they
did on either the thiazide-type diuretic, chlorthalidone, or the calcium channel blocker amlodipine. So that's why the recommendation is different for blacks. 

So we have sort of the big four here as starting therapy, either diuretic, CCB, ACE or ARB. And ACEs or ARBs should not be used together because of lack of benefit and harm that's been observed in trials. 

We did not include beta blockers because we couldn't find evidence from the randomized controlled trials, which, granted, was a limitation. Most of the RCTs used altenolol, and most of the used altenolol once a day. We know that's not optimally effective. But still from the trial evidence, we couldn't find evidence that starting with a beta blocker for the treatment of hypertension was a good idea. 

So given all that, we have Recommendation 9, which is strictly expert opinion saying that the objective of hypertension treatment is to attain and maintain goal blood pressure. This is
correlated with reduction in cardiovascular disease outcomes and mortality.

We had a scheme for if goal blood pressure is not reached with initial treatment, patients should come back in a month and have either the initial drug titrated or have a second drug added. And this continues in rollover fashion, that the patient should be seen about every month until blood pressure is controlled.

If the big three or the big four are not adequate, other drugs can be added that have been shown in trials to be effective in preventing outcomes or contributing to preventing outcomes. It is recommended to be referred to a hypertension specialist if the patient can't be controlled, goal can't be reached on three drugs.

So this is the algorithm. This is published. It's online and published in JAMA. We agree that lifestyle modification should be implemented in virtually everybody. Only about 5 percent of Americans don't have lifestyle risks for cardiovascular disease; thought that a goal
should be set, and that it should vary somewhat based on age, whether the patient has diabetes or chronic kidney disease.

The idea was, as in the polypill but we took a different approach, to simplify treatment. So if you look at this algorithm, everybody except people over age 60 who do not have diabetes and who do not have CKD had a threshold goal of 140 over 90. For the latter group over age 60 without these comorbidities, the threshold goal was 150 over 90. The drug choices, you can see here.

The only differences are in blacks, a RAS blocker was not recommended as first-line therapy, and for people with CKD, an ACE or an ARB should be part of the mix, not necessarily to prevent cardiovascular disease but to prevent the progression of the renal disease.

Then the titration strategy. Now, this we did not get time to do a literature search on, do the same rigor as in the first drug choices, so we thought that there were three approaches you could use: maximize the first medication before adding a
second; add a second before reaching the maximum
dose of the first; or start with two meds, either
separately or in a fixed-dose combination. We did
not have time to discuss this and review the
literature. And this is just the Web file of the
additional steps of adjustment and, finally,
referral to a specialist if necessary.

We did say that it's a good idea to use
doses of drugs that have been shown in RCTs to be
beneficial. Some of these studies are old, so some
of the ranges may not so comfortably suit modern
practice. For example, altenolol was used once
daily in most of these studies, and that's no
longer acceptable. So these are general doses that
were thought to be useful to primary care to adopt
in their treatment.

We had like 25 critical questions that the
committee thought about that we would like to
address when we started this process. We only due
to resource limitations got to deal with three.
This is question 4: When should one start with
single therapy and step up the dose? How high
should you go versus switching to new drug and adding new drug or starting with two or more drugs, or using fixed-dose combinations?

The question, should these choices depend on the level of initial blood pressure? Other risk factors, overall CVD risk, we did not take that approach in this guideline. Other comorbid conditions, sex, race or age, we didn't have a chance to look at that.

This is the excellent study of Wald and Law, which I'll skip over because you've seen these data, supporting not titrating.

There's one study that I do want to mention, the STITCH study, which was done in Canada. And they looked at the use of a fixed-dose combination as initial treatment versus the Canadian guideline for blood pressure management, which advocated more of a titration approach. Two thousand patients, 45 primary care practices in Ontario, and you see the numbers of practices.

The primary endpoint was reaching blood pressure target at six months. And this is the
design. The STITCH algorithm was initial therapy with low-dose ACE diuretic or ARB diuretic combination. The Canadian guideline started out without any other compelling indications, and the target was the same, less than 140 over 90.

So in the Canadian guideline, you could start out with a thiazide ACE, ARB, CCB or beta blocker; then go to the combination if you needed to. And the treatment algorithm, you can see here.

So basically, this is starting out with monotherapy versus the fixed combination, and you can see at the final visit, the delta in systolic blood pressure was over 22 millimeters of mercury in the fixed combination group versus 17 and a half in the usual care group, highly significant. The diastolic blood pressure differences were significant, also.

The fixed-dose combination clearly did better. There were more titrations, and blood pressure control was significantly greater with the combination.

This is medication used. There are too many
details for this. So the paradigm for achieving blood pressure goal from the STITCH trial was use aggressive to reduce blood pressure, better control, better adherence. Fixed-dose combination can target multiple mechanisms of disease, result in better control and better adherence and retard the progression of new disease.

You've seen this before. Clearly, the fewer pills you have to take, the better you are at adhering to the pills that you are being prescribed. And this just looks at a meta-analysis of fixed-dose combinations versus free combinations on treatment adherence in patients with hypertension, a significant benefit in all of these studies.

Thank you for your attention. I'm sorry that JNC8 didn't get there, and we'll have to see what happens with subsequent guidance that we'll get from people like Dr. Smith. Thanks for your attention.

(Applause.)

DR. LINCOFF: Thank you.
Dr. Smith.

Guest Presentation - Sidney Smith

DR. SMITH: Thank you very much for the opportunity to speak to this group. My task is to talk about the use of lipid lowering therapy in secondary prevention based upon the new ACC/AHA guidelines, which were derived directly from the NHLBI systematic review.

My role with that review was to chair the executive committee, which oversaw six different writing groups, and I served as a member of five of the six. I have no conflict of interest related to this presentation.

The thing which was driving the work at NHLBI was this recommendation, which came from the Institute of Medicine in the year 2000, that we needed to focus strongly on evidence as we developed recommendations and guidelines for patient care. The three guidelines that had been developed by NHLBI, which were all ready for an update, were the blood pressure, which you've just heard from Dr. Oparil, the ATP guideline on
cholesterol, and obesity.

Now, this work was started in 2008, and the systematic review was not completed until 2013. So the existing guidelines at the time of completion were all 10 years old or greater.

During the process, towards the end of the process, the NHLBI determined that their role in the development of guideline recommendations should change, should evolve into one where they associated themselves with the development of evidence but allowed professional organizations to make recommendations that were derived from that evidence.

The panels are shown here, blood pressure, cholesterol, obesity, and then two others, a lifestyle working group, which looked at diet, exercise and so forth, and then risk assessment working group.

Initially, the panels were asked to develop critical questions, and most panels came up with 10 to 15 critical questions on their subject. It became clear with six panels and 10 to 15 critical
questions that resources were just not available
for systematic review to go over all these critical
questions. So you'll see that each of the panels
are really limited reports based upon the results
of a systematic review of three critical questions
with the exception of obesity, which was allowed to
address five.

The principles by which the systematic
review and guidelines were developed were in line
with these two publications from the Institute of
Medicine shown here, a good reference to which I
would refer you. The report, which I will review
with you, deals with cholesterol.

The makeup of this committee is also
important. All of the working groups had a
combination of a sub-specialist, in this case, Neil
Stone, who's a cardiologist, and a primary care
physician, Jennifer Robinson in this case, and
other representation from primary care, in some
cases trialists, epidemiologists and pharmacy.

So the development of these guidelines in
addition to the strong focus on evidence also was
somewhat more inclusive broadly of background expertise.

Critical questions with regard to the cholesterol guidelines, the three of them, the first one, what is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of atherosclerotic cardiovascular disease?

For this question, 19 RCTs were reviewed. We found no data to support the treatment or titration of cholesterol lowering therapy to specific LDL or non-HDL goals. Fixed-dose strategies using statin therapy were basically used in the majority of studies. So we were unable to find evidence to support or not support the titration to LDL of 100 or of 70.

The second question dealt with primary prevention, which is really not a topic that I was asked to address here, but I will mention that we reviewed six RCTs involving patients without evidence of atherosclerotic vascular disease, and they all used fixed-dose strategies. And again, we had no real evidence to support titrating to a
specific target LDL.

The final question dealt with primary and secondary prevention. What is the impact on lipid levels, effectiveness, and safety of cholesterol modifying drugs used for lipid management in general and in selected subgroups?

We involved interventions that used either single dose or combination therapies, which included statins, fibrates, nicotinic acid, bile acid, sequestrants, ezetimibe, omega-3 fatty acids, which were all approved agents at the time of our work, and found the strongest evidence to support the use of statin therapy.

The theory behind the development of the initial ATP all the way up to ATP III update, which occurred in 2004, was developed upon a combination of observational studies, which showed that the higher the LDL, the more likely events are to occur, and the higher the risk group, the higher events.

One then could fit a series of dose-related trials showing that either comparing a statin dose
to a placebo non-statin or a high-dose statin to a moderate-dose statin improved outcomes. And again, based upon the risk of the population treated, the change in outcome might differ. But in all cases, the treatment with statin therapy either against placebo or high versus moderate dose improved outcomes in the various groups studied.

That led to important questions in the development of the early guidelines because the attempt to fit the trials to a curve led to an understandable question, and that is, whether or not the relationship between improving outcomes was linear, the lower we lower LDL cholesterol, the better it goes. So we ought to just keep driving it down.

Possibly, there was a threshold below which one would not see benefit, but it might be curvilinear. That is, at higher levels of LDL cholesterol, one would see greater benefits than at lower levels.

Two important studies came after the publication of ATP III. Shown here is HPS. HPS
looked at the use of simvastatin 40 milligrams in a
group of patients age 40 to 80, no evidence over
the age of 80, that either atherosclerotic vascular
disease, diabetes, or hypertension, and a total
cholesterol of greater than 135.

I direct your attention to the left-hand
column here, which shows the LDL. Now, the
previous ATP III would have said in patients whose
LDL was already less than 100, no therapy was
indicated. If it was between 100 and 130, it was a
dealer's choice, treat either with a statin or a
trial of diet first to try to get below 100. And
if the LDL was greater than 130, ATP III
recommended therapy to lower LDL cholesterol.

The important findings with HPS were that
regardless of the LDL in this patient population
with defined atherosclerotic vascular disease or
high risk, there was a significant reduction in
event.

So this idea that there was a target LDL
below which one might not see benefit was not -- it
was disproven by this study. So this was a very
important trial in terms of thinking. This came out after the data used to publish ATP III.

The second trial which came out was PROVE IT-TIMI 22, which serendipitously showed -- it was an interesting trial. It was designed to compare atorvastatin 80, a very high-dose new statin, to an existing statin to see whether or not the higher dose would actually improve outcome. And these are patients with a recent acute coronary syndrome.

Here as it turned out, the LDL cholesterol came to 95. Now, it was not titrated to 95. So there's no titration going on here. This is a dose comparison. And the LDL in the higher dose group, it came out to 62.

I was on that committee, and the question came up, gee, we have now set an LDL cholesterol of 100. What do we do with this? It looks like the higher dose statin is doing more. And so we felt that we'd gone from 160 to 130 to 100. These are 30 milligram increments. Let's go to 70 as an ideal target.
But an important point here is that the concept of treating to that specific target, that there was something that made that target of 70 better than 80 or 78 was in fact a proven concept. What was shown here was the benefit of higher dose of statin therapy. Nevertheless, the guidelines were recommended.

As our group began to look at the question of treatment to goal, the first thing we found was in all of the studies that we looked at -- 19 of them that I mentioned -- they were fixed-dose trials. There was absolutely no evidence of titration available to support the concept of titrating to a specific LDL.

Now, important parallel work was going on at Oxford during this five-year period and was actually published in 2010, the cholesterol treatment trialist, involving multiple patients up over almost 130,000 patients, statin versus control and intensive versus less intensive in nearly 40,000. This meta-analysis was also included in our work and actually was consistent with
observations that were independently derived from our review. And I'll show them here.

The first is that regardless of the LDL level -- and this is down to an LDL of 2, which would be corrected to roughly 80 milligram percent. The initiation of statin therapy improves outcomes in a comparable manner, and it makes no difference whether it's statin versus control or more versus less statin. But significantly in secondary prevention trials, which is where more versus less is used, the higher dose statin therapy appeared to achieve even greater results.

The results seen did not vary, as shown here, regardless of whether it was a coronary, any major coronary event, whether or not it was the benefit on revascularization, or stroke. However, it is worth noting that this issue of haemorrhagic stroke was -- the numbers were low, but it was hard to show any benefit for sure on haemorrhagic strokes. So the question remains there. We're really dealing with ischemic stroke. And then finally, independent of the underlying risk factor,
whether it might be known atherosclerotic vascular
disease, diabetes, male/female, age, BMI, smoking
status, the benefit of statin therapy was clear.

During the course of our work, we did
identify an increase in new onset diabetes among
patients, particularly those that were treated with
higher dose statin therapy, but the incidence of
diabetes was much less than the substantial benefit
in reducing atherosclerotic vascular events.

The second consideration that the committee
dealt with was the FDA's statement and recent
advisories on simvastatin, that the use of
80 milligrams simvastatin be restricted to those
who had been on simvastatin for greater than
12 months and using it safely, that others be
switched. And that if an LDL cholesterol goal was
not achieved with 40 milligrams, another more
potent statin be used. And they also noted the
interaction with other medications as shown on the
left side of this slide.

So this is really a new perspective based
entirely on evidence. Firstly, we found a lack of
RCT evidence to support titration of drug therapy to specific LDL cholesterol or non-HDL cholesterol goals. We found strong evidence that appropriate intensity of statin therapy should be used in those to reduce atherosclerotic vascular disease. A quantitative comparison of statin benefits showed a much greater benefit than risk. We did not find in the non-statin therapies that I mentioned a significant benefit over statins or in combination with statins.

Why not continue to treat to a target? First of all, we have no evidence to tell us exactly what the target should be. We don't know the magnitude of risk, weighing one target to another. We don't know adverse effects from adding new drugs to statins. The development of target had led to a new strategy in treatment, where if patients did not achieve the target, let's say of 70, other medications were pulled off the shelf and added to statin therapy in order to achieve it. That benefit is yet unsubstantiated and may have additional risk.
For that reason, we felt that the strongest body of evidence supported the use of statin therapy. We found four groups that would benefit, and the group that we're talking about today are those with clinical atherosclerotic vascular disease. Importantly, we found a paucity of data in older patient populations, and for that reason, moderate intensity statin, not high intensity statin, was recommended for those over the age of 75. It was felt that the side effects potentially would be less in that group.

These are the doses of statins that were present in the RCTs that we reviewed. In general, high intensity statin was considered to be a dose that reduced LDL cholesterol by 50 percent or more, and in that group would be atorva 80 and rosuva 20. Those are the two that were used in trials.

Moderate intensity statin therapy would be statin therapy that reduced LDL 30 to 50 percent, and the doses are here, atorva 10, rosuva 10, simva 20 to 40, prava 40, lova 40, and fluvastatin 40. And then low intensity statin is
shown on the far right panel. The recommendations dealt with either high intensity or moderate intensity statin.

In patients that were not able to take statin therapy, it was recommended that a non-statin cholesterol lowering drug be combined. And these generally were patients with FH or patients -- other group that would benefit from this would be patients that were unable to tolerate statin therapy.

That's the end of my presentation. I'll be happy to answer questions later. Thank you very much.

(Applause.)

DR. LINCOFF: Thank you.

We will have an opportunity at the end of all the presentations to ask questions of the presenters.

So at this point, we'll take a short 15-minute break. Committee members, please remember there should be no discussion of the meeting topic during the break amongst yourselves.
with any member of the audience. We'll resume at 10:30 a.m.

(Whereupon, a recess was taken.)

DR. LINCOFF: We'd like to get restarted, please. We will now proceed with the guest presentations. We'll continue with the guest presentations from Dr. Dudl and Dr. Yancy.

Dr. Dudl.

Guest Presentation – R. James Dudl

DR. DUDL: Ladies and gentlemen, I want to invite you to relax. I think all the heavy lifting of data has been done. I'm not here to show you a randomized controlled trial and try to convince you our poly combination saved a lot of heart attacks and strokes.

I'm going to show you some observational data that's compatible with it, but that's not the purpose of what we want to get across from Kaiser Permanente. I'm going to build on a quote, and I'm going to say even very efficacious drugs don't work if you don't take them. So really not going to talk about the efficacy of medication but the
effectiveness of implementation. And that depends
on which drugs we have available, to whom they can
be given and how they are offered. And so this
combination idea may have an important implication
in implementation.

We did an actual experiment at Kaiser, actually, one that might be of some interest. We
started out treating people with high cholesterol
with a low-dose of a statin and titrating up, and
we observed heart attacks and strokes. And then
later we did a fixed-dose combination in people who
have a CVD risk and did the same. And I think
it'll be of interest to see what happened.

So the question is looking at fixed dose
with our experience, called the ALL
observation -- so questions were what's the
clinical utility of using the FDC with the
antihypertensive, aspirin, and statin on fatal and
nonfatal MIs and strokes and the results of the
ALL? And is it generalizable? Could it be
implemented in the underserved? And the pros and
cons of using it in a situation where additional
follow-up may not occur. So we do have some clinical data on all of these points.

Actually, I'm going to go back to 1996 and go back to a study we did called CRIS, which involved pitting niacin against this new drug lovastatin 10 milligrams. Niacin was started at 50 milligrams with six titrations planned to get to 2 grams, and lovastatin won hands down. Not that it's a better drug, but we only got 1.5 titrations when the protocol was to get to six and we pushed to get to six. Titrations were tough, but I thought, well, yeah, it's niacin. It's a tough drug. That's just the way it is.

But fast forward to 1998, we advised people with diabetes above LDL target to start with lovastatin 10 milligrams, a drug that's easy to titrate, easier than niacin, and until target. And the results we looked at, and in 1998, there were 15 per thousand heart attacks. And in 2001, there were 16 per thousand. So clearly, I was very devastated, disappointed, I should say.

So we asked why. Well, we looked at the
people we treated, and my analyst said, "Look, Jim. They're at high cholesterol, but they're low risk."

Half the people were under a 7 percent Framingham risk. And so were the worried well coming in, and we're not getting in the people that are high risk? That was a question.

"Statins alone could get you the most 42 percent, but, Jim, you never really used anything over 40. So you're really at 30 percent. You're not going to wipe out disease with that.

And it was difficult to titrate. By the way, you got to 22 milligrams percent. One titration is all you got."

So about that time, I said, gee, if I'm going to redesign, I'm going to design out titration. The ideal number is zero, and let's set it up that we can do one as a stretch.

So we then went ahead and correct this. We went to stratifying for high CVD risk and outreaching. So we thought people with CVD -- and we liked Salim's criteria in HOPE, a person with diabetes who's over 55 years old. And 90 percent
of those in our population had either high cholesterol or high blood pressure.

We then gave a fixed dose of lovastatin 40 to get down to only one titration if necessary. And then we looked around for other things, and this editorial, I think by Salim, had come out looking at lovastatin and aspirin as potential other things we could do. But we wanted to model that, and we modeled it using a program called Archimedes.

Has anybody in the room heard of Archimedes?

So this is actually going to conclude roughly what you saw in the other models, about the same. It's a large model built on a representation of physiology, and it included pathways at that time of coronary artery disease, congestive heart failure, diabetes, obesity, hypertension, and stroke, only variables for which good data existed and was validated against 74 trials.

This is the one that I saw. This was November 2002. And on the Y axis is the events per year, X axis on the left side. You'll see MIs in
the blue bar. We did nothing in the green bar if
we used the ALL, and it came out a 71 percent
decline. The red bar is A1c controlled just to
fill you in and to show that this is all as valid
as possible.

We liked that. We thought that was
important and impressive, so we decided to go ahead
and implement that bundle. Now, we didn't have a
lot of proof, but the thought was we know the risks
of statins were a lot of muscle aches but very few
rhabdos, cough with ACE with very few angioedemas,
and the benefits looked really high. So we thought
it was reasonable to promote this.

So we then did a retrospective analysis, and
we were able to look at ACE, ARBs, and statins, but
not aspirin because it wasn't a prescription. It
was delivered very parsimoniously because we really
had problems getting people on these. So we said
one visit, one call follow-up, one to two lab
tests, no titration, people at high risk. And we
went after the ones with high risk significantly.

It was a three-year observational study;
170,000 Permanente members qualified; 77.8 percent had diabetes; but 53,000, 31 percent, had CAD, and as you could do the math, about a little less than 10 percent had both.

We used an instrumental variable analysis. My statistician said we have to correct for people who had been too aggressive on the high side. We assessed the impact on hospitalization rates for stroke and MIs.

At baseline, 25 percent of people were on ACEs, 33 percent on statins, so we had a long ways to go. The Kaiser population is pretty diverse. Caucasians 43 percent, Hispanic 40, African Americans I think it's 12 but 14 perhaps. I think that's an error. I think it's 12. And Asian Pacific Islanders is 5.

So what did we do? The protocol was lovastatin, lisinopril, aspirin, lova 40. Baseline blood pressure, lipids, ALT and creatinine, really as simple as we can get, one blood draw. No exclusions for normal blood pressures or lipids.

The HOPE study had come out, and we had seen
that the 4,900 that were normotensive got the same
benefit as the 4,300 hypertensive. HPS had come
out and shown those -- you just saw some of the
data -- with high or low LDLs to start with came
out the same.

This was a real-world study. It wasn't a
project. This was real-world quality improvement.
You could exclude people from treatment if their
blood pressure was too low or their LDL was felt
too low at that time, and if people were worried
that they were too high, they had permission to
repeat the blood pressure and lipids and intensify
treatment if they want. Frankly, very few did.

Exclusions were minimal, the usual,
creatine over 15, liver disease, allergies, and
anything on the package insert. And we used
population tools because we really wanted to do
this. We gave every doctor a list of their
patients that qualified, point of service,
electronic decision support, monthly conference
calls to help implement, and nurse practitioners
and pharmacists to help. So we started out with
170,000 people that qualified.

At the end of two years, we had not treated 101,000. We wished we could have, but it was a big job. We did, however, treat over 47,000 with what we call low exposure. What we did is we just divided the people in half. Those who took the drugs under half the time we called low exposure, over half the time, high. And under half the time turned out to be 22 percent of the time, so adherence was the big problem. On the high exposure, 21,000 people took it 68 percent of the time.

So what did we get? Well, we got a reduction in heart attacks and strokes in the low exposure of 15 per thousand, but let me analyze that quickly for you. It turns out that all of the benefit was in strokes, none in heart attacks, and it was marginal, the confidence interval minus 30 to minus 1.

Our conclusion was actually this isn't -- our clinical conclusions don't recommend doing this, recommend taking them at higher dose.
This isn't significant clinically. But, however, on the higher side, things worked out better. There was about a 10 per thousand drop in heart attacks, 14 per thousand in strokes, and for whatever reason when they did the analysis, it was 26 per thousand.

Now, in our highest incidence quintile of facilities, which is what we used in the instrumental variable, it was 27 to 38. So we felt that was a fairly significant drop.

Limitations, well, we couldn't tell or test if facility rates used could have been causally related to outcomes, of course. And behavioral interventions could have affected it, but I can tell you obesity has increased in Kaiser. Diabetes has increased in Kaiser. Hypertension has increased. I didn't get a fix on smoking. It's been sort of very slowly gradually going down. We didn't put a new program in. So I think those are less likely to be a problem.

The risks, we had five reported events, four drug-drug and one other. I couldn't get a reprint
of the list, but I do remember one drug-drug was that they received from a patient inside Kaiser a second prescription for an ACE when they already were on one. We corrected our algorithms, so that won't happen again. But the exact same thing happened with somebody getting their drugs from the outside. So we cautioned everybody to be careful. There were no rhabdos in this group, and they were all resolved.

Benefits. Decreased MIs and strokes.
Simplicity of starting three drugs at once full dose may have overcome some of the therapeutic inertia we had with the titrations issues.
Feasibility, the providers engaged well. Patients when you're saying, hey, we're decreasing MIs and strokes, they actually responded a lot better than when we said we're looking your cholesterol and blood pressure, and rapidly scalable, 70,000 in two years. Reduced cost by using generic drugs. One visit, one call, no titrations. And then the savings of infarcts that happened, it was modeled to save $300 per patient
per year.

    Generalizability. Kaiser's people are mid-class. We had good ethnic race mix, minor inclusion criteria, accepting to be high risk.

    Could the underserved benefit? Now, this is really almost more important than the Kaiser stuff. We at Kaiser, we try to give this to all of the underserved we could. Since 2005, we've given grants to 85 community clinics, California, Oregon, Colorado, Georgia, and Washington, D.C. At the present time, over 89,000 underserved are now on the ALL. Combination was both feasible and rapid.

    The underserved have two big problems. One, people don't come back. So if you could do something in one visit, they like that. Number two, they don't have any money. If you do something cheap, they like that.

    Comments. Provider and patient satisfaction were high. Patients like the simplicity of one bundle a day. It costs now 25 cents a day for this and only one visit. Providers like the idea very much of one visit and achieving significant benefit.
for the patients.

The cons of blood pressure and lipids may still be above target after this is done. However, you're going to get the benefit to CVD of the drugs you've already gotten. And you are able to -- if you can get them to come back, you certainly may bring them back and titrate.

By the way, we have moved to a fixed -- if the person has diabetes and hypertension, we ask them to go to a thiazide ACE right from the start. And we feel that inside Kaiser using that bundle was one of the main reasons we were able to get to 85 percent blood pressure control. So we thought bundles have been good, and we've been using that since 2005.

Lipids or blood pressure could go too low, but there is no negative benefit to too low a lipid. If blood pressures already start out low, too low, we can skip it altogether or start at half and bring them back before you move on.

So pros, decreased MIs, strokes, less therapeutic inertia, simplicity, feasibility,
scalability and decreased cost. And ALL is promoted for people with CVD and normal cholesterol and blood pressure. I just ran a quick NHANES check. Twenty percent of people with CVD had an LDL under 100 and wouldn't get this drug if we were just titrating to 100. Forty-seven percent with a systolic pressure under 140 were not on an ACE.

This, you've already seen, so we'll skip it, but I'm not sure you saw this. This was a meta-analysis of using antihypertensive drugs, decreasing CVD in normotensive patients. And you can't read it, I'm sure, but on the top is strokes, 23 percent drop. The bottom is MIs, 20 percent.

So I'm just about done. ALL adherence was significantly lower, and that's a major problem. Everything recently were reminders, automated mailings, live calls. We have gotten above 80 percent, but it's hard, and it cost a lot. Further efforts are warranted.

The resulting data are observational. They do not have the strength of a randomized controlled trial, but they're consistent with improvements in
CVD. But they have demonstrated that we could rapidly in the U.S.A. implement this fixed-dose combination HMO chosen only for patients that are only high risk.

It was scalable. It also spread rapidly to the underserved. It was feasible. It may have overcome the prior therapeutic inertia, facilitated drug initiation, and adherence was able to be increased with this. And compare usual titration was done with less process, therefore, likely less cost to the medical care system. Thank you.

(Appause.)

DR. LINCOFF: Thank you.

Dr. Yancy.

**Guest Presentation – Clyde Yancy**

DR. YANCY: Good morning to the members of the panel. I am delighted to be able to address you and to provide you my input on today's discussion.

I've been given a unique task, that is, to scope for you a path to clinical utility of a polypill and to specifically address what might be
required. I've had a chance to preview your discussion questions today, and so I hope that the points of emphasis I make will be able to add your discussions as the day progresses.

Let me frame my comments by telling you that my perspectives, my prisms, if you will, are formulated from a long experience working with the FDA cardiovascular devices panel and from working in the generational clinical practice guidelines. With that in mind then, I'm going to restate the question that I was asked to address, and the question is thus: Asked to discuss the kinds of information a clinical cardiologist might want to decide about the clinical utility of a polypill.

I think this morning has been illustrative of the information that is available. We've seen data that have largely talked about the ability to move surrogates in the right direction. We've seen data that demonstrate the ability to improve adherence. We've seen data that suggests that this may be a usable strategy in certain populations. The question becomes are those data points
I think the relevant answer here is that clinical use, and more importantly, patient benefits, will be driven not by information but, in fact, by evidence and especially evidence sufficient to inform clinical practice guidelines.

Many of you in the room have been deeply involved in the generation of clinical practice guidelines like I have, and I think we've understood that a cultural shift has transpired. And so the clinical cardiologists now are aligned with the paradigm of clinical practice guidelines and refer to those guidelines as a strategy, as an algorithm to inform their care practices.

Let me also quickly add that not only should the evidence be sufficient to inform clinical practice guidelines, but it should be pertinent for populations that represent the breadth of those that might be affected. That includes women. That includes older individuals. That includes individuals that are non-white. That includes individuals that are in at-risk socioeconomic
strata. And that includes the individuals that are
in at-risk built environments. And so those kinds
of data points are to be considered.

I really want to frame the rest of my
commentary around what's necessary to elevate the
discussions to the threshold of a clinical practice
guideline statement, understanding that it's my
belief that this now is the lever that is most
influential in determining clinical utility for new
interventions, drugs, or devices.

I refer to the document previously
acknowledged by Dr. Smith, and that is, the
Institute of Medicine report in 2011, the statement
on clinical practice guidelines entitled "Clinical
Practice Guidelines We Can Trust." And
importantly, the definition says that these are
statements that include recommendations intended to
optimize patient care that are informed by a
systematic review of the evidence and an assessment
of the benefits and harms of alternate care
options.

This is a schematic that works us through
how clinical practice guidelines are to be
developed. That is, there is a very rigorous
systematic review, some would argue by an agnostic
evidence review committee. There are a collection
of peers and then a group of peer reviewers that
develop, that is, narrate or compose, the clinical
practice guidelines. And then there is an
opportunity to understand the impact of
implementation science, that is, to drive the
uptake of these clinical practice guidelines, if
you will, to market those clinical practice
guidelines, and ultimately to result in better
patient outcomes.

These systematic reviews that begin the
process are then shared with a multidisciplinary
panel in much the way that Dr. Smith and Dr. Oparil
identified the pathways for the statements on
treatment of dyslipidemia and the statements on the
treatments of hypertension.

I want to emphasize again the importance of
having data that targets specific patient
subgroups, having a process that's transparent, and
as many of us in this room have experience, having a very rigorous conflict of interest and bias review. The statements should be logical, and importantly, the statements should be tiered with strength of recommendation and quality of evidence.

I've highlighted here that there has to be a critical review of benefits versus risk. We've heard statements today with which I don't disagree, that in large measure, the elements of a polypill are safe. But we have an obligation to be absolutely certain that safety is an important attribute that exists in these formulations.

Importantly, it is the assignment of a hierarchical class of recommendation that is very important. This graphic that is listed from a recent report by the ACC and the AHA looks at the prevailing systems that allow us to create a hierarchy for the use of clinical practice guidelines.

Importantly, there are two streams of thought here. One is to look at the strength of the recommendation, and the other is to look at the
level of evidence. Ideally, most statements should be supported by the highest strength of recommendation, class of recommendation 1, using the vernacular with which I'm accustomed, and by the best level of evidence, which ordinarily would be the level of evidence A. You saw again reference to this process in Dr. Oparil's presentation and in Dr. Smith's presentation.

It's important, I think, to really start this conversation by recognizing that FDA approval is the floor. It's the minimum that's necessary. True clinical utility, I think, will be driven by the development of an informed clinical practice guideline statement.

To that end, I would make the argument that we already have evidence that when we have very rigorous evidence-based, guideline-driven interventions, we can, in fact, change outcomes for patients with important issues in cardiovascular disease. I'll share with you several reviews from my own efforts in research.

These data come from a cohort of over 15,000
patients with heart failure, all of whom were exposed through a quality improvement process to the most rigorous interventions that we know to be beneficial in the setting of heart failure. With the exception of only two, you can see that of these seven interventions, there was evidence looking at each one for decided advantage on mortality just over a 24-month exposure.

Admittedly, heart failure is a higher risk condition, meaning the primary prevention or secondary prevention, but the hypothesis is sound, that the correct application of evidence-based therapies leads to an improvement in outcomes.

We did further calculations and demonstrated that when we are taking an evidence-based guideline-driven approach, for every 10 percent improvement in guideline-recommended composite care, there was a 13 percent lower risk of death at 24 months. And for a single intervention for which a patient is eligible, those patients who receive that intervention versus those who didn't had a 38 percent lower likelihood of a poor outcome.
These are persuasive data that, again, begin with the importance of having evidence-based guideline-directed care.

We went further, and through a series of additional analyses, identified the incremental benefit of again, the incorporation of evidence-based care. You can see that by maximal utilization of appropriately indicated care, we reduced the risk of death from zero percent down to 81 percent reduction compared to those that were not on all indicated appropriate therapies.

Again, the strength of this depends upon the importance of the guideline recommendations that are driven by evidence. And I'd like to highlight this presentation to audiences, when we have discussions about the importance of guidelines, by indicating that for the heart failure patient in today's world, absent the benefit of recent discoveries, the combination of an ACE or ARB plus beta blocker plus indicated advice therapy gives you a 90 percent, 9, 0, reduction in the risk of death.
These kinds of data drive clinical decision-making, drive clinical utility because they indicate the effectiveness of an evidence-based guideline-driven strategy. This is the depiction of the aggregate benefit of a progressive increase in adherence to guideline-driven strategies going from two to three and beyond, showing the incremental advantages that one can realize, again, for the condition of heart failure.

So why is that I'm making this passionate argument about the strength of evidence and suggesting that that is the bar that will drive clinical utility? These recent data published just within the last several months, I think, are quite noteworthy because they identify the durability of Class 1 ACC/AHA clinical practice guidelines.

One looks across the board here, and we can see that there are represented a number of guideline statements that are either downgraded, as you see in the column to your far right second from the end, or frankly, omitted, as you see in the final column.
If I reduce this to simple language, of the 619 recommendations, 80 percent were retained. The remaining 20 percent were either downgraded or omitted. Ninety-plus percent of those that had the highest class of recommendation 1 and the best level of evidence were retained. Seventy percent of those that had the highest recommendation but had the weakest level of evidence, expert opinion or consensus opinion, experienced an odds ratio of change of 3.5.

So this identifies, I believe, that the most durable guideline statements are driven by a confirmatory evidence base consisting of at least two randomized controlled trials. And so addressing the question of the tier that needs to be reached to drive clinical utility I think it is driven by evidence and is driven by these data that demonstrate the importance of the evidence.

This is a dynamic process, as many of you know, again, that are involved in the generation of clinical practice guidelines, and the bar is being raised even further. And in a document that
several of us were co-authors, we identified -- we scoped out, if you will -- the new direction.

The new direction, number one, will incorporate patient representation. Have we heard from any patients today? We are entering a world that is patient-centric where we talk about shared decision-making, yet we've had no input from how patients would feel about the incorporation of a very novel, very different, maybe even a disruptive strategy.

Even more rigorous systematic reviews will take place. There will be new standards for assessing the quality of evidence, if you will, semi-quantitative standards, and in standardizing the synthesis of evidence. The patient representatives will already be incorporated in ongoing ACC/AHA clinical practice guidelines, and their comments will be incorporated in the final decision-making.

A format many of you may be accustomed to, PICO(TS), will be used, and this gives us more rigor. What's the population that's appropriate?
What is the exact intervention? What are the prevailing comparators? What are the outcomes that are important? What's the timing and what's the setting?

All of this matters when we're talking about the polypill. Is the setting an urban environment, a rural environment, an international country, an already westernized country? What's the timing? When is the appropriate time to actually introduce these agents?

What about the outcomes? Are we comfortable with surrogate endpoints as outcomes, or do we need hard outcomes? We see that there are trials underway to achieve those hard outcomes. The comparators we recognize. The intervention we understand. But are all of the interventions similar? Are all of the formulations comparable? These are questions that have to be argued.

Then as we heard so eloquently positioned by Dr. Yusuf, the population studied is very important because there's a dichotomy here, the primary prevention population and the secondary prevention
population. But this kind of format that requires
a dedicated thought process has become embedded in
our guideline structure going forward.

The quantitative assessment tool has been
developed, and this will be applied by an agnostic
evidence review committee to determine whether or
not the evidence base is sufficient before those
that write the guidelines would be able to begin to
generate their statements.

What's important is that there are three
domains that will be considered: freedom from
bias, relevance, and fidelity of implementation.
These are precisely and especially important in the
development of a new compound that will be widely
distributed and need to be addressed a priori and
not after the fact. The studies will be judged
accordingly, as you see, low, intermediate, high
quality, or insufficient.

This new direction will be very helpful. It
will help us in understanding the background
information that informs the guidelines. Where
appropriate, we've already begun to introduce
Bayesian analyses to help provide better insight in those meta-analyses in understanding whether or not the statements that are being rendered can be justified by the evidence review that has already transpired.

So this is my summary statement, and this summary statement is, I think, consistent with the discussions today. For new therapies to receive the endorsement of the clinical cardiology community and to experience truly meaningful clinical utility, I think it's very important that a confirmatory evidence base of high quality data be required.

The endorsement of a new intervention as guideline-driven -- I believe the data support this -- facilitates implementation, or as you've identified, clinical utility. And importantly -- and I think this cannot be overlooked -- has been shown to drive meaningful patient outcomes. A tier of evidence less than truly confirmatory, whether it's observational data, data with surrogate endpoints, data with
small numbers, is associated with a high likelihood
of either modification or elimination of moderate
or modest recommendations.

So I will rephrase the task I was given by
reviewing what I think are the critical questions,
the polypill. Number one. What is the evidence
base? We've seen quite a bit of information this
morning. Is that evidence base deemed to be
sufficient?

Number two. Is it confirmatory? Is it
sufficient to confirm that we can move the
surrogate measures or do we need more confirmatory
evidence than that?

Are there any unforeseen consequences with
use of a polypill? You might say this is an
unreasonable question because these are generically
available compounds already deemed to be safe, but
one has to argue that the other consequence that
we're concerned about is what is the influence of a
polypill, particularly in a westernized culture, on
lifestyle decisions?

If there is a mindset that is a one pill
that takes care of risk, will that deemphasize the importance of lifestyle modification? How can we keep the bar high for the necessity to have parallel improvements in lifestyle?

What are the meaningful endpoints needed? I think this is a high bar that this committee will need to deliberate. Are the only acceptable endpoints cardiovascular mortality and stroke reduction? Are surrogate endpoints sufficient? Would non-inferiority endpoints compared against standard therapy be sufficient?

I think these are important questions that need to be answered by the FDA, and similarly, these are questions that would be considered in the generation of a clinical practice guidelines statement.

Will the evidence base merit top tier guideline recommendations? I think we're in an era now where the guideline statements really do drive practice change. If guideline statements addressed in the polypill are coming forward at the topmost tier, there's a high likelihood that these
interventions will be incorporated in everyday practice and will meet the bar of driving clinical utility. If they don't meet this top tier, such may not be the case, and again, it's the evidence that will make that difference.

How will implementation proceed? This is incredibly important. Who will get this drug, how will they get this drug, and what will be the ongoing data acquisition to demonstrate that the promises that have been offered are fully realized in clinical utility? I don't think we're in an era now where we can simply approve a drug or a device without some consideration of implementation science.

Then finally, as has been mentioned today, but it is important particularly in the U.S. population, will we face unprecedented liability issues? We can look at the population-based data of which I'm an advocate and recognize that the observations are consistent with the likelihood that we can reduce the burden of disease. But as practitioners, we don't take care of populations.
We take care of people. And if someone has an event and there's evidence that we didn't fully control a risk factor or didn't fully adjust that risk factor, is there an exposure there that has to be considered? And is this concern sufficient to thwart implementation?

I present these questions not as an advocate, neither as a detractor, but as a person that's deeply involved in generating clinical practice guidelines, understanding that those guidelines are used to drive implementation. And I think these are the kinds of questions that need to be addressed.

This is answering the question you've directed to me, what kind of evidence is necessary for clinical utility of a polypill? Thank you very much.

(Applause.)

DR. LINCOFF: Thank you.

We'll now move on to the FDA's presentation.

FDA Presentation – Sudharshan Hariharan

DR. HARIHARAN: Good morning, everyone. My
name is Sudharshan Hariharan. And my presentation for today is intended to be brief to provide a short outline of the clinical pharmacology studies that are required for the approval of a polypill.

As you've heard from other speakers, polypill for the purpose of our discussion is a combination of aspirin, a statin, and one or more antihypertensive agents. Clinical trials have clearly established the safety and efficacy of each of these components. And it is also known that each of these components, that is, aspirin, statins, and antihypertensive agents, improve cardiovascular outcomes independently.

So with that understanding that these components have cardiovascular outcome claims, what clinical studies are then required for the approval of a polypill?

In general, the studies required are clinical pharmacology-type studies designed to ensure the following objectives: Number one, the new formulation does not affect blood levels of each component. In other words, when these
components are put together into a new formulation, we need to ensure that the blood levels of drugs between the polypill and the individual components are similar, a concept which is routinely used in the approval of generic products.

These studies should also ensure that there are no interactions between the drugs used in the polypill not only from a pharmacokinetic perspective but also need to ensure that the pharmacological effects are not compromised or is preserved when used together in a combination.

Finally, we also need to be aware that there are no novel food effect for the polypill when compared to the effect of food that is already known for the individual components. And we believe that by satisfying the above objectives will ensure therapeutic equivalence of the polypill to the individual components thereby obviating any cardiovascular outcome trials.

Keeping the objectives in mind from the previous slide, the polypill development program can actually start with the pharmacokinetic study.
designed to ensure similar blood levels between polypill and the individual components administered separately.

So this is usually achieved by a single-dose, multiple-arm crossover study with a number of treatment arms dependent on the number of components of the polypill. For a polypill with three components, we are looking at a four-way crossover study.

Further, this study should be aimed to demonstrate bioequivalence in pharmacokinetic measures of drugs between polypill and the individual components. Therefore, the study should be adequately powered to achieve this objective, taking into consideration the pharmacokinetic variability of the drugs used in the polypill. Typically, we have seen such studies to enroll between 24 to 48 subjects.

Other important design elements are that the study should use approved listed drugs in Orange Book as referenced for the individual components so as to borrow FDA's finding of safety and efficacy,
and the study should also use validated bioanalytical assay methods to measure plasma concentrations of drugs in the study.

With respect to the study outcome, demonstration of bioequivalence will then ensure that there is no pharmacokinetic interaction between the drugs nor is there a formulation effect.

While in the context of discussing pharmacokinetic studies, a polypill development program is also required to evaluate the effect of food on the pharmacokinetics of drugs used in the polypill. As food effect is partly driven by formulation components and the properties, it is important the effect of food be evaluated for a polypill even if the individual components are devoid of any food effect. And typically, a food effect study is again a single-dose, two-way crossover evaluating the PK of drugs in fasted and fed conditions.

Last but not the least, certainly not the least, the development program should also include
a study ruling out any undesirable pharmacodynamic interaction between the drugs used in the polypill in spite of the absence of a PK interaction. As Dr. Stockbridge mentioned in his opening remarks, a classic example is the one between aspirin and ACE inhibitor.

As an outcome trial is not envisioned in the scenario, it is important that the primary pharmacodynamic action of the individual component is preserved when used in combination.

With respect to the design elements, typically, these studies will involve chronic dosing up until the steady state of effect is achieved in a parallel arm setting between polypill and the respective individual component.

The study is powered to rule out a clinically meaningful difference in an appropriate pharmacodynamic marker, which for an antihypertensive agent is blood pressure and for a statin is LDL cholesterol. For the aspirin component, markers such as serum thromboxane b2 or inhibition of platelet aggregation are not
adequately sensitive. Hence, at this point of time, we will rely on the PK bioequivalence of the plasma exposures of the acetyl salicylic acid, which is the moiety of interest here.

That in short is our perspective of how a polypill development program would look like.

Thank you.

(Applause.).

Clarifying Questions to the Presenters

DR. LINCOFF: Now we'll move on to if there are any clarifying questions for the guest and FDA presenters. So please remember those who were asking to state your name into the record before you speak, and there should be a microphone set up for the presenters to answer the questions into the record.

Yes. I'm asked to ask you to speak directly into the microphones. If you're looking at the presenters when you're talking away from the mic, it doesn't pick up. So Dr. Kaul?

DR. KAUL: Thank you. I'd like to thank all the presenters for very informative and
illuminating presentations. My first comment and question is for Dr. Smith. I want to take this opportunity for acknowledging your efforts in aligning guideline recommendations with high quality evidence.

I've said before that when evidence does not change but guideline recommendations do in alignment with the evidence, then that's a sign that the guideline development process has evolved. It has become much more refined, objective, dispassionate, and less conflicted. So congratulations.

My question to you is what are the criteria for the WHO list -- of getting on the essential medicines list? For communicable diseases, we have medicines that target tuberculosis, malaria, and HIV on the essential medicines list. How come the polypill is not on that essential medicine list?

So can you help us illuminate what are the criteria that the WHO looks at?

DR. SMITH: So you're asking what are the criteria that the WHO uses for implementation?
DR. KAUL: No. For getting on the essential medicines list.

DR. SMITH: I'm not sure that I know the criteria for the WHO to have an essential. I've been involved in the development of the metrics for 25 percent reduction by the year 2025.

Mark Kaufman is here. He has done some work for the WHO.

Mark, do you know the criteria for the essential --

DR. LINCOFF: We can't actually have other speakers.

DR. SMITH: Okay. So I'm not aware of the criteria that the WHO will be using for an essential medication.

DR. KAUL: This question is for Dr. Yusuf. In keeping with the FDA's requirement of lack of pharmacodynamic and pharmacokinetic interaction, there was a very interesting observation that you made in the TIPS study. The effect of simvastatin was lower in the fixed-dose combination compared to simvastatin alone despite the fact that the acid
metabolite of simvastatin, which some argue is the active metabolite, was increased. And a similar observation was made with the aspirin treatment effect being attenuated in the combination arm.

Has this been systematically addressed, or this was just a fluke finding on one small study?

DR. YUSUF: Good question, Sanjay. We reported what we found. Yes, there was an effect on the RAS in the polycap on the LDL levels, but not the reverse. There wasn't an effect of simvastatin on the thromboxane b2. We used that. And contrary to what Dr. Hariharan said, I think thromboxane b2 is a good marker of the effects on the platelet, at least for this purpose. So we didn't see that.

I know of no other data that has reported it, so it is possible it's a fluke. On the other hand, even if you believe it's real, the effect is very modest. And obviously, .83 was lowering of LDL without simvastatin alone. It was .7 in the polycap.

So it was P 0.05. Remember the number of
comparisons. So you make a good point.

Mr. Chairman, with your permission, can I address the question that was asked of Dr. Sid Smith regarding essential medications?

DR. LINCOFF: Yes.

DR. YUSUF: Dr. Hoffman [ph] and I and a group of other people had made an application to the WHO last year, and we're going to be putting another one in. The criteria: efficacy, safety, affordability and availability.

We were turned down last time, and the biggest comment was it isn't widely available, i.e., the regulatory approvals haven't happened. So we've got it into a chicken and egg situation where if the regulatory approvals are available in many countries, it is more likely to get onto the essential medication list. And we were hoping that by getting onto the essential medication list, it will wave a flag saying it should be regulatorily approved.

So that's where it is. We have sought advice, and we are resubmitting again because now
Polypills are available in 14 countries now, are approved or in the process of being approved. The only thing again is they said which specific polypill are you going to propose, and obviously, we're trying to get the generic thing out there.

So I think we will ultimately get an essential medication approval. Whether it will happen this time or the next time, I don't know.

DR. LINCOFF: Dr. D'Agostino.

DR. SMITH: Mr. Chairman, could I -- I do have that definition. It was not part of the NHLBI work that I chaired, but it's very short and straightforward.

DR. LINCOFF: Okay.

DR. SMITH: The definition from the WHO of essential medicines is that "they are those that satisfy the priority healthcare needs of the population." The criteria for selection include "due regard to disease prevalence, evidence on efficacy and safety and comparative cost effectiveness," so three things there and then the definition.
DR. LINCOFF: Dr. D'Agostino.

DR. D'AGOSTINO: I have sort of a fundamental issue with -- a problem with some of the discussion here. I'm involved, as we mentioned earlier, with the Framingham study, and I've been involved with a number of development activities of the risk functions and so forth. And in those, we get real populations, and we look at them. And I'm always asking the question, how many people are taking more than one drug, what type of drug, and what have you?

Now, you quite often find in these studies, especially if it's secondary, that people are taking multiple drugs. So this idea of a polypill, putting them all together in one pill, I mean, all of the interactions they have would have been seen -- or why wouldn't they have been seen when people are taking the drugs separately? They're all taking them in the morning before breakfast or something like that.

I mean, we must know an awful lot about these interactions with the drugs. Is the concern
that -- and this is more for the FDA. Is the concern that once you say the polypill is fine, then what will happen is the manufacturers are going to rush to the polypill and not look at the individual components and see how the individual drugs are doing? And as they rush to the polypill, and then there's the titration, will be much harder when you're trying to do the whole thing as opposed to individual components. Is that what the issue actually is, or am I missing something?

DR. LINCOFF: Please identify yourself.

DR. GRANT: Steve Grant, deputy director of the Division of Cardiovascular and Renal Products.

Dr. D'Agostino, can you repeat that question?

Well, let me make a couple of comments from the point of the view of the FDA because we convened this advisory committee because we're seeking specific information here.

The advice we're seeking is about secondary prevention and its use in the United States, and as far as you can, I would try to confine your
comments to that. The speakers, who gave excellent presentations, obviously talked about some of the intellectual underpinnings for this whole concept. Not all of that could be germane to your discussion today.

As far as what we would require, we would require all polypills to demonstrate what Dr. Hariharan talked about. They would all have to show that the PK is consistent with the PK of the individual components and that there are no untoward interactions between them. Absent that, they would not be approved.

I think beyond that, what we're sort of asking you today is each of the components that are in these polypills, they all have cardiovascular outcome claims. Aspirin clearly has cardiovascular outcomes claims. We have a guidance out that says all antihypertensive drugs have an outcome claim on the basis of lowering blood pressure. Not all of the statins specifically have an outcome claim, although the two that were discussed here, both atorvastatin and simvastatin, do have outcome
claims.

So I think it would be a little bit hard to suggest that the outcome claims that adhere to each individual component aren't going to occur with the combination as long as there aren't PK or PD interactions.

I think what we're asking you here is how much additional information we might need to approve this concept. There is a claim here that adherence will be better with one pill as opposed to three. You might reasonably discuss whether that needs to be demonstrated or whether an individual physician can make that decision.

I think you might also reasonably discuss here whether the availability of a fixed-combination drug not meant to be titrated could somehow worsen outcomes because people will no longer be titrated.

That was kind of a long answer to Dr. D'Agostino's question, but I think those are some of the things you're trying to get at. But again, I just want to encourage you, remind you
that what we're seeking advice here for is about secondary prevention in American patients and what this might do, hopefully, if a polypill is successful, what hopes it has, effects in other countries and the United States, but that's not germane to the discussion today.

DR. LINCOFF: Dr. Temple?

DR. TEMPLE: Steve or Norm, when drugs are approved like a statin, there's usually a fairly thorough test of what they interact with by known mechanisms and other things, and that would be true for new antihypertensive drugs.

So one of my questions is, how much more information would we really need on those matters? It's also noteworthy that every outcome study with a statin has been on top of aspirin and frequently on top of antihypertensives. Now, they don't look particularly for interactions there, but there is fairly extensive experience.

So how does that influence what would be needed here? That's sort of what Dr. D'Agostino was asking.
DR. D'AGOSTINO: That was what I was trying to get at. We have a plethora of information from clinical trials, epidemiological studies and what have you, and we see the overall effects or the multiple effects or what have you.

The question that I'm trying to get at is what is the concern if you switch to the polypill where you pack them all together? Is there something that's going to be missing in terms of practice? And as far as the PK and what have you, that I think you routinely would do. But is there something about the practice that might be detrimental, once it's out there, will the physicians not do the titration in a reasonable fashion or what other concerns?

DR. STOCKBRIDGE: Does Dr. Hariharan want to speak to this?

(No audible response.)

DR. STOCKBRIDGE: Fine. I think the likelihood of uncovering a significant PD interaction is not very high with this set of drugs for all the reasons people have said.
Nevertheless, I don't think we were smart enough to have predicted an interaction between aspirin and ACE inhibitors. It's possible -- and the data on that aren't all that terrific, but we decided a decade ago that all the ACE inhibitors needed a warning to that effect.

So I think it's prudent if you're going to promote the use of a set of drugs together in this way to check. It's not onerous, and it reassures you that you don't find something else you don't expect.

DR. LINCOFF: Dr. Fried?

DR. FRIED: Just to beat this to death, but really when you're talking about the aspirin, ACE inhibitor interaction, it's on mortality. So it wouldn't be that simple if you really wanted to prove that pharmacodynamic interaction.

I guess that's what I was asking, is how much pharmacodynamic data would the FDA want? Would they require that the mortality rates were not, say, different?

DR. STOCKBRIDGE: No. There's been no
discussion on our part. There's obviously at least
one person in the room who thinks maybe you'd like
to have mortality data on things, but we have never
proposed you have any outcome data at all. This
was all going to be done based on convincing
yourself that the primary pharmacological
mechanisms were intact.

DR. LINCOFF: Dr. Sager?

DR. SAGER: This question is for Dr. Yancy,
and thank you very much for your talk and the focus
on evidence-based guidelines.

In thinking about what kind of evidence is
needed here, I think it'd be really helpful to get
your viewpoints on that, and specifically, were you
alluding to a need for outcome studies for a
polypill in order to have really hard evidence?

DR. YANCY: Thank you for the question, and
I'd like to be very clear. Yes, we can look at the
available data and can appreciate the delta changes
in blood pressure and the delta changes in
dyslipidemia. And we can even accept the fact that
there may be non-inferiority even though the
studies may not have been designed to achieve that.

But I think to reach the tier where we can use the imprimatur of the large organizations that convene the groups and write the guidelines in today's world, we would like to see outcomes data. And since we're talking about cardiovascular outcomes with a very high event rate, the develop time would not necessarily need to be that long.

So yes, I think outcomes data would be beneficial in the generation of clinical practice guidelines.

DR. LINCOFF: Dr. Temple?

DR. TEMPLE: Can we pin that down a little further? What would the outcome trial look at? Would this be a comparison of the polypill with exactly the same drugs given separately, or would it be treating people with hypertension and a lipid abnormality only with a lipid lowering drug and ignoring the blood pressure and seeing if adding a blood pressure drug helps? Which is obviously an unethical trial that you can't do. What trials are we talking about here?
DR. LINCOFF: Isn't that the first question for the -- do you want the panel to answer that, or do you want the --

DR. TEMPLE: No. I wanted Dr. Yancy's opinion.

DR. YANCY: That's either a fair or unfair question, but I'm happy to address it.

I think that when we're talking about a totally novel intervention, something that's really necessary for very obvious public health benefits, we have to temper our rush to incorporate this new intervention by making certain that a real benefit can be achieved. And I think the definition of benefit right now, understanding that issues related to adherence reflect a different dynamic, would be that, in fact, we are saving lives, at a minimum not harming lives, but we are saving lives. There's every reason to believe that we should, but we all have been down the road where interventions that we thought should have saved lives haven't always been realized. So again, to drill this down further, I think the design of the
trial, the outcomes necessary, would be saving lives.

Now, it is contextual, and so it all depends on the profile of the cohort being studied. If it's a profile that's inclined towards hypertension, we may want to look at things like the progression to worsening renal function or the diminution of the risk of stroke.

If it's more inclined towards a group that starts with defined atherosclerotic burdens, i.e., previous evidence of angina or peripheral vascular disease, that might change what we're looking for. Perhaps non-fatal MI would be necessary.

But nevertheless, a heart outcome that is something that we can represent to the larger community would be necessary.

DR. TEMPLE: One other comment. Not to state the obvious, but a lot of this will depend on how the drug is labeled. If it's labeled as this is way better than anything else if you give it separately, oh, that's one thing. No combination's been ever labeled that way, for what it's worth.
If it's merely to say if the person needs this and this and this, give it this way, that raises a different question of what has to shown. Anyway, I know that will be discussed later.

DR. LINCOFF: Dr. Unger, you wanted to make a comment?

DR. UNGER: This may be obvious to some in the room but maybe not to everyone. So there are two thresholds here. One is the regulatory threshold of getting a polypill approved. And the gentlemen on my left and right I think would agree that if you had a convenience polypill that was labeled for secondary prevention in patients who had also dyslipidemia and hypertension, previous MI, and you had no drug-drug interactions, and you looked at the PD effects and everybody was satisfied that the three together behaved as they would individually, we would just approve it.

That has nothing to do with use, adoption, and practice guidelines. That's not within the realm of our control. So that may be the more important question. I don't know. But once it
gets on the market, then people obviously will
prescribe it as they see fit.

So there are two separate thresholds here, I
think, and the regulatory threshold, we don't think
is all that difficult, at least I don't think we
do, depending on the labeling.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: Question for Dr. Dudl, and it
really fits to this argument here. I'm interested
to know what your position and what you believe
Kaiser's position would be if the fixed-dose
combination were available and approved with regard
to the bundle that you're currently using versus a
fixed-dose polypill.

DR. DUDL: Well, first of all, we pay a lot
of attention to labeling, so we want to be sure to
consider that. But clearly, our
biggest -- adherence is a huge, huge issue. And
for us, this would be, if indeed we could improve
adherence 10, 20 percent with the people we are
already using on these three drugs, we would do it.
And we would see, and we would look at it because
we can.

If that seemed -- because I think from the discussion we have here, we believe these drugs work individually. We don't believe putting them into a single pill is going to change that. And if we can get 10 to 20 percent better adherence and better effect, that would be something we would very much appreciate.

DR. DELEMOS: And would you need anything more than the fact that it was FDA approved and available to make that change?

DR. DUDL: No.

DR. LINCOFF: Dr. Wilson?

DR. WILSON: So I have three questions that I'm thinking who I might use this drug for or this product. And it sounds like it would work pretty well and be easy to prescribe in a simple patient, but I see a lot of complex patients, so that's where my question is, is either a high or a low potassium, a history of heart failure in the chart, and if a person has declining or already has chronic kidney disease.
So that's my question to any of the presenters. What are the data for these special groups? Because for the prevention of recurrent disease, those are the types of patients that I have to look at that information, and do they have safety information.

DR. LINCOFF: Would any of the presenters like to approach that question, and if so, please identify yourself into the record.

DR. YUSUF: I'll have a stab at it, Peter. First, there are no data in those people directly, so you have to use clinical judgment in answering the question and make extrapolations.

First, you've got to understand -- and I'm sure you all understand -- that there is no commercial backing for these products right now. So doing these trials is entirely writing peer review grants and pleading with your friends to do the trials for next to nothing. So these trials are very hard to do, so please understand that context in terms of doing the trials.

The companies we have worked with have said
if the drug gets through regulatory hurdle, then we will start to invest. Again, it's a chicken and egg thing. And I've spent six, seven years trying to raise money for these.

Now, addressing your specific questions, let's take heart failure as an example, and I run a heart function clinic. Today, diuretics are indicated, beta blockers are indicated, and ACE inhibitors are certainly indicated. The role of aspirin in heart failure is debated, but 70 percent of heart failure patients have atherosclerosis, so you could make an argument to use that.

So you could say this could replace three or four drugs, but on top of it, I might add a loop diuretic or something like that.

The second thing to remember is we're not talking of a single polypill only that will be available. This group might approve one polypill, but that could lead to two or three different versions of the polypill being available. For instance, you've already seen from the UMPIRE study, there are two forms of atorvastatin.
We ourselves are working with three versions of the polypill, we've done without aspirin; we've done without ACE inhibitors. So you might end up with polypills that will be targeted.

Let me also say something very general, which is in the pursuit of perfection, let's not allow what's possible to be lost. So that it could be that high-risk hypertensives, high-risk diabetics, high-risk average people with vascular disease, which will probably constitute 80 percent of the people, the community will treat, will benefit from existing polypills. And you're right. We may need to have slightly different versions for the complex patients that you raise.

DR. LINCOFF: For the record, that was Dr. Yusuf.

Dr. Temple?

DR. TEMPLE: Just to say again what Ellis said before, all of these questions have to do with -- the previous question -- have to do with how it's labeled. If it's labeled for people who need this, this, and this, then presumably the
doctor's going to check to see they don't have a contraindication or don't have a drug that interferes with it. If it's somehow got a more broad label -- and obviously, people thinking about ex-U.S. use or thinking that there may be environments in which you can't get all that -- that changes a lot of the thinking. It's just worth keeping that in mind.

Could I ask one question, too? Is anybody interested in chlorthalidone as the diuretic? I haven't heard a word about it. I mean, 12 and a half milligrams of hydrochlorothiazide has never been shown in an outcome study to do anything. I'm just curious.

DR. LINCOFF: Please identify yourself into the mic if you want to make a --

PROF WALD: Having another stab at the question that Professor Yusuf answered, I think he's right. A person who's had a heart attack or stroke in the initial stages is an acute medical problem in which the care has got to be tailored to the individual. There'll be all kinds of
complications and issues that require a one-to-one relationship between the doctor and the patient.

But once a patient's been stabilized, that person's going to have to stay on long-term preventive treatment to prevent a second heart attack or stroke. And it's once one's reached that stage that it appears to me that there's evidence that adherence and the simplicity offers many advantages, and several of the speakers today have brought that out.

So I think one shouldn't as a medical, scientific community create hurdles that prevent effective and simple things happening. And at the end of the day, it's not a new drug. It's the combination of the drugs that would be standard in someone who's already had a heart attack.

In my own view, if you can show that that combination given to people leads to the reduction in blood pressure and cholesterol that you might expect, you're there. Who cares if there's a bit of an interaction? If it works globally -- and there are likely to be small interactions -- to say
no interaction is too extreme a barrier, and it's
trying to prove a negative.

So as long as it's acceptable and it's
building on the core of evidence that we have over
the last 20 years, try it. At the end of the day,
it'll be a clinician and a patient's choice as to
whether they take individual components or whether
they take a combination. I don't think anyone
should particularly legislate on that.

DR. LINCOFF: Thank you, Professor Wald.

Dr. Lewis.

DR. LEWIS: I want to follow up but actually
emphasize, 30 years ago when I sent one of my
patients to the cardiologist, they told me why are
you worried about this person. And I said, "I
think there's a connection between the kidney and
the renal [sic]. I think there's a big
connection." And it isn't just that renal patients
are at risk for cardiac disease. A very high
percentage of cardiac patients have abnormal renal
function.

As I went through all these polypill
studies, pretty much anybody with a creatinine
greater than 1.5, which could represent a wide
range of GFR depending on your age, were excluded.
There is good reason to believe people with renal
disease could be at greater risk versus benefit.
Like the risk/benefit ratio with these kind of
polypills could be greater.

I think that this whole labeling issue isn't
so easy in this whole -- I mean, this is a huge
segment not to have been studied. Maybe a third, a
fourth of this cardiac patients have renal disease.
We have no idea if we're going to help or hurt
them. Look at ACCORD. Look at lots of things.
Lower blood pressure isn't always better, guys. I
mean, ACCORD says it's not in a randomized trial.

Also, you could start a patient, and their
renal function might be good then, and then it gets
worse. What do you do? Stop it then? Do you
remember to do that?

I think it's quite complex. I don't think
the populations that you would even recommend this
in are quite complex. So I'd like them to comment,
why were renal patients excluded from all these trials? One of the speakers, and then I have a follow-up comment.

DR. LINCOFF: All right. So could you suggest which speaker you'd like to address this or -- so we can --

DR. LEWIS: They can choose amongst themselves. Dr. Yancy, I don't think would be the one, but I think one of the others could choose why were they excluded.

DR. LINCOFF: In the interests of time, we do have other questioners who'd like to ask, so if we could address this by one speaker.

DR. YUSUF: I think I can tell you why in our trials we had restrictions. It's the same reason why trials of individual agents had restrictions. Because when you're concerned, especially when you're doing your very first trial, you tend to take patients where you have concerns out of the equation to start with.

Just like when ACE inhibitors were developed, first you used it in patients who you
had no reason to be concerned. Once that
information was out there, people started to use it
in people with higher and higher creatinines
because we wouldn't have got it past any ethics
committees in these centers we worked if we said
there's no threshold at all on creatinine.

So I think what you ask is relevant, but if
you're saying can you show me you can swallow the
whole elephant at one goal, the answer is I can't.
None of us can. You couldn't, either. So when I
say "you," this entire committee couldn't, either.

You have to approach this stepwise. The
information you request is completely relevant, but
it's the next stage. It's an expanding indication,
but there is going to be the majority of people who
the points you raised don't apply to.

So I think let's think of where we can use
existing data and existing clinical experience to
move the field forward, and then identify the areas
where we need new information and recommend
appropriate trials there. And then we'll be able
to raise the resources to do this.
You see, those of us who are doing these studies, we don't have a deep bank balance.

DR. LINCOFF: All right. Thank you.

Brief, yes. Okay. Dr. Li?

DR. LI: So all of the individual components of the polypill are now generic, and patients can get them all relatively cheaply. And so if an industry -- this is a question to the FDA. If industry goes forward to go through the regulatory steps and develop a formulation, are they going to have marketing exclusivity, and is the price going to go up? And what is going to be the economic impact to patients and third-party payers about implementing such a product?

DR. TEMPLE: Anybody else know enough to answer? If they bring forth data from a trial of some kind, including a PD trial, I guess I think they would get three years of exclusivity, but that's subject to correction from people who know more about this than me. But I think they would. But it would only be for three years. And of course, that doesn't stop people from taking the
drugs individually.

DR. STOCKBRIDGE: If you only did PK and PD as the basis for --

DR. TEMPLE: I didn't say PK, no. But if they did a -- you know, we're talking about an interaction study looking at various measures, I think that might get you exclusivity.

DR. STOCKBRIDGE: Yes, I don't think it does.

DR. TEMPLE: Maybe not.

DR. GRANT: Just be careful about what you're saying. I think what you're asking, Dr. Li, is if one polypill came on the market, all other polypills would be excluded, or are you talking about the specific combination of medications? As you've seen, there are different -- and presumably, you've seen some proposals that have different components. If we go forward, presumably, other people may come up with other combinations.

So are you asking about polypill in general or a specific combination of drugs, 20 of atorvastatin, 160 of valsartan, and 75 of aspirin?
DR. LI: Well, yes, because I would assume that the manufacturer would get exclusivity, and they could market that -- it wouldn't be a generic form anymore, whereas consumers and third-party payers will say you can get these individual components a lot cheaper, so why should you be taking this polypill?

So there are a lot of economic implications to patients and payers, and I just want to know what the financial implications would be and if that would really limit implementation of a polypill.

DR. TEMPLE: I don't think we know fully, but for what it's worth, many people have made new antihypertensive combinations of drugs that were available generically. And I'm sure they did it because they thought there would be some benefit in what they could charge, and I'm sure many payers say, no, I don't want to. But I don't think we can give you full total answers on exclusivity here. We'd have to check.

DR. LINCOFF: Dr. Flack.
DR. FLACK: I think Dr. Temple's comment about chlorthalidone is one that shouldn't be overlooked. Chlorthalidone is clearly a superior diuretic. It's a little tougher to use, will cause more hypokalemia, but compared with a RAS blocker, it's probably going to be minimal, and also, too, works to a lower GFR.

I believe in data, too, but I think we need to -- at least my take on it -- won't try to prescribe anybody else's -- is if you've already got the individual combinations approved, and you put them together, and there's no demonstrable deleterious interactions, then you got to make a really strong case why you want to make this combination jump through a hurdle; what is about putting them together in the absence of an interaction that would cause you to throw money to do huge, huge trials?

Now, what I would say, though, is this is going to be harder to implement in clinical practice than it was in Kaiser. And it's going to be harder because the doctors, this is a very
foreign concept for the way we usually practice. Is a single pill that you don't titrate for the most part better than regular therapy within individual components? I don't necessarily know that this is optimal therapy.

I'm a little bit skeptical about the data showing that there's no benefit of getting cholesterol down because when you do the meta-analysis and you look at the graph, when you go down, you basically see something you can't see in the individual trials. It stays on the same line, implying that there is no threshold. So is this really optimal therapy per se?

The way we interpret trials is very idiosyncratic. I don't interpret ACCORD as negative, particularly when it was an underpowered trial and the stroke was reduced over 40 percent. And the event rate, through no fault of the investigators, was half of what it was predicted. And so I think falling on the sword for an underpowered trial, to me, is not something I really want to do.
So at the end of the day, I don't know if it's necessarily optimal, but I don't necessarily know from a vantage point of making a recommendation about whether it should be approved. In the absence of interactions, I don't think you have to have this huge outcomes trial. But I will say at the end of the day, at some point, it would be nice to know if this is equivalent, non-inferior, or better than simply the way that we currently do it. But I don't necessarily know that that's an approval issue.

DR. LINCOFF: We've got five minutes left and a couple people left. I'd like to try to confine this part to questions of the speakers because we will have discussion time.

Dr. Davis, you're next.

DR. DAVIS: Yes. This may have already been addressed a little bit, but I just want to get clarification on the exclusion criteria for such a drug. I mean, what's been presented is that 90 percent of the people who are in these studies had high blood pressure, 90 percent had high
cholesterol. But what about the people who have cardiovascular disease but don't have high blood pressure or have a very low cholesterol, or even the people who are at risk of bleeding? Were there exclusions?

DR. YUSUF: Barry, I don't think 90 percent had high cholesterol and 90 percent had hypertension in these trials. I think in the trials we did, which is two that we've done, they were either vascular disease or people with one high-risk marker like diabetes or hypertension.

Now, the trial that I showed 90 percent had hypertension is the trial we're doing right now that's ongoing, the TIPS 3 study, where 90 percent have hypertension. We used a risk scoring at threshold in order to get high-risk people. And it just happens that 90 percent or 87 percent have high blood pressure.

I think a lot of the trials were people with vascular disease, so if they had a previous MI or previous stroke or peripheral artery disease, that was the usual inclusion criteria. And obviously,
if there was a contraindication to any single drug, like aspirin to GI bleeds, those people weren't included, and that makes a lot of clinical sense.

Let me add that the contraindication to the polypill should respect the contraindications to each of its components, otherwise, it wouldn't make any sense. And I think that's something that there would be hopefully a consensus on.

DR. LINCOFF: And Dr. Scott.

DR. SCOTT: I have a question for Dr. Smith, and it's around the interpretation of the ACC/AHA guidelines. The suggestion is that there's no requirement to titrate, but I think actually what the guidelines say is that it's intended to facilitate using a high intensity statin and that one should be aiming one's therapy to get at least a 50 percent reduction in LDL. And in that context, you may have to titrate.

Isn't that correct?

DR. SMITH: Partially. Thank you for the question. The recommendations were to use a high intensity statin -- and before I get -- I'm going
to get back to Dr. Kaul's question because I have looked under essential medication, and the one lipid lowering medication that is mentioned for WHO 18th edition, which is the current edition, is simvastatin in the dosage of 5, 10, 20 and 40, which is consistent with the safety range that is recommended in the new guidelines. But in fact, that would be a moderate dose statin.

So to continue with your excellent question, the dosage of statin recommended for those patients who are 75 or younger is high-dose statin, and that is defined as a statin which generally would result in a 50 percent reduction in LDL cholesterol.

We wanted to be very careful to emphasize that a 50 percent reduction in total cholesterol is not a target, just as 70 LDL is not a target, but that's the range of a change in LDL cholesterol that should be seen. And if that is not seen, it should lead the clinician to ask whether or not the patient is taking the medication on a regular basis or consider the dosage that's being given.

DR. LINCOFF: All right. I anticipate we
will have some time for more questions before we actually start the discussion part after 2:00, so we're going to break now for lunch.

We will reconvene again in this room in one hour, 1:00 p.m. Please take any personal belongings you may want with you at this time. Committee members, please remember there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:02 p.m., a luncheon recess was taken.)
Afternoon Session

(12:59 p.m.)

Open Public Hearing

DR. LINCOFF: All right. We'll resume. So now this will be the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include payment of travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the
beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, speak only when recognized by the chair. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the
record.

PROF ROGERS: Thanks very much. My name is Anthony Rogers. I'm a professor of global health at The George Institute based in Sydney, Australia. And thanks very much for the opportunity to speak today.

So in terms of those conflicts of interest to declare, I don't have any personal financial interest in this area. But I think it would be fair to say I'm invested in it. I've spent about 15 years trying to raise public money and persuade companies to develop products in this area. So it's obviously of interest.

Also, I raised grant monies to my institution for research in this area. And my institution took on a license for the products you'll see in the data I'll show following a decision by the manufacturer not to take forward the product because of some regulatory barriers. So there are those things to declare.

So what I'd like to do today is take a little time to bring the committee up to date with
three trials that we've conducted over the last five or six years and combined into this prospective individual patient data meta-analysis that we're calling the SPACE program.

There's about 5 and a half thousand person-years of randomized evidence addressing polypill versus usual care in the patient population that is the subject of discussion today in front of the committee. About 85 percent of that evidence comes from these three trials.

There was a trial, half the patients in Europe, half in India, you've heard about today. Also a trial just conducted in Australia and another in New Zealand, and half the participants were indigenous in those trials.

The eligibility for those trials was very simple. First of all, it was patients with established CVD, and so I understand that's the focus of the committee today. And most of those patients did have established CVD, but we also recruited people with similarly high risk who were over 15 percent five-year risk on the Framingham
function.

All of the patients needed to have a recommendation for treating with the four drugs in the combination pills, but they were not necessarily on them. And there was randomization to polypill-based care or continued usual care with no attempt to change the great variety of usual care.

Follow-up was at least 12 months, and there were three primary outcomes: self-reported taking aspirin, statin, or two blood pressure drugs, the indicated drugs, LDL and blood pressure.

There were two formulations provided but no dose versions. I know that's a thing of interest to the FDA, committee, in the questions today, what are the risks of providing no variations at all in the doses, and that's something will come forward later in the slides.

These dose versions, the pill was designed in 2002, and at the time, these were the most commonly used dose versions in the U.S., the U.K. And I believe that's still the case for these
particular drugs.

   In terms of the patient population, there was just over 3,000 people in total, and the baseline blood pressure 139 over 80-ish. And as you can see, about two-thirds of the patients had coronary disease. Another 15 percent or so had cerebrovascular disease, and about a quarter were over 15 percent five-year on the Framingham risk function but no established vascular disease.

   In terms of other baseline characteristics, I'll just point out one. Most of my slides are in millimoles, I'm afraid, given our European components, but it was about 93 LDL at baseline. And physicians had to agree before randomization which polypill people would start on if they were allocated to the polypill, and it was roughly half and half who chose the different versions.

   Before we go on to show the slides, I'd just go through a couple of the potential biases to take aware of. It was an unblinded trial, so there's always the possibility of differential investigational diagnosis. And we were mandated by
IRBs to provide the study medication free in the UMPIRE trial, but that wasn't the case in the other two trials. And also, there were a number of centers within the UMPIRE where all medication was free for all patients, and we looked very closely and couldn't see any difference among those trials or with the other two trials.

It was a self-reported adherence outcome, but that was validated in several ways, both with objective measures. And we were able to get almost exactly the same results from prescription data, and it made no difference whether one defined taking medicines just one day a week or seven days a week.

Now, one particular issue, though. I think it's worth bearing in mind to the committee. Even though we aimed to do usual care, it ended being considerably better than average care. And that's a very important consideration when one's thinking about the importance of clinical trials. But the importance of clinical trials for interventions like this that are meant to improve adherence and
the kinds of populations that need such interventions are almost by definition the kinds of populations that are hard to get into clinical trials.

So it's a very important consideration. People who need to get these kinds of adherence-improving therapies are those that find it difficult, the whole consent rigmarole follow-up process, et cetera, and it's hard to include them in trials.

Just skip very quickly through the main outcomes. Adherence was improved by about 50 percent, so overall about 80 percent were on all four medications in the polypill group compared to about 60 percent in the usual care group. There was statistical heterogeneity but not great quantitative heterogeneity across the trials.

In terms of the objectively measured outcomes, there was about a 2 and a half millimeter lower systolic blood pressure overall in those who got allocated to the polypill group and about a .1 millimole LDL advantage. And I'll show some
more detailed findings of those.

So just breaking down by the modalities, there's a lot of focus on the different modalities here, and it's very difficult to see this data. And that's kind of the point. These were very well treated patient populations, so in terms of individual therapies, anti-platelet therapies, statin therapy, and any blood pressure lowering was up at the 80 to 90 percent mark in the usual care group, so much better treated than the average in the population.

You remember the slides Salim showed earlier. About 50 percent of people in the U.S. aren't taking blood pressure, statin, and aspirin post-MI.

Overall in the polypill group, there was about 5 percent improvement for each of those individual modalities. There was a much larger improvement in the number taking two blood pressure drugs or more.

Now, this is perhaps the most important slide, I think, showing that adherence outcome
broken down by the number of modalities patients
were taking at baseline. So just starting out
here, this is the focus of regulatory guidelines to
date, the focus of product developments to date, is
straight substitution among people who are already
stabilized on the same drugs at the same doses.

You can see there's a slight adherence
advantage for the polypill in that situation. You
start off at adherence of 100 percent, and it goes
down gradually over the years and a bit less
quickly in the polypill group.

But that's kind of not the point of this
therapy in some sense in that if you've already got
people on the right drugs and the right doses and
they're stable, then why change it? I think
clinically in public health a much more important
group is -- and it's still the majority of patients
in the U.S. who aren't on all three treatments.
And in this trial, it was about 40 percent who were
only taking two of aspirin, statin, or blood
pressure lowering, and there was about 10 percent
of people who were only taking naught or one
modality at baseline.

You can see in both those settings, of course, allocation to the polypill shoots you straight up to 100 percent. In the first few weeks, people can't tolerate that, and they go down onto separate medications. And there's a gradual diminution over time, but out at 18 months, there's still a very large absolute benefit in terms of adherence.

I would say this is the challenge, the opportunity, for the committee to think about how one can come up with some kind of labeling to promote, to think about the appropriateness of therapy, combination therapy, for stepping up treatment in these partially treated patients.

The committee's remit is focused on established cardiovascular disease, so I'm just showing here the subgroup analyses according to raised CV risk versus established CVD. And you can see the yes group, very similar findings with that subgroup compared to the high CV risk group.

Now, this is a fairly busy slide, but I
think it's very important in following up on a
couple of issues that the committee's been asked to
address. Here, as I said, we made no attempt
whatsoever to change the usual care, and that
included both people who were on no statin at all
at baseline, many of whom got started. But there
was also 10 or 20 percent of people who were on
more potent statins that were randomized to a
polypill containing 40 milligrams of simvastatin.

I'll just focus on that group for the
moment. So you can see there's five different
statins that are more potent than simva 40, but in
all of those cases, there's no evidence of an LDL
disadvantage from being randomized to simva 40.

What you're seeing there is a combination of
a couple of things. Most importantly, just because
you've written the prescription, that doesn't mean
that people are actually taking your high potency
statins. So you have an adherence advantage with
the polypill. But also, in about 15 to 20 percent
of the time, people were stopped the polypill and
then prescribed open label more potent statin.
But the take home message is that there's no LDL disadvantage from bringing a polypill onto the market even if you're switching people straight off from more potent statins. And there's a light advantage when you randomized from equally potent statins and a larger advantage obviously with less potent or no statins.

A similar kind of analysis on blood pressure regimens, so if you were on monotherapy at baseline, there's a clear advantage of being randomized to a polypill containing combination therapy, whether it's ramipril monotherapy or perindopril, which were the most commonly used ones, and a much less advantage or about equivalent is you were on combination therapy at baseline, but certainly no risks of going to a polypill with relatively low-dose combination therapy.

Now, this I think is a very important slide, and it's an attempt to bring us towards perhaps a less risk factor specific focus, which is inevitably the result of focusing on the risk factors by risk factors. And here we have divided
the patient population just in one of the trials according to whether people are on no statin, less potent, equally potent, or more potent statin. And what you see is that there's no difference in the LDL finding when people were randomized to the polypill, but there is an aspirin adherence advantage of about 3 percent, and there's a blood pressure advantage.

So it's just the importance of managing all risk factors at once in the same patient. The people on no statin, there were benefits for all those risk factors, but people on more potent statins, no difference for LDL advantage for aspirin and blood pressure.

Looking at exactly the same thing, but for blood pressure lowering, people who were on three or more blood pressure lowering agents at baseline, no difference at all in the blood pressure at 12 months' follow-up, but they had an advantage for LDL and for aspirin. And there was no difference in the number of people taking three or more agents.
So in answer to the committee's question around tailoring, tailoring is still possible with people adding medications on top of a two-component polypill. And so you see exactly the same finding, equivalence for the well managed risk factor, and you get the added gain of adherence for the other two risk factors.

Now, this analysis also speaks to one of the committee's potential risks. What about those people who are well managed? And again, I think I'd point out to the committee that that's the tiny minority of patients, even in the U.S. So in this patient population, it was 10 percent of the entire trial, and that's probably -- maybe it's 10, 20 percent of patients in the U.S., in all western countries reliably for years after their event to take aspirin are reliably taking a more potent statin.

They're on three or more blood pressure drugs. And it was basically a draw. So there's no diminution in their care. There's no benefit clinically, but they were getting about the same
risk factor reduction.

The large majority of patients were in this middle group where there's some slight benefits, but clinically, the most important group is this undertreated group who aren't taking all the medications. And that's where the largest benefits were seen.

The mean risk factor reduction sizes were a bit underwhelming, but of course that's because every patient contributes to a mean value, and thresholds are a bit more informative. And this is an interesting analysis showing that there was an improvement in people getting below blood pressure thresholds, LDL thresholds, and aspirin adherence. And those benefits were multiplicative, so this threefold increase for reaching all three targets simultaneously.

So what that means is in the usual care group if you hit your LDL target, it didn't matter. It didn't make any difference. You weren't more or less likely to meet your blood pressure target or be aspirin adherent, et cetera. But obviously, in
the polypill group, you're more likely to reach all three targets simultaneously.

Something that's been very prominent in the literature, I think can be safety dispelled now. This set of evidence provides very clear data showing that in groups that know they're on the polypill whether they haven't had an event or whether they've already had an event, there's no difference in their BMI levels, self-reported physical activities not shown here, smoking rates, et cetera. So there's no adverse effects on their lifestyle measures with very tight confidence intervals.

We had hoped to recruit many more patients into these trials, but as Salim alluded earlier, it's a great challenge getting funding for low cost medicines research. So the average follow-up was only 15 months, and there was only a few hundred events so less 200 events shown. So you don't expect to start seeing event reductions until you've got much larger follow-up and much longer follow-up, but these were the findings such as they
were able to be generated in this patient population.

Safety and tolerability is, of course, very important. And this shows the rate of reporting of serious adverse events in all three trials combined over 24 months. Overall, there was about a 10 percent increase in SAEs reported, and it looks as if that was reported early on.

There's a mixture of things going on here. It looks as if there was a lower threshold for reporting SAEs in the polypill group because it was an unblinded trial. The trialists were reporting things that they wouldn't otherwise report in usual care. There was no excess of fatal events, hospitalizations, life-threatening, et cetera. These were all events that were regarded as medically important.

But the other issue may well be is you're switching people off stable albeit undertreated medication regimens onto more potent regimens, and so there may be -- there looks as if there is an increase of issues early on.
There was about 20 percent stopping the pill per year, and the main reason for that was possible side effects. And so we looked very closely at this, and the vast majority of time when people have stopped the polypill, they went onto separate medications. And these were the main reasons for reported stopping.

Unfortunately, it doesn't quite lend itself to knowing how many times it was possible side effects and how much it was wanting to control risk factors more. But one assumes that this quarter was for aiming for better risk factor reductions, and the side effects and the patient choice were side-effect related.

Very high patient acceptability, patient demand, a lot of demand to get into the trial. A number of the trials, we weren't allowed to do the trials unless there was post-trial access scheme for all patients whether they were in the polypill or the control group, and I think that's a very important issue.

In the UMPIRE trial -- after the end of the
trial -- so this is the group that had had access

to the polypill -- about 86 percent said they want
it if it came on the market, and that was about
81 percent in the usual care group.

Some other data on patient acceptance, we
ran a crossover trial of morning polypill versus
evening polypill versus the separate components,
which I can show separately if needed. And about
90 percent of people preferred the polypill versus
the separate medications, and 8 percent had no
preference.

Part of that patient preference is reflected
in the number of people who are prescribed but
don't actually even take it up from the pharmacy,
and there was a significant increase in primary
non-adherence.

So in conclusion, we'd say from these data
that there is clear evidence of improvements in
adherence, blood pressure, and cholesterol. It's
consistent across a wide variety of settings, a
very varied patient population in these six
countries. But the largest improvements are those
who are not taking recommended treatments at baseline.

And I'll just spend a couple of minutes, if I might, just giving my two cents on the questions that are posed to the committee. And the first one I think is the most important. What is the target population? And I'd say it's very important clinically to add a target population of those with clear indications, with guideline level 1-A evidence of treatments they should be on but aren't on. And as I said, it's very important to remember that half the patients in the U.S. aren't on the treatments they need to be a year or two after their heart attack.

Does one need benefit in this setting? I'd say these trials and the FOCUS trial provide the benefit one's needed. And for the key patient group, the undertreated patient group, you don't need events because they're not getting all the treatments. So if you genuinely -- requiring randomized trial evidence means that you think there's some uncertainty that there's benefit of
aspirin in people post-heart attack, and I don't think that's a reasonable position anymore.

The committee's been asked to think about are there risks of this going to patients who are on optimal care, that tiny portion who are on optimal care, and I hope some of the data that we've shown show that those risks are surprisingly low because of the benefits of adherence.

The patients that are well treated are those that get blood pressure drugs added on top of the polypill, et cetera, are those that get their polypill stopped and a more potent statin added if necessary, et cetera.

I think it's also worth pointing out that we're in an environment where there are many, many single drugs that are available to be switched onto, so perhaps an alternate step would be adding some labeling to those drugs saying that they shouldn't be used singly and that aspirin shouldn't be used without statin as a co-prescription.

So thanks very much for that opportunity to talk. Thank you.
DR. LINCOFF: Thank you.

Will speaker number 2 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. CHOUDHRY: So my name is Niteesh Choudhry. I'm here representing the American Heart Association.

By way of disclosure, the major focus of my work is on medication adherence, and my institution receives grants from all kinds of people, NHLBI, CVS Caremark, the PhRMA Foundation, Commonwealth Fund, and Merck. I receive funding from other organizations in the form of consultancies that really have nothing to do with anything we're talking about today.

Neither I nor the association have received for funding for participation in today's meeting, nor do we represent the interest of anyone other than the public and patients.

So the mission of the American Heart Association is really to build healthier lives free
of cardiovascular disease and stroke. This graphic on the lower left-hand side shows large reductions in cardiovascular death rates that have occurred over the past decade, which are really attributable to reductions in both risk factor modification or improvements in risk factors and the more effective use of cardiovascular therapies as the graphic on the right seems to indicate.

Despite this, as we all know, heart disease and stroke really remain the leading causes of death in the U.S. and abroad, and there are many reasons for this. But non-adherence to evidence-based cardiovascular medications is likely a central contributor.

So the graphic on the right shows data from a trial that I ran several years ago among commercially insured patients in the U.S. showing that about a year to a year and a quarter after hospital discharge from MI, adherence rates here estimated using pharmacy refill data were in the 30 to 50 percent range.

So it has been widely argued, and many
agree, that improving long-term adherence to these evidence-based cardiovascular therapeutics could really effectively reduce cardiovascular morbidity and mortality.

A polypill obviously fits very nicely into this construct, and in the U.S. context, the potential benefits of a fixed-dose combination polypill are really on improving adherence. Other potential impacts like access, while no doubt relevant for some parts of the U.S., in general are probably less of a concern for us here.

The impact on adherence really, as we've talked about this morning, is through improved or reductions in regimen complexity. And as a consequence, the improvements in adherence that have been seen in the polypill trials that have been talked about several times, although the metrics used to calculate these changes are different from trial to trial, should in principle really be associated with clinically meaningful results.

So to give you some context, in our MI free
trial, we showed simultaneous improvements in statins, beta blockers, and ACE inhibitors of about 5 percent, and that reduced major vascular events by about 14 percent. So these improvements of 20 to 21 percent in UMPIRE, regardless of whether it was the free drugs part of it or the reducing complexity part of it, should in principle be associated with substantial reductions in cardiovascular morbidity and mortality.

So while there are lots of reasons to be enthusiastic about the potential benefits of fixed-dose combinations, we believe that there are several key questions that still need to be asked. So really is the polypill as effective as the individual agents?

The improvements in adherence, as we've talked about, while the trials that have been for polypills have been relatively small, there really hasn't been a very clear overwhelming signal of the translation of those adherence improvements into the biomarkers of biometric measures that follow from them.
While small and potentially clear in some cases, far from large, in other cases, for example, in the case of cardiovascular mortality or major adverse cardiovascular events in UMPIRE with a p value of .09, there was a relative increase of 45 percent in those events. So at least there's the question of is it really as safe when they're compounded together.

Secondly, will it be safe for use in actual practice? In general, efficacy trials are underpowered to detect safety signals. That is almost universally the case for all registration trials, and when someone has an idiosyncratic reaction like a rash or a gastrointestinal upset, in practice, patients will need to be switched back to the individual component agents. And this in and of itself may actually add some complexity to the process.

Third is will non-titratability be a problem? Obviously, the charge before the committee is really for a non-titratable pill. And in our view, numerous drug combinations will almost
be unavoidable because of the beta blocker and/or antihypertensive component of a polypill.

As a consequence, adding polypills on top of the numerous other agents that are already available could paradoxically add complexity to the prescribing process. So while certainly a potential simplifier for patients and ultimately for clinicians, there is also the potential for complexity.

There are other considerations, some of which are slightly beyond the mandate of the FDA, but nevertheless are worth considering. As was brought up by a committee member this morning, if a polypill gets approved for use and it's a branded agent, then the added cost of the branded agent needs to be weighed against the reduced complexity from these products. And as a consequence, there may be really no impact for public health at all.

Second, this idea, which still I think remains to be addressed in routine practice, about whether a focus on drugs may make prescribing drugs almost a little bit too easy, as we have documented
before, recent reductions in cardiovascular mortality are really the result of drug treatments and risk factor modification.

Thirdly, for practitioners and for patients, there are a wide variety of strategies to improve adherence. And so the question before us will always be how does a polypill compare to some of those, and therefore, which of them should be chosen and/or should they be combined?

To speak to the questions that the committee asked for comment on with a little more direction, firstly with patient population, the existing data really does not identify which subgroups of secondary prevention patients benefit most. In principle if a polypill is safe and effective, more precise targeting may not actually be necessary. This could be given to everybody.

If you're looking for clinical outcome benefits, then as we did in MI free and other people have done in other trials, focusing on people immediately post-acute coronary syndrome may be the easiest way to show that benefit.
But in principle, the adherence benefits should really be seen across the spectrum. But because off label use is almost always the case for newly approved agents, it is almost certainly the case that the use of these agents will expand to other populations even if that's beyond the labeled indication. And so at least being cautious of the fact that they may be used by primary prevention patients should be taken.

Secondly is the idea of which polypill. The idea of chlorthalidone versus thiazides really begins to get at what is probably part of a much larger conversation about what the components really should be. And figuring out what the specific component agents are is as important as figuring out what their impact on adherence might be.

So as a question for your consideration, should a polypill with less effective components or those for which the data is less clear, for example, rosuvastatin as compared to atorvastatin, be chosen over evidence-based single agents when
that's a tradeoff that patients may be asked to 
make, especially if it's a branded agent that's 
coming to market.

So the AHA has several recommendations to 
provide to the FDA, and I offer these for your 
consideration. So first of all, the polypill may 
be a very effective strategy for improving 
adherence and reducing the burden of cardiovascular 
disease. And there's great reason to promise that 
this is a very effective adherence improvement 
strategy.

But there are lingering concerns about their 
efficacy and safety. And so as a consequence 
before approval, we would recommend that more data 
really is needed, both in terms of clinical trials 
of sufficient duration, of adequate power for 
safety subgroup and patient population 
identification, and which document clinically 
relevant outcomes. Maybe not necessarily major 
adverse cardiovascular events, but certainly clear 
documentation about blood pressure and LDL, which 
should be able to be seen over relatively short
period of time.

Because of the differences between trials and the real world, even after they're approved, we would recommend that postmarketing surveillance for safety is really a necessary part of any approval process and should therefore be taken seriously in consideration of a polypill. Thank you.

DR. LINCOFF: Thank you very much.

Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. NEUTEL: Hi, everybody. Good afternoon. My name is Dr. Joel Neutel. I'm a professor of medicine at the University of California Irvine and the director of research at the Orange County Research Center in California. And in terms of disclosure, I am on the advisory board for CardioPharma and also for Daiichi Sankyo, Forest, and Takeda Pharmaceuticals.

I appreciate the opportunity to spend some time with you today and really enjoyed this
morning's sessions. One of the things that came up in an area that I've been greatly interested in over the past few years is why is it that we have so many hypertensive drugs, a little over 100, and yet do relatively poorly in terms of blood pressure control.

Over the years have come to understand that this issue of physician inertia, or clinical inertia as it's referred to, is a major problem that I think we all have to deal with. And if we want control rates, as I'm sure we all do, that is something that's going to have to be addressed.

It's becoming clear to me, having spent many years studying the combination drugs that we have available, that combination therapy, fixed-dose combination therapy, is a very good solution to clinician inertia, or clinical inertia, and also has many benefits in terms of patients' compliance.

So just a few slides to discuss some of these issues. I think we're all very familiar with the fact that as you increase the number of cardiovascular risk factors, the risk of
cardiovascular disease increases dramatically. And I think it's important to remember that not only is it an additive effect, but when we look at data such as this Neaton data, you can see that the effect is actually synergistic, that when you have both blood pressure and lipid abnormalities, you're actually seeing a synergistic effect in terms of the cardiovascular risk. And I think this is quite well understood by physicians.

I think where the problem arises is that we have to develop a paradigm shift in our management of these cardiovascular risk factors. We all know that these multiple cardiovascular risk factors increase cardiovascular disease, but I think physicians largely look at these in silos, that hypertension is a risk factor that has to be controlled, same with dyslipidemia, same with diabetes, and that's how the disease is approached.

But rather I think it's becoming quite clear, and a lot of our discussion has showed this today, that these risk factors are clustered. They tend to occur in clusters in these patients, and
that they have these synergistic impact on cardiovascular risk. And even when you have two of these risk factors that are either mild or moderate, you can have profound risk in terms of increasing cardiovascular disease. And so we really have to take this approach of managing the syndrome of abnormalities rather than just silos that we approach individually.

With that in mind, it's very clear from the data that you've seen today, and some of this I'll show again just briefly, that when you treat these individually, the benefit in terms of cardiovascular risk, when you treat them all together as is shown in this slide, the benefits are significantly greater.

We've seen this slide, too, from Dr. Fonarow and Dr. Yusuf's data. When you add these drugs together, the risk in cardiovascular disease is as dramatic as you've ever seen in any cardiovascular studies in recent history, and I think very impressive to anyone who sees them. Even from the NHANES data, although the percentage of patients
for each of the disease entities are somewhere in
the range of 30 to 40 percent on each of those,
when you have them on two treatments, the impact on
cardiovascular mortality is quite dramatic.

With this in mind, it becomes quite
concerning that when we look at the data out there,
you can see this clinician inertia. The doctors
are much more likely to control hypertension than
they are to control dyslipidemia, although that
they know in terms of risk, both are very
important. It's just one of those things in
clinical practice that you tend to deal with the
one that seems to have the most dramatic impact in
terms of patient health.

When you get three of these cardiovascular
risk factors, you can see that the control rates in
the patients at goals just drops down for every one
that you add and becomes increasingly difficult to
achieve control in these patients.

So the treatment inertia definition, which
actually came out in the Joint National Committee's
reports in one of the first times that we saw it,
was this failure to initiate or intensify or change therapy in patients who have uncontrolled cardiovascular risk factors in situations in which patients return for visits having taken their medications. They're on treatment. They've seen a doctor. They've taken their medication, but they still have higher than recommended guidelines, and physicians don't tend to respond to this.

This is data taken from a large Canadian study, and Canada has been very interesting in terms of blood pressure control because they've kind of gone from one of the worst in the world to one of the best in the world. And I'll talk about that a little bit more in a minute.

But you can see here, even in Canada where control rates are very good right now, in this study, 41 percent of the patients treated did not achieve a blood pressure goal, and yet in more than half of the patients, no change is made to their medication.

This occurs not because they're bad doctors, not because they don't know what the goals are, but
because there are so many reasons in clinical practice which entice us to accept inadequate control: patient factors, try non-pharmacologic treatment, cost, side effects. All of these things induce us to accept inadequate control.

Now, one of the interesting conundrums that I've come across and that we've had lots of debates on is how is it that when we look at control rates here in the United States -- and let's just take blood pressure for a minute -- that the control rates are relatively poor when you look at the NHANES data, but yet when you look at studies, such as the ALLHAT study or any of the other large studies that have been conducted in the same patients by the same doctors, that the control rates are so much better.

Here's data from the STENO-2 study, which was diabetic hypertensive patients, and it was very interesting to see that when you let doctors do what they normally do in clinical practice and you compare that to physicians that are now following a protocol, those on intensive treatment -- and what
that meant is they had to follow a study protocol -- do much better in terms of control than what they do when left to their own devices.

The reason for this is simply because we're forcing them to use a polypill. What does the protocol do? It tells you to titrate. Don't think. Don't listen to the patients telling you that they've joined the 24 Hour Fitness. Just titrate up according to the protocol, and when we do that, you get them onto the polypill, and you end up with much better control.

In the studies that we've done using combination therapy for factors that again prevent doctors from thinking, just to titrate, they don't worry about side effects or cost, and obviously because of patient factors, when you use these fixed-dose combinations, your control rates are better than when you use the drug separately.

As I said, in Canada, it was very interesting because from the time that CHEP came about and started advocating the use of fixed-dose combination, the control rates went from about
14 percent in Canada to somewhere around 64 percent. And I spent many hours trying to figure out why there had been such a dramatic improvement. And the only thing that we could find that correlated to that improvement was the increased use of fixed-dose combination therapy. When it's available and recommended, doctors use it, and the outcome of that is much better control rates.

Of course, there's some important patient factors as well. This is data from Mancia's group, but clearly showing that when you increase the number of drugs even once a day -- we all know that if you do it twice a day, it impacts compliance. But even if you do it once a day, every time you add an additional drug, compliance rates go down dramatically.

Here you can see compliance rates of patients on a single dose of an antihypertensive, single dose of a lipid lowering agent, roughly the same for the two. But as soon as you use two different drugs, then your compliance rates go down
dramatically.

Another thing that was very interesting that came out of this study from Jaime Caro showed that the more we fiddle around as clinicians, the less compliant patients become. And they showed if you could control blood pressure with just one change, the compliance rates after one year was 93 percent. As soon as you started more changes, a second or third change, you can see the compliance rates drop dramatically.

We see this in other studies, too, where if you start off with an antihypertensive agent and then add a lipid lowering agent later or you do the converse, start off with a lipid lowering agent and then an antihypertensive agent later, your compliance rates are roughly the same. But if you start them both concurrently, the compliance rates are much better. Patients don't like it when we fiddle around too much.

Here you can see control rates for diabetics on a fixed-dose combination versus two individuals, much more adherence to the fixed-dose combination.
And of course, going along with adherence and going along with convenience is going to be a savings in cost for many of the reasons that I think we discussed earlier.

So I think it's very important that we realize that dealing with clinical inertia is something that we're going to have to deal with and we're going to have to take care of, and I think the polypill may add something dramatically important to help us eliminate this problem.

Thank you so much.

Clarifying Questions to the Presenters (cont.)

DR. LINCOFF: Thank you.

The open public hearing portion of this meeting has now been concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

Now, before we actually go to the questions -- we'll now begin the panel discussion...
portion of this meeting, although this portion is
open to public observers, public attendees may not
participate except at the specific request of the
panel.

So before we actually go to the questions
since we had limited time beforehand, are there
more questions, clarifying questions, from the
panel for any of the speakers or for the FDA?

Dr. Kaul.

DR. KAUL: Yes, thank you very much. I have
a question for Professor Rogers. I'm interested in
sort of connecting the dots. You have improved
adherence. You have a rather modest effect on risk
factors. And there seems to be a temporal
influence on the impact on risk factors. At
12 months, you have a greater impact, and it's
somewhat attenuated at the complete follow-on.

Yet the outcomes, even though the studies
were not powered for outcomes, are going in the
wrong direction. Even accounting for the modest
effect on risk factors, one would have anticipated
the outcomes to go in the right direction.
So that brings me to the issue of the quality of the data. Adherence and discontinuation, did adherence account for discontinuation? How did you measure it? How did you account for missing data? What was the temporal trend in the missing data? Did more people drop out in the polypill arm early on, and were they accounted for in terms of the impact on risk factors?

PROF ROGERS: There are a number of questions there, but perhaps if I just start at the beginning. I think in terms of the risk factor reductions, there wasn't any evidence that they attenuated over time. But with those kind of risk factor reductions of two systolic and about .1 LDL, you'd need a clinical trial of many, many tens of thousands of patients to reliably show what kind of event reduction you'd expect with those kind of reductions. And because the main follow-up was about 15 months, you don't get the full benefit until about two years.

So I certainly wouldn't read anything into
that with that relatively small number of events. I don't think -- things going one way or the other, you really need many more patients to look at that reliably.

In terms of data quality, the data quality, the follow-up availability was very high and wasn't differential.

DR. KAUL: In terms of missing data?

PROF ROGERS: Yes, that's right. There are no differential.

DR. LINCOFF: Dr. Sager.

DR. SAGER: Hi. This question is for Dr. Dudl. First of all, really nice work at Kaiser. In thinking about the polypill, obviously, one issue on this pill versus for some people being on nothing, and I think that's really pretty strong in terms of benefit there. But let's say at Kaiser where they'll be patients who are on a polypill, but let's say maybe their blood pressure goals aren't reached.

Would it be useful to have potentially several different doses, realizing that most of the
patients' needs would be met probably with the first dose of the polypill? But still having that option for people who are going to get more intensive follow-up and more careful care, would that still be useful?

DR. DUDL: A really good question. Actually, we've dealt with this for a long time partly because of the thiazide ACE type of thing with a fixed dose. So first of all, not uncommonly, we rig the dose to the allowed to use half dose and still get an effect, especially if you're anticipating that you could go up to the full dose. So we could start with a half, go to one, and we actually go to two on some of our concepts of what we do.

Secondly, it's actually fairly easy if we are on, say, a fixed dose of thiazide ACE and we need more to add a calcium channel to that. So the only problem really seems to be when the pressures are extremely low that we're worried about causing trouble.

But going up and controlling -- and then if
you're using the calcium channel blocker along with this other combination and you're not there, then you break out of the polypill.

DR. SAGER: Right, but if we had a polypill that had, let's say, a standard blood pressure regimen and a more intensive one, again, it would be all one pill, that would probably -- it sounds like that would increase adherence.

DR. DUDL: Yes, and that would be, of course, ideal. And my guess is that if there's a demand for that, it'll happen. And I would hope that it would. Thank you.

DR. LINCOFF: Dr. Fried.

DR. FRIED: Don't sit down because my question -- this is a question for Dr. Dudl. I have some sort of logistic sort of questions. You reported that there was one adverse event where somebody got an outside ACE and was on the polypill. I was wondering, you have this process. Some of the individuals were on either a statin -- could have either been a statin or an ACE at the beginning.
As it gets rolled out to other facilities -- because Kaiser has electronic ability to warn people that they're on two drugs; when you're rolling it out to the underserved areas, the logistics about making sure that individuals weren't on two different, say, ACE inhibitors or two different statins or double a dose of aspirin or something like that.

DR. DUDL: I think that's really an excellent question. We warned them. Because of this event that has happened twice, we do warn when we talk to the people in the underserved. And so far, we have not heard any feedback that we've had further difficulties.

So far the rollout -- of course, we aren't asking that we get every adverse event, but we do ask for any problems that people have had. And so far, we haven't run into that again now that we are somewhat careful about warning them to watch what people are on.

DR. FRIED: But do you think that if you were going to, say, have polypill out in the
market, that that was going to be given the
fragmentation of care outside of a system such as
Kaiser, that that would be more of a problem, that
people would essentially be sort of double dosed?

DR. DUDL: I think it's just a very
important warning. I think the package warning
should be there. I think we should be sure that we
cover that as an issue. But again, we haven't
really had -- had two issues. We took an effort to
correct them. We haven't heard anything more about
it. I don't think that that's a game changer, a
stopper, but I think it is worth maybe noting and a
rollout being very careful.

DR. LINCOFF: Dr. Scott?

DR. SCOTT: This is also a question for
Dr. Dudl. If there was a polypill out there that
included simvastatin 40 milligrams and was based on
a generic pricing for all other components, would
Kaiser use it in secondary prevention?

DR. DUDL: And let me quote inside package
labeling. Absolutely, we would really welcome it.
We have 600,000 diabetics, 150,000 CVD people, 10
and 20 percent better adherence is serious business to us. We really want to use everything we can.

It's hard. It's very, very difficult to get adherence up.

DR. SCOTT: Would you be concerned that you would actually be reducing with compliance with the guidelines for cholesterol management?

DR. DUDL: I'm sorry? I'm not quite following that.

DR. SCOTT: Because simvastatin isn't a preferred -- it's not a high intensity statin, so it falls into the moderate intensity group.

DR. DUDL: This becomes an issue of money. Inside Kaiser, our preferred statin at the present time is atorvastatin 40 with the bundle. It is four times more expensive than simvastatin 40. So if people can afford atorvastatin, we recommend 20 for the low-dose.

But this is not really -- yes, we recommend the best therapy you can afford always. And if you can't afford the best, we recommend you get on some statin.
DR. SCOTT: So even with atorvastatin is now a generic --

DR. DUDL: Yes.

DR. SCOTT: -- and in fact, the branded version is available pretty cheaply now as well. You'd still not feel concerned about --

DR. DUDL: No. Let me quote. I call Costco because they fix their dose or their price increase at 15 percent for drugs, and you can get simvastatin 40 milligrams, 100 for $10. And as of just two weeks ago, I checked again, it's $40 for simva --

DR. YUSUF: Atorva.

DR. DUDL: I'm sorry. For atorva 40. So it's just a matter of funds. I think it's a better drug. It's more powerful, and I'm sure it will come down sometime. So the idea is the best care you can afford.

DR. LINCOFF: Dr. Sager?

DR. SAGER: I think maybe to Dr. Smith, we're going to be talking about what might go into a polypill, so I'd love to get your thoughts on
simvastatin versus atorvastatin. One of them obviously reduces the LDL-C to a greater degree and falls into the more intensive group, but the other one is drug-drug interactions.

DR. SMITH: I didn't hear the question, well.

DR. SAGER: For a polypill, the choice between simvastatin and atorvastatin, one is obviously more intensive LDL-C lowering, fitting into the upper group, but the other one is around drug-drug interactions and your thoughts on that.

DR. SMITH: Yes, the recommended dose for secondary prevention is high-dose, and the qualifying -- between those two statins, the atorvastatin 80 would be the one that would be consistent with the guideline recommendations. Simva 40 would fall in the moderate dose recommendation.

So it's interesting that the WHO has approved simvastatin from 5 to 40 as an essential medication. The 80 would not be -- was not recommended because of the problems with the higher
I don't know how the cost would enter into 40 versus 80, but in terms of the recommendations from the committee, 80 would be the one for secondary prevention unless you're over the age of 75 where the moderate dose statin is recommended.

DR. SAGER: Thank you.

DR. LINCOFF: I actually have a follow-on question for Dr. Dudl. So you said several times it's the best that you can afford. So who is "you," you Kaiser or the patient? The reason I ask is right now you said your preferred agent is atorvastatin 40, which over 75 would be the recommendation. I'm not sure what your preferred agent is for secondary prevention for a 50-year-old who's had a myocardial infarction.

But if the polypill were available with simvastatin 40, would there be a shift within your organization to use that preferentially?

DR. DUDL: That would be a tough call.

Again, when we -- the answer to the question is to whom. Inside Kaiser, we feel that if people have
drug coverage, that we can afford to use the atorva 40. When you talk to the people who pay, that's a really big difference, and so we will move our way down.

Now, the issue is with better adherence at 40, if atorva 40 didn't exist, then we really have a tradeoff, and I don't know how it will go. I'm hopeful that one polypill would have atorva 40 and one would have simva 40 and that we wouldn't have to make the choice. But the other choice then, we'll just to have to weigh what would be the best for the people that we can do. That's the decision.

DR. LINCOFF: Other questions?

(No response.)

Questions to the Committee and Discussion

DR. LINCOFF: So we will begin then -- we'll start with the questions. So we have a long introduction here.

"The Agency has approved numerous two- and a few three-drug antihypertensive fixed-combination drugs based solely on the demonstration that each
component drug contributes to the effect on blood pressure. Aspirin plus pravastatin and atorvastatin plus amlodipine are approved for patients for whom treatment with both component drugs is appropriate.

"The approvals of aspirin plus pravastatin and atorvastatin plus amlodipine were based on demonstration that neither component drug interfered with the other, either pharmacokinetically or pharmacodynamically. Although all of these drugs carry cardiovascular outcomes claims, no study was sought to establish the preservation of the outcome benefit when they were administered together.

"The Agency initially required sponsors of combination antihypertensive drugs to develop, and then approved, all of the reasonable dose combinations, seeking to prevent the combination product from inhibiting titration of each component drug. It should be noted, however, the Agency could not require the manufacturer to market all the approved doses, and some doses disappeared.
"Over the last decade, the Agency has actively discouraged antihypertensive monotherapy and combination doses with effects that were very close together, considering them a nuisance to physicians seeking to get patients to goal.

"The proposal to market a fixed-combination drug composed of aspirin, a statin and one or more antihypertensive drug, which has been termed the 'polypill,' all of which have cardiovascular claims, extends this discussion. While optimal care may require titrating the dose of some of the proposed component drugs to treatment goal, titration requires regular fruitful interaction with a learned intermediary.

"We believe there are patients in the U.S.A. for whom cardiovascular prevention therapy is appropriate but who cannot get the follow-up necessary for titration, for reasons that include geography, finances, and patient preference.

"While it is possible that a manufacturer may decide to market multiple doses of a polypill with various doses of the component drugs, what has
been discussed in scientific literature has been
fixed-dose combinations not intended to be
titrated.

"We are asking then whether people who are
not, for whatever reason, going to receive regular
follow-up are better off on some reasonable doses
of drugs for secondary prevention of cardiovascular
disease rather than none, even if they are not
getting what is believed to be optimal care."

So question 1. And I'll remind you that
when we do these questions -- this
discussion -- this whole panel is supposed to
address the issue of secondary prevention. So
although much of the discussions by the speakers
related to primary prevention from a standpoint,
the FDA really wants us to focus all of our
discussions and answers on secondary prevention.

Is there an appropriate target population
for fixed-dose, untitratable combination drugs to
reduce cardiovascular risk? Do you think you need
to see data establishing benefit in this setting,
i.e., is some type of outcome study required?
Dr. Rich?

DR. RICH: Well, I say the answer is yes, and I have a lot of comments to go with it because I've given some thought to this.

So the first thing that strikes me is that this represents a paradigm shift for the agency in many ways. One is that we've been buying into appropriately personalized medicine, really focusing on the right dose, the right patient, and now what we're saying a one size -- we're going back to a one-size-fits-all and accepting good rather than perfect following the quote, "Perfect is the enemy of good" here.

But the issue that I see is not one of efficacy nor is it one of safety, it's one of adherence, which has not really been the charge of the agency in the past. And so you're asking us to address the issue of adherence, which is kind of a healthcare policy rather than prescription alone.

The challenge of adherence has been a huge PhRMA issue outside of this, right? I think it's a 30-billion-dollar industry. They complain a lot
that if they could just the patients to take their
prescriptions, their profits would go up because
it's so poor.

Then we talk about adherence and
prevention -- I mean, there are areas in this
country where the children can't even get one
injection for a lifetime of prevention, let alone a
pill a day for prevention. So prevention is tough
because you don't see the reward, whereas if I go
to a doctor with a sore shoulder and he fixes it, I
get the reward, and I want to go back every time it
hurts.

So the challenge is huge. We're in a
culture here where the biggest marketing I see is
Big Mac, Whopper, all you can eat, supersize, which
is going totally against what we're trying to do
here today, which is undersize and get better
lifestyle. And then the overweight epidemic that
we face. So all of this really is a
counterculture. Going to a polypill is kind of
counterculture to America today.

The other comment I would say is, with all
of the studies we've seen in other countries, I
don't think they're relevant to the United States
because we are the most expensive -- I think this
year came out from the high income countries, we
were number one again, 300 percent higher than the
other 16. And we were also the worst, number 17
out of 17, in terms of healthcare quality. We've
had this challenge from day one for lots of
reasons.

So what we're saying is let's see if we can
do a better job in terms of improving quality and
monitoring costs. So again, we're going
counterculture.

So I don't think you can compare to a
country that has universal healthcare because we
don't. And in fact, even the suggestion in this
current administration of having a government
option causes convulsions around the world. It's
unbelievable how we would never want to go there.
So we have to kind of look at this country, if
we're going to talk about behavior, which is
adherence here.
The other thing I would suggest then is that we look forward and not backward, not look back to what's been done and try to do it again, but start looking forward to where healthcare is going. So one of the things that strikes me that I think is a big positive is the fact that the Caremarks and the Walgreens are now going to have walk-in clinics.

I think for someone who's looking for preventive care, there's no ideal place better than where you go buy your drug, you go in, no wait. You get your other stuff that you need, and you see your nurse practitioner. And your charge is 10 bucks. And you come twice a year, and you don't need all this kind of testing.

I think adherence would skyrocket compared to going to your private practitioner's office where you've got to drive, and you got to park your car, and you got to pay, and you've got to stand in line, and you get other tests that you didn't even want because that's just kind of the way it's practiced.

Another thing is apps. So Apple had their
big explosion yesterday, but they're investing in healthcare apps. And I think going forward, we should have the polypill app because it can be done at very little cost. And here since I think the statistic is more than 90 percent of Americans have cell phones, and those that have them have it every single day of their lives, that your app could either remind you to either take your pill or tell you your adherence or things like that.

So if you're going to go forward with an outcomes study, I would go forward with where healthcare is going in this country and take advantage of those opportunities because you want to look at how can we get the best adherence to this as possible going forward.

So then the other issue to me is patient engagement. I think Dr. Yancy addressed this, the fact that there is no patient advocacy group here. But my God, it's all about people and their behavior. And I think before you structure your trial, you better get a whole crew of patient advocacy groups here to tell you what the patient
wants because I think we make presumptions over reasons why people don't take their pills, but we don't ask the patient why they don't take their pills. And I think we need to hear that so you can tailor what you're doing better.

In the little things I've read, cost is one issue. Why don't you refill your prescription? I couldn't afford it, simple as that. Why don't you refill your prescription? No one told me. I got discharged from the hospital. No one told me to refill it. They just said here's your medication.

There are so many things that have been documented that we fail as physicians in terms of communicating with patients. We have to start engaging these patients, putting them back in the center of the healthcare universe and let them be part of this because it's in their best interest.

Then the last comment is whatever we do should probably be real world. So I don't think I need a randomized placebo-controlled blinded trial for this. I really want to see an observational study in the real-world settings because we have
enough data to know what the expected rates of heart attack and stroke are in people that are in these risk groups to see if there's going to be a huge change.

Because in the clinical trial setting, it's not real. You've got your visit. You get your phone calls. You have to come show up. They chase you down if you don't. That doesn't exist in day-to-day. And what you show in a clinical trial, you just can't really translate when the issue really here is adherence.

So I would suggest you do a real-world observational study, thousands of patients you can follow prospectively. And I also beg that there be a measure of healthcare costs saved because if you show that you reduce strokes and heart attacks to the point that the healthcare savings to the country is in the billions and billions of dollars, you might even get the government to start a campaign promoting polypill the way they promote stopping smoking, which would just improve the adherence more and more.
So I'd say if you're going for the big picture, go for the big picture because I think some of the data we heard this morning is compelling regarding the potential of what this could do. And I think that the issue is how well can we realize the potential and achieve that as best as we can.

So that's kind of the conglomerate of what I was thinking based on what I heard.

DR. LINCOFF: Dr. Sager?

DR. SAGER: The way I see this, this could really have major public health benefits. I think the lowest-hanging fruit are those individuals who don't have very good access to care, only have intermittent interaction with healthcare providers and aren't getting therapy now. So this is clearly for secondary prevention, which is the focus today, could really add a great deal of benefit to that population.

But even in Kaiser where patients have good healthcare insurance, they may not all have full drug coverage, but many of them do have full drug
coverage, it still had a significant impact on adherence and reducing critical biomarkers.

So I think really this could be widely used for secondary prevention. I would encourage thinking about having some higher doses with more aggressive blood pressure lowering because we wouldn't want people to be put on this who really are having very frequent and very good medical interactions but never get their blood pressure brought to goal. And while one could add other drugs, being able to then go up on the higher dose of the polypill still would be a single pill.

Obviously, patients who've got contraindications to one part of this, have a bleeding disorder or something like that, have to be appropriately contraindicated, but I think this could be widely used.

There were issues brought up about it being used off-target. That hasn't been a big problem. We're not seeing lots of patients receiving blood pressure medications who don't have hypertension. We have quite the opposite problem. I just didn't
really see that as -- I saw that as a theoretical issue, much less of a real practical issue and a concern.

I thought the plans for approaches to PK/PD studies made a lot of sense to me. I don't see a need for an outcomes study. I take the comments that were said in terms of guidelines and being able to have really evidence-based medicine. And while that would be theoretically ideal, I think the fact that we do have lots of studies where these drugs have all been used together in combinations to me is very reassuring, as long as there is not some very major PK/PD interaction.

Some type of observational database, be it electronic medical records or some other approach, that looks at safety as well as efficacy on biomarkers I think would be very nice to have, but I think this could really be a real major advance and could be very widely applicable.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMAS: I think the argument for secondary prevention is obviously so much more
straightforward, and I think the FDA's plan outlined for a minimal pharmacology-type approach is all I need to move forward in the secondary prevention indication.

I think it would be a mistake to demand outcome studies that would be inevitably small, under resourced, underpowered, and run the risk of giving erroneous answers. There's just not going to be the resources to do that kind of outcomes study to prove with a level of confidence what we would want. And I think those sorts of studies can happen after the drug achieves a modest level of regulatory approval in the implementation setting.

I think the way to figure out how to use these is to license them, get them out there, and then let healthcare systems figure out how they fit, whether they offer advantages from a cost standpoint, an adherence standpoint. But I certainly wouldn't need that to be approved.

I think the target population is obvious. It's anybody who's taking individual components who wants to use this instead. And then where I
practice, there would be a sizeable minority of individuals who have poor follow-up and would not be good candidates for the individual components that I might select this for a priori.

So I think it would be used. I think it would be individualized. I think the bar should not be set high. And I would also say that even from a guidelines standpoint, my concern with the evidence base for guidelines is that it rewards the deep-pocketed pharmaceutical companies.

This is never going to -- I shouldn't say never, but I find it unlikely that this will ever get the size of outcome study, given what this drug is likely to sell for, that would ever lead to that sort of evidence base. But I would hope that if the adherence data looked good, that it could achieve a high level of evidence.

DR. LINCOFF: Dr. Wilson?

DR. WILSON: I agree with everything Jim DeLemos just said. But I would focus a little bit more on what Dr. Rogers showed, this tremendous difference for people who are not doing well. And
I think that's where we need more data, and that's where this may really help all of us who care both for individuals and care for populations.

I share his enthusiasm for making the path simple. Let's keep it simple so that we can really get a polypill program going in the United States. This is happening elsewhere, whereas we should be involved. We should have some programs going.

I think what we really could be planning for is a phase 4, not a phase 2/3 type of project, but a phase 4 comparative efficacy. And once we have some experience, to know exactly where that pointed efficacy is so that we can satisfy our needs for guideline development as we move forward in the years to come.

DR. LINCOFF: Dr. Scott?

DR. SCOTT: So I really like the idea of the polypill. What appeals to me is simultaneously optimizing treatment across several different axes of risk management. And I don't think we need outcome studies to show that any one proven dose and drug to another shows benefits and outcomes.
What I am concerned about is the choice of what goes into the polypill and the lack of titratability and whether we might be also simultaneously creating suboptimal management across several different axes of risk management.

So I think that there is a number of patients who do take their drugs regularly who are titrated to goal, and what might we do to those patients if this is available? So I think that there does need to be some demonstration, perhaps in a simple study in real-world application, to show that we don't actually make management of these patients worse.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: Well, I have to say that I read all these papers, and I actually did not find the evidence in any of them to be overwhelmingly positive. And I thought the safety evidence in most of them was limited.

I think we have to be careful. I think this is a huge paradigm shift. I think the FDA's responsibility, in my opinion, extends beyond just
saying these drugs don't interact pharmacokinetically because the reality is it's going to have an effect on our public's health.

You could think of lots of unintended consequences in our healthcare system, not in India, not in any of these other places. Someone's told to stop their aspirin, and they stop the entire pill. And all of a sudden, their blood pressure is 210 over 120, and they have a stroke. Or they go to a doctor and just say I'm on some pill, I'm not sure what it is, and then they get doubled up of whatever's in the polypill.

I am deeply -- I guess I shouldn't worry about it because none of my patients should ever get this pill, but I'm concerned about a very huge subset of the cardiovascular population. We have like no data on whether this is a great idea for them, particularly lowering their blood pressure below a certain level. There's a lot of on target. There's a lot of data to suggest that that may not be good for their kidney.

So I think that it would require more than
just the pharmacodynamics and pharmacokinetic studies. I think that we would have to -- and I don't know that it's our job. I think the fact that it's so hard to even think about how you would design this study suggests that there is an issue that bears study. So that's what I think.

I will say one other comment that hasn't been made. Having recently been filling a pill box from seven days a week for someone that has a lot of pills, you would reduce the error rate. We don't ever talk about that. We talk about adherence, but it's really hard to make sure that you've got exactly the right pill, and when you're putting a lot of them in, it is really hard.

So reducing the -- I like the polypill. I'm not against it, and I would have loved to have had it the last month. But I think that we don't know all the unintended consequences. I'm concerned about that.

DR. LINCOFF: Dr. Temple, you have your light on, does that mean --

DR. TEMPLE: Well, I remain curious about a
lot of things here. Presumably, if there were a product like this, it would say if the drug is intended for people who have elevated blood pressure that needs treatment, whose lipids need treatment, and who need to be on aspirin because they need to be on aspirin.

If one were to try to carry out a study in that population comparing, say, the polypill with individual therapy, maybe the polypill would work a hair breadth better. But if you were responsible in talking to the patients and telling them how important it is to take their drug, I almost guarantee there's no going to be any difference. Why would there be? They're the same drugs. People already take them all together.

So I'm a little interested in what kinds of studies people would actually do, but let me just finish my first thought. If it were labeled that way, I think the presumption -- and that's where the question comes from -- is, is it possible that some of the people would be put on this would turn out to be people who don't show up for -- whose
doctors don't want to see them very often or who don't have enough money to come to the doctor? Of course, then I don't know how they'd get their prescription refilled, but leaving that aside.

I think the thought was that maybe there are some people who are inherently not as good about their therapy as others who might benefit from having this product because maybe they would have all their stuff in one place and they wouldn't have to come back a lot or something.

But the basic nature of the combination is not fundamentally different from what we've already done, as Norm explained. We have drugs that do both things. We have aspirin combined with other stuff. We have multiple drug, including three drug, antihypertensive combinations.

So it doesn't seem that different. And what I think people are worried is sort of unexpected behavior as a result of this availability, which is not easy to test for. So I'm just trying to figure out what tests we -- which of Dr. Rich's tests are they going to do? How would they do it? How would
you do a test of any of this stuff?

By the way, if the study is an epidemiologic study, I'm not prepared to believe the people who get one kind of treatment are the same as the people who get the other kind of treatment, so I'm very worried about that.

DR. LINCOFF: I want my opinion on this topic. I agree with Dr. Lewis. I think there are substantial concerns, but for the reason that -- in the secondary population, we're talking about a population for which at least the statin dose has pretty good guidelines. And you'd want -- this is not a population where you'd want to settle for second best because you know that you're focusing on a group for which you have pretty clear data regarding dose superiority, not targets of LDL, but dose superiority.

So the initial premise of whether or not -- if there are people who aren't going to get care any other way, would they be better with a polypill? Of course, they would. How can that be a question? Something is always better than
nothing. But this is a population for which intensive is better than something, and so you'd want to know that the right polypill was being used for this population.

Short of that, though, the hypertension data, the half of max dose plus another one, gets you most of the way. There you've got a little bit more in the way of assurance that you're probably not going to be too far from goal.

So to me, the biggest issue is that I wouldn't want to see a polypill with a less than optimal dose of a statin for a secondary population. And then depending upon if it were ever extended later to the primary population, that becomes a lot more difficult.

I also don't think that trials are going to be practical here because by the very intrinsic definition of a trial, you have follow-up of patients and you have more intensive -- every study that's been done that looks at it, the control group of trials do better than patients who aren't in trials.
So the very patient population that you'd be aiming this at, the patients who wouldn't follow up or can't follow up or whatever, are going to be either excluded from or artificially treated in the trial anyhow. So I think we have to take on faith the outcome because we know what these drugs do and try to decide how practically to target it.

Dr. Rich: But to continue the debate, the data that I heard was that intensive one-on-one care is a short-term success and a long-term failure. And so if you're going to make the polypill prescription so complicated that you have to come back to the office every two weeks for the first two months, you've already failed before the train left the gate because we were being told that these are patients typically that don't want to keep coming back. And the more you fiddle, the less they're going to take it. And the more you make them do this, the less you're going to be here.

So the argument is that having them on something simple is still better than the perfect
prescription. And so I think the concept that I've listened to I think is rational, is make it as simple as possible.

So you have a couple of versions, one with a thiazide, one with a beta, whatever it is. It's secondary prevention. You could take your best guess as to what to put in A, B and C, but then you want to -- again, I can't stress, patient engagement. You want the patient to say I'm willing to do this even though it's not going to make me feel better. You claim I'm going to live longer, but we will never know if that's ever going to be true, right, of course?

But I hate coming to your office. I hate getting in the car. I hate doing all of this. I hate taking all these pills. And so you go fine, fine. Still, this is good. It's not great, but it's good. And good is still better, and it's still going to be beneficial.

I agree with your issue about the clinical trial. That's why my suggestion is do observational, collect data to see what's going on
because it's not good enough to say it's approved, it's out there, and not know what impact it had.

I think when you're talking about something like this, which is epidemiologic to affect the American population, you need to have data to know whether it had an impact or not.

DR. LINCOFF: Ms. Arkus?

MS. ARKUS: I am a consumer representative, so there's actually two people here that represent patient communities. And I particularly am interested in women and heart disease and the definite need for tailoring medicines in the personalized way for the female human body.

As I understand it, the statins do respond differently in women. Women are more sensitive. Their livers are affected by the estrogen as men's are by testosterone. So we have to look at the personalized medicine and not just a polypill that just maybe will include women's dosages or not.

There's been cardiologists that have come to our organization, Women's Heart Foundation, complaining that women are very sensitive to
statins and what do they do, do they give the medicine every other day? I mean, there's a real dilemma out there already. So that's my concern.

What is the consumer hearing on TV about statins? Well, you have Dr. Oz interviewing people like Steven Sinatra who say, well, if you look at the Framingham study, what have we learned? We've learned that people with high cholesterol levels live longer, healthier lives.

So I'm hearing a lot of different information about cholesterol levels and statins and what's the right path. So it is subject to interpretation by many. And we hear more and more about women and heart disease and also the statins that are misprescribed, and Dr. Barbara Roberts who wrote "The Truth About Statins," is opening a lot of questions, and unanswered questions, about why doctors are ordering statins for women that are perfectly healthy and do not fall within the guidelines for need for this drug.

So those are consumer concerns that I have.

DR. LINCOFF: Dr. D'Agostino?
DR. D'AGOSTINO: This morning I was asking the question about we know a lot about these drugs already and how they're viewed and prescribed and so forth, and the answer is clearly yes.

When we look at the question, it doesn't say a fixed-dose untitratable combination drug. It says -- what I'm reading is a potential set of these fixed-dose drugs. And I think the discussion with the individual patient doesn't have to go on forever and ever, keep bringing them back.

I think that's part of the key here is that we know a lot from the literature in terms of what the doses should be. I think the cholesterol guidelines, as you point out, made comments on, and we know quite a bit about the combinations of drugs with the antihypertensives. And we have to worry about the different female situations.

But I would envision this to be a small set of combination drugs which you try to zero in very quickly and get the one that you think is best, not taking months and months to do it.

As far as a follow-up and so forth, I would
think that being a statistician -- I want to stay employed -- that we'd want to put together some kind of studies where you would follow the individuals. But the more complicated you make it, the more useless it's going to be, and I think the higher it's going to be. But you will be making these prescriptions and so forth in hopefully these individuals that you will follow, and they'll be adhering, and you can get good data on that very quickly.

DR. LINCOFF: Dr. Kaul?

DR. KAUL: Well, thank you. I think the concept of combination poly pharmacy using the fixed-dose drugs is intuitively very appealing to me. But I must agree with Dr. Lewis that the current body of evidence does not appear to be strongly supportive of the polypill hypothesis. When I scrutinize whatever information is available in the public domain, there are two clear sets of messages I get.

In short-term follow-up studies, which are primarily done in primary prevention cohort, you
get large treatment effects in terms of risk factor
modifications. Yes, they were not designed to
study adherence, but when you look at longer-term
studies, which were done primarily in a mixed
population and one that was exclusively secondary
population, the FOCUS study, you do see improvement
in adherence, but the differences in adherence
rates are not very overwhelming persuasive, granted
that the comparator arms had high compliance rate.

But when you look at the risk factor
treatment effect size, it is quite underwhelming.
And so the key question to me is that, yes, it is
not strongly supportive, but is it sufficiently
supportive for the regulatory decision-making?

I think there are three elements that come
to the mind. I am interested in making sure that
with these fixed-dose combinations, there is not an
issue about pharmacokinetic interaction, so
bioequivalence studies can do that. There's not an
issue about pharmacodynamic interaction, and
therapeutic studies can do that. We don't really
require large outcome studies.
Then there is a concern about safety. Ultimately, we should not view these drugs as a tool for improving adherence. We're interested in improving health outcomes. And so the safety studies, in my opinion, can be conducted, as Dr. Rich suggested, in some sort of a phase 4 observational study.

So those are the things that I would require before the FDA moves on it. And I am reassured by the fact that there is a large body of trials, nearly 25,000 patients focused on primary prevention cohort, that will be coming out in the next few years, and that will be quite informative. So I think that, yes, we need to recalibrate our expectations of treatment outcomes that were derived based on rosy predictions of modeling exercises done 10 to 12 years ago. But nonetheless, I do see a path forward for the regulatory agencies to make decisions based on the current body of evidence.

DR. LINCOFF: Dr. Flack?

DR. FLACK: One, I like the concept of the...
polypill, and I certainly recognize the huge paradigm shift. What I would say is target population that I could see it used in, one is in people who literally have already achieved pretty much control, and for convenience, you switch them. I think that's the easy low-hanging fruit. People who are either documented to be non-compliant or highly suspicious of being non-compliant could actually be shifted over to this.

I think ultimately, though, you're going to need -- even though you're not necessarily titrating, you're going to need a range of doses to be able to effectively be sure that you're giving people adequate treatment. On the other hand, if you've got a polypill and you need another blood pressure drug, you can add it. And there's nothing that prevents you from doing that.

The government is broke. Nobody wants to pay taxes. Private industry is broke and got money sequestered all over the world. Nobody is going to pay for all these huge outcome studies that we're kind of demanding. So at the end of the day, I
think we're going to have to take the individual components as long as there's no interaction, deleterious interactions identified, accept the fact that putting them together does not automatically create some magical risk that doesn't already exist in the prescribing population.

Then try to get some data -- and I agree, get some real-world data on if people are, for example, already controlled and shifted to a polypill, do they maintain their control? And conversely, if they're uncontrolled, if you put them on there, do they actually improve their level of control?

Finally, I would say that the tough animal in this treatment of the polypill is going to be the blood pressure. The blood pressure is harder to treat, I hate to say, than the lipids. You can throw a statin at somebody and you get them on 10 of atorvastatin, and you've got a pretty good chance of getting a dang good response.

On the flip side, blood pressure is not that way. And I think a three-drug polypill with a
evidence-based diuretic use like 15 of chlorthalidone in there really minimizes the
difficulty that practitioners have in putting
together effective combination antihypertensive
therapy. And so I would like a three-drug polypill
with a chlorthalidone-like drug in all.

But at the end of the day, I'm not going to
say that somehow I know that putting these drugs
together that are already out there and used in
combination, if you can show there's no deleterious
interaction, is somehow magically going to create a
problem. But I do think that we need real-world
data but not necessarily outcomes-type, phase 3
clinical trial data.

I love clinical trials and I love evidence,
but sometimes there's an infallibility about
clinical trials that we don't recognize and don't
acknowledge, that that's not the answer to
everything. And these are proven drugs, and I
think that I agree with the people who say that we
can not necessarily do outcomes trials but we do
need data with this. But I think we can collect it
in a more parsimonious, economical manner.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: Okay. You guys are going to beat me down soon, but the NIH does do research. We're doing the SPRINT study, and we're providing antihypertensives compared to goals. No pharmaceutical company would do it. The study is getting done. It's going to have 10,000 and some people, and we're going to look at cardiovascular outcomes.

If this is so important and is potentially going to be a paradigm shifter to make everybody have so many less heart attacks, it seems like it's something that someone could approach the NIH about studying. And I do think it could be studied.

However, just to play the devil's advocate, if you studied it -- and I think this is a complex study, but you could provide -- usual care is not free drugs. You could provide the free drugs. You could provide the polypill. You might discover that people have some sort of side effect to the polypill and stop it altogether, whereas the
titrated drugs that are providing for free, they
stop the one that bothers them and continues the
other three.

There are a lot of aspects of it that I
don't really think we know. I don't know that the
right answer is to throw your hands up and just say
no one will ever fund this, therefore, we should
make this available.

We don't know who this drug is going to be
used in. It's a single drug. What if payers
decide this is a cheap single drug, this is one
we're going to pay for, and individual drugs are
now on a higher tier? What if, what if? Well, how
do you know?

DR. LINCOFF: Dr. DeLemos, you happen to be
next.

DR. DELEMOS: I think there are very valid
issues that adherence is going to be all or none
with this as opposed to -- you know, you're either
adherent to all four drugs or you're adherent to
none with this pill.

So I think that's a totally valid point
about the concerns if somebody goes to the dentist
and the dentist stops the polypill or whatever
might happen. But that's just individual patient
education, physician behavior. I do not think
we'll learn about that through real-world studies.
We're just going to have to deal with it.

I think the one thing that everybody agrees
on, though, is that there are concerns about the
dosing of statins. And we would probably all agree
that at least 40 milligrams of atorvastatin, maybe
80 milligrams, should be the statin component. And
we would all agree that low-dose aspirin would be
the preferred aspirin dose.

So I think you could come in this -- forget
what's already out there, but the FDA could come at
this by saying we're interested in these
combination products, but we're interested in
making sure that our patients don't suffer statin
disadvantage. So we won't consider products that
contain anything less than a 40 milligram
atorvastatin equivalent and have a baby aspirin.

Then what those other components are, I
think is up for debate, and there may be a variety of components with beta blockers and ARB or ACE diuretic combinations. But I think you could set a bar that says we're just not going to consider an inferior statin because there's no reason to. Atorva 40 is generic. It's cheap enough to put in the pill, and if nobody's making it, they should make it if they want to get in the U.S. market.

DR. LINCOFF: Dr. Sager?

DR. SAGER: In terms of coming back to Bob to your question about clinical trials, I'm really comfortable with what the FDA's proposed. I don't feel -- I feel these are drugs that are well known. They're going to be prescribed for people, ready with the indications. And of course, there will be some people who develop side effects and will seek medical attention, I hope, instead of just stopping them, but that's what happens today. And I don't think this is any different than what happens today.

In terms of a study, I wouldn't -- if someone wants to study this post-approval like the
NIH, that would be a very interesting thing, but I don't think that's something that should hold the regulatory process. That should be separate from the regulatory process.

DR. LINCOFF: Dr. Scott?

DR. SCOTT: I also wanted to come back to the clinical trial aspect, and I don't think it's that hard. You could take a large number of patients and randomize them to switch to the polypill or tell the physician to continue to titrate and manage their risk factor as they normally would. It would have to be very low touch so you're not disturbing the normal practice. You could follow up the outcomes through electronic medical records if you do it in the right places.

But personally, I would be impressed by whether they continued to meet the same levels of risk factor modification. And I don't think it has to be better, it just shouldn't be worse.

DR. LINCOFF: Dr. Leighton? Ms. Leighton?

Sorry.

MS. LEIGHTON: That's okay. I'll take the
DR. LINCOFF: I'm not sure it's a promotion.

MS. LEIGHTON: Okay. First I'd like to thank Dr. Rich for his comments about patient engagement because that is absolutely critical to this issue. Bottom line, we're the recipients. We're the ones that are going to be taking this drug, so it's very important that we're engaged in the process.

As far as adherence goes, we all know adherence is better when you're in a clinical trial. Patients participate when they're in a clinical trial, so that's not showing us what's happening in the real world.

So I think the idea of an observational study, probably post-approval or whatever, would be an excellent idea because we need to know how patients are going to use this drug in the real world.

There is funding out there that's available for those kind of studies. For example, the PCORI funding for patient engagement studies, for
patient-centered outcomes research that goes
directly to this point: Is this better than the
other treatment? Are patients going to be treated
with this? Are they going to comply with this?
Are they going to adhere?

The second thing, it would greatly help us
with an observational study like that, would be to
help us identify are patients really participating
in risk reduction and lifestyle changes if they're
on this medication or do they see this a panacea
and say, hey, I've got this pill, now I don't have
to do any of this. So that would help us engage
our communities and help them understand what the
outcomes are for them. Thank you.

DR. LINCOFF: Dr. D'Agostino?

DR. D'AGOSTINO: Actually, the comments I
was going to make have been made in the last two
speakers.

I don't view this as a clinical trial that's
going to be put together to see this. We're
talking about -- specifically it says an
appropriate target populations and so forth. These
may not be the populations that want to be randomly
assigned to some sequencing of titration and so
forth.

I do think it shouldn't be an impossible
task to do an observational study, NIH funding,
some other, or drug companies funding it and so
forth in arrangements with the FDA and the drug
companies to do some of these things. I think
they're quite sensible, and I think they'd be very
informative, I think actually would be very
important; that we just can't say we know about the
particular drugs, let's put them together in a
package, and then forget about it. Let's see how
successful they actually are.

DR. LINCOFF: Does anyone think that perhaps
some sort of cluster randomization or randomization
based upon the site in vulnerable populations would
be -- I'm sorry. Dr. Wilson?

DR. WILSON: I was going to say as you get
closer to -- the difference between trials and
observational studies is potentially to do a site
randomization, a comparative effectiveness trial,
which is almost observational and you don't get as much drop in and drop out because it's done at a site level. You have to go to a totally different site.

DR. LINCOFF: And at the site, normal care can be normal care. It can truly be normal care, and you could randomize what each site does. Obviously, they're various structures, but that might be an intermediate step.

Dr. Temple, you have your --

DR. TEMPLE: Well, there are some interesting problems. Under HHS rules, if you can determine that this is a minimal risk protocol because all of the therapies are all right, you don't have to get individual informed consent. But it's not clear that we can do that with studies directed at our use, but we're actively thinking about it and trying to work it.

Cluster randomization with individual consent sort of defeats the purpose of it. I'm not sure you can really get it. So posting something in the lobby is an alternative.
I had a question to ask. There was some discussion about primary versus secondary prevention. And although that's a problem for aspirin because we're not persuaded about the primary prevention, the other treatments, antihypertensive treatment and lipid lowering is very well studied as primary prevention. So is that a problem for anybody?

DR. LINCOFF: I'm told the problem was that we're not allowed to talk about primary prevention --

(Laughter.)

DR. LINCOFF: -- because this committee has not been vetted for primary prevention so if we --

DR. KAUL: How can you not borrow information from well reasoned --

DR. LINCOFF: Obviously, we receive data, but our discussion is supposed to -- our opinions are supposed to be confined. But you know what, you're the boss. If you'd like us to talk about --

(Laughter.)

DR. TEMPLE: Don't talk about it, but I will
say that trials of antihypertensive are typically not in people who've already had a heart attack or stroke, and there are plenty of statin trials in people who haven't had either of those two. So you don't have to say anything.

DR. D'AGOSTINO: I thought that was the second question actually, going to different populations.

DR. LINCOFF: I've been told very clearly that we're not -- since we've not been evaluated for conflicts, et cetera, on the primary prevention, we're not allowed to talk about it.

Dr. Rich?

DR. FRIED: Unless you don't want to talk about it.

DR. RICH: Just quickly, why wouldn't a strategy making this a post-phase 4 study, but contingent upon the phase 4, and combine together FDA, NIH and industry -- so NIH could get kick in what they want to, but they would be entrusted in working with you for the protocol. And industry, which is going to give the drug, will fund the bulk
of the study. And get what you want going forward and say we'll approve this polypill contingent upon commitment to a phase 4 so it's win-win across the board. You're getting your information. You're getting your drug approved. You're getting funding for it.

DR. KAUL: But that does not necessarily --

DR. LINCOFF: Wait, wait, wait. We can't have a free-for-all. Dr. Temple?

DR. TEMPLE: Well, if we thought it was necessary, we could ask for postmarketing studies, especially related to safety. And what Dr. Lewis was talking about was concerns that people would abruptly stop all of their medicines except the one that was really the problem or that there'd be some kinds of safety problems of that kind.

I'm having a little trouble figuring out what all these studies are really designed to detect. That would have to very carefully defined, obviously. But if we eventually concluded something was necessary, there are ways to impose either requirements or commitments, especially
related to safety.

DR. LINCOFF: Some of this is the topic of question 3.

Dr. Kaul, did you want to make a comment?

DR. KAUL: Sorry. I was going to say the same thing. It's very difficult to envision a trial design that will address Dr. Lewis' concerns about zero versus 100 percent compliance other than in a real-world setting. And in response to you, it still doesn't absolve the sponsor from doing the appropriate or required PK/PD studies. I don't think that has been systemically addressed.

DR. RICH: No. We're not saying that. We're saying to get approval. And certainly under the guise of safety --

DR. KAUL: The observational study.

DR. RICH: -- because you'll collect the efficacy and the safety at the same time.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: But you wouldn't believe it. That's the problem. You've got tens of thousands of people that have gotten all these drugs in
combination before from a safety standpoint, including in the at-risk populations you're talking about. And some medium quality NIH combination funded study that ends up looking at this after the fact is not going to provide more definitive data than what's already out there. I just believe you don't need it.

That doesn't mean that you don't need to figure out how to use this in practice. We absolutely would. But the idea that we don't know enough about the safety of these drugs in combination doesn't pass muster to me because we've done all these studies. And they're all better than what we would do postmarketing here with the polypill, I think. They're all more definitive. They're larger. They've enrolled -- anyway.

DR. LINCOFF: Dr. Flack?

DR. FLACK: The one caveat is that these are high-risk patients, and the unintended consequences are certainly possible. And so I would be in favor of actually doing this kind of observational-type study, not necessarily to replicate, say, what
already has been done. I think safety is an important part of it. But now you've got all the medicines sort of in a single pill.

My patients quit their medicines. They think they're having a side effect from one drug, and about 80 percent of the time, they stop the wrong drug. It's either side effect is probably not drug related or if it is drug, it's probably another drug. And maybe 50, 80 percent of the time, they're wrong.

So here you've got a group that's really high risk, and so the stakes are actually higher. And I think that with this new paradigm, I would be more comfortable with not assuming that just because we know the drugs and are willing to put them together and approve it that we know all the behaviors and consequences of those behaviors once it gets out there.

So some of the kind of studies I've already talked about, and others, I think would make sense in an observational way to try and gain information that perhaps we don't know from studies that have
never put all these medications together.

    I think it is different. I think it's interesting, maybe even exciting paradigm, but I want to kind of look at it 360 before I just said, yeah, yeah, we know everything because we know the individual components, even though I feel really comfortable about seeing a pill like this and getting approved.

    DR. LINCOFF: Dr. Unger?

    DR. UNGER: Well, pursuant to what Dr. Lewis said -- and Dr. Lewis talked about the potential for patients to stop all three drugs because of a perceived side effect -- the converse of that is that patients are going to get double dosed with things. We have a big problem with acetaminophen and liver toxicity because the common cold preparations contain acetaminophen. Patients didn't know. They took Tylenol, and they just destroy their livers.

    So you're going to have people on the polypill who are going to get started on warfarin, and they're going to bleed. And oh, there was
aspirin in the polypill. So that kind of stuff is going to happen.

So I think that if the group were of the mind that using a combination of three pills together that is the same as the individuals, that there wouldn't be a difference in safety or efficacy if everything were perfect.

Then the issue is kind of compliance/saturation versus mishaps. And the mishaps I think are medication errors and people non-compliance, double dosing, all those things I think are the downside that one might want to measure.

Then getting specific about the cluster randomization, I think that would in some respects mitigate the risk of double dosing things because everybody would know, whereas the phenomenon I think many in the room are familiar with is when the patient comes to you with a Ziploc bag, here are my medications. But they're not the same as the bag that they brought the last time you saw them.
It turns out they got this heart pill. They were on it for a while, but they stopped because their neighbor heard something on the Internet, so they stopped it. But they still have it, and they started taking it again. That's the kind of stuff that happens in real life, at least it used to happen with my patients.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: Well, I just wanted to respond to Dr. DeLemos. So I wasn't trying to imply that I didn't think there was enough safety data on using these drugs in combination. But that's not why this pill is going to be developed, right? Because these drugs are already available and being used in combination, and so we believe they're overall safe.

This pill is being developed because there's a hypothesis that it will improve the health of the nation by improving adherence to the drugs. And I think that that's a different -- so I wasn't worried that what you said, that the four drugs together were going to be unsafe. I'm worried that
I don't know, since we're not approving this drug because it's the only way you can get these four drugs. We're approving this drug, or they would be approving, or somebody would, because they believe it's going to improve the nation's health.

So I just think you have to be sure that that's the case, that it isn't actually going to make more people not get titrated who really would have if this simple thing. It's not only going to be simpler for the patient. It's going to be simpler for a lot of doctors.

We have no idea what all those impacts are going to be, and I do think that there's a lot of room for errors. And there are right now, too.

So anyhow, it wasn't like I thought what you guys were doing was bad and not proven yet.

DR. LINCOFF: Dr. Fried?

DR. FRIED: What I was thinking of was actually sort of said. I actually think that the issue is how it's implemented because not only -- if you have a group of three pills, a physician also has to think about whether or not
there's an individual contraindication to any of them, and are you going to be putting somebody on this polypill because you think it's going to benefit them and you're ignoring the contraindication, you're ignoring the drug interactions with their other meds for one of the three components.

We see individuals -- I see a population with very difficult to control hypertension, and it's not uncommon. They're hypokalemic because somebody didn't recognize that they're on a thiazide and a loop diuretic because people have various combination pills.

I think that as you get into a population that becomes more and more complicated, you get more and more -- you might actually increase drug interactions, increase problems, particularly if someone's not aware of what's in it. If it becomes branded, then people may just think, well, I'm on this brand and not realize what the components are.

DR. LINCOFF: I'm supposed to summarize these.
(Laughter.)

DR. LINCOFF: So my best attempt at that is as follows --

DR. DAVIS: Can I get a chance to comment?

DR. LINCOFF: I'm sorry. Certainly. I didn't -- Dr. Davis?

DR. DAVIS: Yes. I like the concept of a polypill. From what I've heard and from what I've seen, it seems that it would be applied to the population that would need those different medications to treat the conditions and is a secondary prevention.

What's been said about personalized medicine I find very interesting because I think the polypill would actually make personalized medicine a little more inclusive. Both the patient and the physician would have a new option as to how to treat.

I think I always would like to see a clinical trial. Like Dr. Temple, I wonder what kind of a clinical trial this would be. I've heard ideas about having a cluster trial or treating one
group versus another to the titration. And I worry about the size of such a clinical trial. But I think at the very least if that isn't done in some way in a phase 4, that data should be collected, and you have to think long and hard about what kind of outcome data would be collected.

DR. LINCOFF: Anyone else that I neglected?

(No response.)

DR. LINCOFF: So to summarize then, I think there's agreement that this potentially could be useful. In general, there seemed to be agreement that we didn't need outcome study, but some dissent, particularly with concerns regarding safety, either regarding suboptimal therapy, double dosing, drug interactions that may not be expected or anticipated because of not recognition of what drugs were actually in there, whether or not all drugs might be discontinued.

So some concerns that there might be some need for some sort of outcome study that would incorporate these potential -- the assessment of these potential risks.
Others felt that we'd want some data regarding improved compliance or control of risk factors, but emphasizing the difficulty in making this real world and how that would be important to identify the potential advantages of this sort of therapy.

It was noted that blood pressure may be the most difficult component of this to get adequate control and that for secondary prevention, we could sort of establish the baseline in terms of what the aspirin and statin dose would be need to be and then other variations within that, and some ideas for how outcome studies might be developed, including site randomization, federal funding with PhRMA or perhaps observational studies.

So now we have two more questions, but we have a break now. We will now take a short 15-minute break. Committee members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 3:15 p.m.
DR. LINCOFF: All right. Let's maybe get restarted, please.

We'll move on to the second question. So is it likely that such therapy would be attractive only to the population for which it is intended? What are the public health consequences of the use of such a product in patients who could be getting care in a "optimal" setting? Do you think that you need to see data bounding this risk? What, if anything, needs to be done to mitigate this risk?

Who would start? Dr. Lewis?

DR. LEWIS: I wonder if someone could define who the population is that we have currently identified. Is it that poor people who don't want to come to the doctor very often? Or who is that population we've identified exactly?

DR. LINCOFF: I think part of the issue is for us to make that suggestion.

DR. LEWIS: I thought that the first part of the question implied there was an intended population. I was just trying to figure out what
was the definition of the intended population.

DR. LINCOFF: So the text before the question begins said, "We are asking then whether people who are not, for whatever reason, going to receive regular follow-up are better off on some reasonable doses of drugs for secondary prevention of cardiovascular disease rather than none, even if they're not getting what is believed to be optimal care."

But I don't believe that's meant to be an exclusive potential target population. I think part of what the FDA may be asking is for us to suggest who we think would be a good target population.

DR. STOCKBRIDGE: I think you had mostly an option in question 1 -- we can revisit it -- to say whether or not you thought that was a reasonable indication, population to indicate the product in. And then in 2, we deal with the issue of off-target use.

DR. LINCOFF: So for whomever you think it should be targeted, are you concerned that it would
also used in people that you don't think it should be targeted? And if so, is that bad? And what would you do to prevent that?

DR. LEWIS: I think we maybe didn't do our job in the first question. We didn't identify the target population.

DR. LINCOFF: All right. Well, we can go back to the first question.

DR. LEWIS: If you think we did, just tell me. I can't tell you if I think it would be bad if it would be used in off-target people if I don't know who the target people are.

DR. LINCOFF: All right. Then let's go back to question 1, please. In effect, so let's -- as an answer to this question, I invite you to define who you think this should target, and then from there.

Dr. Rich?

DR. RICH: I'm under the understanding that we're talking about secondary prevention.

DR. LINCOFF: Yes.

DR. RICH: So anyone who qualifies for
secondary prevention because they've had a previous stroke or MI is the targeted population.

I would not define it based on socioeconomic issues or anything else beyond that because I don't see what's wrong with a private physician prescribing it any more than going to a clinic and getting it from a nurse practitioner.

DR. LINCOFF: So you in effect are saying there is no population -- we're only talking about secondary prevention in this meeting. So in that, you're thinking anything would be --

DR. RICH: No. I think we know so little about adherence that for us to make presumptions to say you look like the type of patient who are not going to be good at adherence, I'm giving you a polypill. That's ridiculous.

DR. LINCOFF: Dr. Sager?

DR. SAGER: I think this is kind of going over where we went, but it seems secondary prevention for the people who would normally be indicated for these medications. And I'm not very concerned about off-target use. There may be some
people who are given it off-target, but I think the
main problem we have with these medications is that
they're being underutilized, not over-utilized off
target. So I don't see that as really a very big
issue.

DR. LINCOFF: Dr. Fried?

DR. FRIED: I agree secondary prevention. Another group where I might add it might be, for
example, sort of the ones where you can argue if
it's primary or secondary, sort of the
moderate-risk diabetics who have an indication to
be on these drugs anyway even if they haven't
already had a coronary artery disease event.

DR. LINCOFF: Dr. Temple, you had a comment?

DR. TEMPLE: Well, I remain confused. It
would be indicated presumably for people who are
both hyperlipidemic and hypertensive and secondary
prevention, okay, because we're staying away from
anything else.

So what would the off-target be exactly?
Someone who doesn't -- who isn't hyperlipidemic?
They just throw them on it? I'm not advocating.
I'm just wondering.

DR. LINCOFF: First of all, I think that's part of the question. Second, my understanding of the word "secondary prevention" is that it means that they have the event you're trying to prevent. And what we're trying to prevent is cardiovascular disease or stroke.

So I'm not sure hyperlipidemia or hypertension, although that was actually brought up by one of the other doctors about what we're really talking about in secondary prevention. So I guess we could also try to define that.

DR. TEMPLE: So the off-target would be primary prevention --

DR. LINCOFF: Well, I don't know or --

DR. TEMPLE: -- which we can't talk about.

DR. LINCOFF: No, because one could say -- and I'm not saying this, but one could say that I intend this only for patients in poor socioeconomic situations that they're unlikely to get regular follow-up, and that --

DR. TEMPLE: Not likely to be included in
labeling.

DR. LINCOFF: But that's your problem.

So if we thought that that's the only setting that this is suitable for, then we'd be worried about the patient who is going to come back every month to get their blood pressure titrated. So that's one way I think you could interpret this. So I think part of this is determining who the target is.

DR. TEMPLE: The thought here is that there are some people who are better at getting back to the doctor than others and stuff like that, and it may be especially attractive to put someone like that on a pill that is stable and you can just keep taking it.

So is one off-target that people who could be monitored more regularly would be put on this and then not monitored as well as they might otherwise be? Is that what people have in mind?

DR. LINCOFF: I think if that's the definition of the target or not target.

DR. STOCKBRIDGE: I think that's the
question. The basic idea here was you weren't
going to have 40 different versions of this with
all the different possible doses to it. You were
going to have one or two or three maybe.

So there is a compromise, concern that
people -- if you think optimum treatment is
titratable treatment, you're giving that up here.
And you might choose not to do that in everybody
who's got secondary prevention need. You might
choose to do it in patients who you think that's
probably the best option for them.

DR. TEMPLE: Okay. So to be specific,
someone who ideally you would monitor or at least
for the few months to see if their blood pressure
came to where you wanted it and their lipids came
to where you wanted it, you'd say he'll never get
here. I'm just going to put him on this and I'm
not going to worry about titration. That would be
one example.

DR. STOCKBRIDGE: Yes.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMONS: I'd make a distinction in
secondary prevention. I think this really has to be post-MI because the beta blocker and ACE inhibitors don't have an automatic indication, to my knowledge, in stroke.

The second thing is it's really independent of blood pressure. These were medications that I think we're giving for secondary prevention without regard to blood pressure in this context, and I think that's the off-target indication. In hypertension, dyslipidemia, that we heard from our speakers earlier, that is the stretch indication that would be off-target, is to lower risk factors beneath the threshold that we would call disease.

So people that have -- to lower blood pressure from sub-hypertensive to lower, to lower lipids from not hypercholesterolemic but just to lower risk factor burdens, that's the off-target indication, in my view, that's interesting.

To me, it would be very reasonable to give anybody who had post-MI this agent and to give anybody that had independent indications for all the components because they were hypertensive,
dyslipidemic. If I was already giving all four components, it would make sense. But then the question is would you ever give it to people just because you thought their actuarial risk for heart disease was above a certain threshold.

DR. LINCOFF: But Dr. Stockbridge has said that the intent of this question is the idea of are you willing to say that everybody with secondary prevention, one-size-fits-all, is as good as the titratable? In other words, do you believe that we would hurt some people or there would be consequences to applying this more broadly than just patients for whom we couldn't get good control?

So I've got a lot of people here. Next would be Dr. Flack.

DR. FLACK: I would say secondary prevention, a patient needs to go through a filter per se. If they're not already controlled, and you're just switching them over for convenience, then the kind of patient that would make sense to me would be secondary prevention where you believe
that they're having trouble with adherence to therapy. And I'll tell you, in some health systems, they've got good pharmacy data. And partly, you could pick up some of these patients even administratively.

I think an off-target area where I could easily see this being used is in diabetes where they don't already have the cardiovascular disease, but diabetes has been labeled a coronary equivalent and all. So I could see it actually being used there. Would I have a problem with it? It depends on the components, but probably not.

DR. LINCOFF: Dr. Wilson?

DR. WILSON: I would have concern in using it with somebody with extreme elevation of either blood pressure or lipids, extreme meaning they've been taking three, maybe four medicines for blood pressure and for patients with familial hypercholesterolemia, for sure. I wouldn't want my FH patients to be put on this product because they just need a lot more attention.

DR. LINCOFF: Dr. Lewis? Dr. Rich?
DR. RICH: A question for the FDA. If you make the decision that you're going to approve a polypill, which has an antihypertensive, aspirin, statin, do you then have the authority to say this is the only statin we'll agree to in the polypill, this is the only ARB we'll agree, or must you then consider every company coming to you with every possible combination to say, well, you're approving polypill, why can't you approve ours with our ARB and our statin? Because if it's the latter, then what you're suggesting, there may end up being 50 different polypills out there when it's all through.

Is that what we're talking about?

DR. STOCKBRIDGE: Well, there may be 50. You should say what you think the constraints on ingredients might be either in terms of targeted doses or in terms of what constituents are included.

DR. TEMPLE: It's worth noting that the way blood pressure drugs and lipid lowering drugs are currently labeled, the expectation is you will see
what the effect is and see if you think it meets
your test.

If there's some thought here that you're not
going to monitor anything, that could change your
attitude toward it. After all, simvastatin may not
be as potent as atorvastatin, but it is on the
market for use as a lipid lowering drug, even
though it's not as powerful as the other two.

So those are good questions. If you really
thought that you were going to -- but see, I can't
imagine this being put into labeling this way. If
you really thought that you were going to give it
and never look, your attitude toward what it should
be might be different.

But just as a prediction, I don't think
we're going to label it as just give it and don't
look. We'll say use it if you need it but monitor,
and then people might not monitor. We know that.
But it wouldn't say don't monitor. That would be a
very big surprise.

DR. STOCKBRIDGE: I agree. I envision
labeling that says people will probably do better
if they've got regular care. It's not going to advocate backing off from conventional care, whatever that is. But if you think the patient's not going to get that, this is something to think about.

DR. TEMPLE: But it remains to be seen whether it would actually say that even if that's true. That would be a big step. That would say treat but don't monitor, big step. It's not a step we've reached yet, but it obviously should be considered.

DR. STOCKBRIDGE: It says "treat even if you can't monitor." That's different from treat and don't monitor.

DR. TEMPLE: Yes, that is different.

DR. LINCOFF: Dr. Li?

DR. LI: I would like to see some kind of thought of an indication not just for secondary prevention of people who've already had stroke or MI, but people who are at very high risk for primary. Because as a pediatric cardiologist, Monday I saw a patient who was 300 pounds, who had
hypertension, hyperlipidemia, insulin resistance,
and his father had died of a myocardial infarction
at age 24. But he was 15 years old, and he, of
course, meets -- and I do have him on an ACE
inhibitor and a statin, but he has terrible
compliance. So a polypill might be a good thing
for this kid because he's at very high risk moving
forward.

DR. TEMPLE: Nobody disagrees, but aren't
we -- you just told me we're barred from discussing
that?

DR. TOLIVER: That's correct.

DR. LEWIS: We haven't been cleared from a
conflict of interest, so it's the Department of
Justice that would care if we talked about it, not
them.

DR. LINCOFF: Dr. Davis?

DR. DAVIS: Is it likely that such therapy
would be attractive? It's possible, but without
any data, it's very hard to say there'd be off-use.
The other thing about the public health
consequences, it seems to me that if the patient is
in an optimal setting and the doctor wants to practice to the guidelines, so be it. It's not that this would say you have to go on a polypill.

This is just another option, and the polypill may be the optimal setting for some patients. If the patient's not adherent and they want to go on this, and the physician feels that it would help, that may be the optimal setting for that patient.

DR. LINCOFF: Dr. Sager?

DR. SAGER: I was basically going to say the same thing that Dr. Davis already said, which is this is just extending the armamentarium. This is extending the armamentarium, and there will be -- there certainly is a significant group of patients there who aren't getting treated or very well treated now that this could be a real advantage for them. And there are other people who are getting frequent medical care that we'd like to try to really optimize their therapy to the best way we can.

Maybe that's using one of several doses of a
polypill or maybe in the case of what's done in Kaiser, sometimes adding, let's say, a calcium channel blocker to their polypill equivalent. But I don't see this as saying you wouldn't want to try to optimize therapy, but rather, it's really extending the tools that we have to treat patients.

DR. LINCOFF: Dr. Kaul?

DR. KAUL: I have a question for the FDA. What will the label say? Will it characterize conditions of use, i.e., first line for initiating patients who are naive to any single component of the composite pill; or second line for optimizing the benefit/risk because one of the risk factors has not been reached; or for convenience as a substitution indication? So what will be the conditions of use?

The second question I have, it relates to requirement for bioequivalence. Does the FDA envision a scenario where it will qualify for a biowaiver?

DR. STOCKBRIDGE: As far as what the label says, we're here to listen to you about what it
should say, and you should answer that. As far as
where a waiver is appropriate, I don't think I'm
qualified to say. I think that's generally not
envisioned.

DR. TEMPLE: One thing about labeling -- I
mean, Norm laid these out before. The simplest
ting to possibly to say, which we used to say for
all antihypertensive combinations, is for people
who are on both these drugs and they want a
substitute. That's the closest to a no-brainer you
can get.

But if you wanted to add a second drug in
the same way or a second and third drug, that's
been part of labeling as well. And then more
recently, we've said for people who won't be
adequately controlled on a single agent, and we've
characterized who those are, that could be
reasonable.

So it could be any of those things, and if
they also had a lipid abnormality, you could start
the lipid abnormality and put them on aspirin if
they haven't been on it already.
So all of those things are perfectly possible, but those are all targeted towards specific claims. They don't contemplate using a lipid lowering agent in people whose lipids are normal. Who knows what the future will bring, but they don't yet. We haven't yet done that yet.

DR. STOCKBRIDGE: I will just point out that neither the anti-lipid drugs nor the antihypertensives say what the goals are, what the threshold is for treatment.

DR. TEMPLE: And the lipids, I think, refer to some guidance -- or they used to. I'm not sure if they still do. But they used to refer to a particular guidance, and we recognize that the world helps decide that stuff. We haven't put our own limits on it.

DR. LINCOFF: There's a member of the FDA. Could you identify yourself, please.

DR. HARIHARAN: Sudharshan Hariharan, FDA. To answer Dr. Kaul's second question, a PK bioequivalence study is actually required for at least one of the strengths of the polypill, and
biowaiver -- I mean, the other strengths can be approved using a biowaiver approach.

DR. KAUL: So one particular strength requires it, and the other strengths will not?

DR. HARIHARAN: Yes, can be waived of an in vivo study.

DR. KAUL: That's helpful to know because I think --

DR. STOCKBRIDGE: Actually, that's not going to work here because we're going to -- it almost certainly will have the same dose of aspirin, so the various doses, if they're available, won't be proportional. I'm not sure how you're going to do a biowaiver here.

DR. MADABUSHI: This is Raj Madabushi. I'm the team leader in clinical pharmacology. The concept of biowaiver is possible, but it depends upon the individual situations. So typically, what happens in these kinds of situations is you look at multiple things. You typically conduct the PK study at the highest strength, which you would want the market or register, and then look at multiple
factors, whether the lower strengths come in a proportion of the highest one and other factors.

So it is possible under certain settings that there could be a biowaiver. For drugs which display non-proportional pharmacokinetics, there is a banding, so you conduct the PK studies at higher and lower strengths, which are envisioned.

So there is no one clear answer, but it depends upon situation to situation. Whether biowaiver is possible, yes, it is possible in certain circumstances, for lower strengths.

DR. KAUL: The statin dose by necessity is going to be a high-dose statin.

DR. MADABUSHI: The PK study would be conducted at the highest strength that would be marketed, so that would be covered definitely in a bioequivalence study.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: I'm a little bit confused now. So I read -- and of course the representatives today, those new things because the clinical trials didn't look at cholesterol targets. You guys now
recommend high intense for certain groups, and there are quite complex based on age and a variety of risk factors, and then moderate intensity and whatever.

So the polypill as secondary prevention, not all those people who qualify as secondary prevention would be in what is currently recommended for the high intensity group. Some of them might not be. Some of them would be moderate.

DR. LINCOFF: Well, no, all of them, except for age greater than 75.

DR. LEWIS: Right, the old people would not be. I knew there was one group that was an exception.

So I think this is really complicating. Yesterday we talked about, or I did, about how if you're going to start a patient who's indicated on two antihypertensives, would it be misleading to label a drug that only had a 1.2 millimeter mercury difference in blood pressure.

Here if you're going to label this or target the population, anyone who needs secondary
prevention, is this going to come across as this is it, this is all you need to treat them? And if their LDL is 190 or if their blood pressure is 210 over 110 -- I mean, it sounds ridiculous and like common sense, the doctor would do more. But aren't you communicating this is the secondary prevention pill?

DR. LINCOFF: I think that's the question. I mean that's the concern in the question.

DR. LEWIS: I think it's hard to imagine that a patient and physician who are willing to titrate to the patient's individual components, particularly the blood pressure, might not have an advantage. And I don't know that this wouldn't be interfering with that.

DR. LINCOFF: Can we stop this? It's just making noise. Oh, okay.

Well, so then are you saying that you believe the intended population are those for whom you wouldn't be -- that wouldn't be well suited for titration?

DR. LEWIS: I think that really the only
thing you could say is if as a physician you were
going to give this patient aspirin,
atorvastatin 40, whatever else it is, and
lisinopril 20 and this other drug, then you can
give this polypill instead. I'm not even sure what
else you could say, because otherwise you're going
to be giving a pill to someone against guidelines
for what the goals are for that person.
    I think you almost just have to tell the
physician if these are the four pills you want to
use, you can use them in combination, and it'll
work the same in the body.

    DR. FRIED: So that's substitution?
    DR. TEMPLE: No, that wasn't substitution.
That's not what you said. Substitution, you're
already on it. You're now contemplating you were
planning de novo treatment, and this is what you
were planning to do to treat their lipids or treat
their -- and this is for that.

    DR. LEWIS: Yes.
    DR. LINCOFF: Dr. D'Agostino?
    DR. D'AGOSTINO: I was going to say in my
interaction with physicians in terms of doing some of these things, the side effects of these drugs can be unpleasant and so forth, and you throw a combination at a patient, and they start getting headaches, start getting muscular pains and so forth.

A person with an MI, are we saying that just because they have the MI, you're going to throw immediately these drugs all in one dose at them, or are you going to play around with seeing how they respond to an ACE inhibitor versus some other hypertension drug, and then mix it with the diuretic, and then how do they react to a lipid drug?

Some people don't have pleasant -- so is this question saying instead of looking at them individually and deciding to see how they're responding to the individuals, you're just going to throw this combination at them?

DR. LINCOFF: Sorry about all the distractions here.

I think the question is somewhat what
we're -- we have to make an opinion about what we think would be the appropriate target population to use this, and then within the secondary prevention population, those who we didn't think would be the optimal, are we worried that it would be used for those patients? And are we worried that there would be public health consequences to that?

Dr. Wilson?

DR. WILSON: So I think it would apply to most patients for secondary prevention, and to take a qualifier, we have data for this for cholesterol in the CTT trials meta-analysis. Even those for secondary prevention who had relatively low LDL cholesterol, they benefited by a statin. And it's about the only really good source for that and a couple of other follow-up meta-analyses. So we do have that for lipids.

What I don't know -- and other panelists and guests can help perhaps -- is if I have a patient post-MI and I already know he ought to be on a statin, but if his -- let's say his blood pressure is completely normal. Let's say it's 120 over 80.
Can I put him on a blood pressure medicine -- and let's say it's in the form of a polypill -- and do that with safety?

So that's where I don't know, and I would need a little help.

DR. LINCOFF: Dr. Rich?

DR. RICH: I think there's confusion because I get a sense that some feel that all secondary prevention now is going to be polypill. If you don't prescribe a polypill, then you're doing the right thing. And that's not what I'm hearing. There will be a lot of people who don't qualify. If your blood pressure is low, you don't qualify for having an antihypertensive in your polypill.

It also seems that given the diversity of types of polypills that may be approved, the label should clearly say this is approved for secondary prevention following MI in this age group and it is not indicated if. And then if it's one of the ones that has an antihypertensive, you can put your upper boundary and say it's not indicated if your blood pressure is above this or difficult to
control.

So I think the label can be pretty clear in terms of directive to the physician as to when the pill is appropriate and when it's not. I don't see that as being a huge challenge.

DR. LINCOFF: Well, part of the discussion we always have is what would be the consequences if physicians don't read the label, which --

DR. RICH: Same as they are now.

DR. LINCOFF: -- occasionally happens.

DR. RICH: Same as they are now.

DR. LEWIS: So are you going to change the label when the guidelines change? You guys just changed the guidelines. These are dramatically different guidelines. Are you going to change the label? What if they decide over 75 it is okay? So we're going to change the label.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMONS: I think the key is that they have to obviously have the secondary prevention indication. Their blood pressure has to be reasonable, and then you have to have a plan not to
titrate any of the individual components.

I think that's the third piece of it, is you're going -- and that will either be physician or patient choice or a function of their blood pressure that your plan is to use the dose of that medication in perpetuity of those drugs in the combination. And then I think that covers it.

DR. LINCOFF: Dr. Sager?

DR. SAGER: We have other drugs already, combination blood pressure pills. We usually try not to give those to people who are hypertensive.

(Laughter.)

DR. SAGER: I'm not sure this is really that different. I do hope that people who would prescribe it would understand what's in it, and the contraindications will be in the label. So I think we're making this much more complicated than it really is.

DR. LINCOFF: I'm not sure we are. I may be wrong, but my understanding of the intent of this, or at least part of the intent, was that this -- most antihypertensive combinations we still
titrate. We just use one pill instead of two, but we treat it just like anything else. And we bring them back in a couple of weeks or a couple of months, and we check their blood pressure, and we go up in the next incremental dose.

It sounds like the idea for this -- certainly for the indication I'm not allowed to mention -- was that it wouldn't a titratable thing. And it sounds like this is not -- although it doesn't mean you couldn't, but it would be intended for care of patients for whom titration may not actually happen.

So this is a little different, I think, and that's the question. Are we worried about patients who could well be titrated getting a drug that the physician or the patient may understand is not to be titrated?

DR. SAGER: Well, we said that there might be several doses, so the physician would have the option of -- if the effect you get isn't what you want -- potentially going to a different dose. And often combination therapies for blood pressure are
started as the initial therapy.

So I think it isn't totally different, actually. I think it's got a lot of similarities. And I do think that we have to -- I think obviously the physicians need to understand what the contraindications are here and the indications, but I think this is really mimicking the therapy that we hope these patients are getting in the first place.

DR. LINCOFF: Dr. Kaul?

DR. KAUL: I was just going to say at the point of repeating what everybody else has said. The label should be very simple. You say that the polypill is indicated for indications for which apply to the individual components provided there are no safety, tolerability, and contraindication issues. That's what the label should say.

The label should not define whether it's for convenience, substitution indication. It should not define as optimizing benefit/risk. That's where the clinical judgment comes into play.

DR. LINCOFF: Dr. DeLemos?
DR. DELEMOS: There's a duration issue. The new guidelines now are putting a three-year window on beta blockers post-MI, so there would be an issue with potentially being a little out of lines with the guidelines if somebody was continued indefinitely on a beta blocker when there's now a suggestion to reevaluate that after three years. So I think some of how this gets labeled will depend on the individual components that end up making the list.

DR. LINCOFF: I don't have any idea how to summarize this one.

Dr. Lewis?

DR. LEWIS: I just want to comment. It's a comment to the FDA. In a way, we are the right people on the panel to some extent, but also, these issues that we're talking about, we don't -- or at least I don't -- design adherence studies. Some of those people were in our audience. I don't design healthcare delivery studies.

There are a lot of -- kind of the reason we're talking about this isn't because we all -- it
has to do with healthcare delivery and adherence. And how to approach that, you may want to access people who that's their area of expertise.

   DR. STOCKBRIDGE: I haven't heard anybody say -- insist that we demonstrate that a product like this achieves better adherence.

   DR. LINCOFF: Well, let's -- I think that's the third question.

   DR. KAUL: I was going to ask the FDA the question, is that within the purview of the FDA, to ensure adherence?

   DR. TEMPLE: It's not necessary for the product to be available. We make fixed-dose combinations of various sorts available if they do what the single entities do. We have not insisted that they show that they actually do increase adherence, even though many people believe probably a lot of people do. But we have not made that a requirement.

   It may just be for convenience purposes. That's probably okay, too. The primary reason for most fixed combinations is convenience. We like to
think maybe people comply better, but we have not insisted that people show that.

DR. LINCOFF: All right. Then to summarize, I think we can say that the general population with patients with secondary prevention may be candidates and that there doesn't seem to be excessive concern that it would result in suboptimal care for patients who could get optimal care if it was appropriately labeled to exclude the right patients; and that if patients weren't reaching -- if possible to continue to monitor patients, not to use it as a no-monitor option and to make appropriate adjustments if patients aren't reaching the targets for their risk factors.

Now, for the third question. So if such a product were submitted for marketing approval, what do you think they need to show beyond components' potential for pharmacokinetic and pharmacodynamic interaction?

Now, I want to clarify this because we've talked. So recognize, of course, none of this is about a drug, but if now a company were to bring a
drug to the FDA, it's time to talk about what studies you would expect them to have as part of their PMA package. So not what postmarketing studies and not the pharmacokinetic and pharmacodynamic, not phase 4, but what package? What would you like to see? What trials, what data would you like to sit here as a panel a year from now when somebody brings a polypill and make a decision whether this drug should be approved? So that's what we should try to focus on.

Dr. Kaul, you look like you are eager to answer this question.

DR. KAUL: I was just thinking aloud about do they need to commit to post-approval or do they need to --

DR. LINCOFF: Demonstrate --

DR. KAUL: -- preapproval.

DR. LINCOFF: If you would let them walk in here showing pharmacokinetics and pharmacodynamics and say approve the drug, then say that. But if a year or two from now you're going to say wait a
minute, you don't have enough data, so what data
would you want to see for an approval application?

    DR. KAUL: Well, I think we already
addressed that or at least some of us did, that at
least at a minimum, they have to fulfill the PK/PD
requirement. And the concern has been raised about
safety issues, which may stem from interaction,
tolerability, or non-compliance due to
discontinuation or whatever. That can be addressed
in a safety assessment in a phase 4 or an
observational-type study.

    So beyond that, is that what the question is
asking? Beyond that, what do we need?

    DR. LINCOFF: The PK/PD, we've already heard
from the FDA that they would do it, they would
require it. So the question is would you require
more for approval, not post-approval or a
commitment post-approval?

    Dr. Wilson?

    DR. WILSON: So I'd like to see a corpus of
safety data for the product that's likely to be
developed, which means probably, as Jim DeLemos
said earlier, low-dose aspirin, atorva 40, and at least one blood pressure medicine. And much of the data has been developed for simvastatin, and it's not likely to be the statin. So that was my concern about that.

DR. LINCOFF: Dr. Flack?

DR. FLACK: Yes. I'd like to see the safety data as well, and also like to see the data showing the effect on the risk factors being treated are equivalent or on par with what you get with the individual components. I think that's reasonable. If there's no deleterious action, you get a product that in all likelihood is being taken at a higher level.

There's a lot of data showing that when you simplify the regimens, you do get a higher compliance rate. You ought to be able to get over the bar of showing that if you take this, you're at least going to get as good a reduction in blood pressure or lipids or effect on aspirin metabolites that you would get if you were dosing these drugs alone.
DR. LINCOFF: Dr. Unger?

DR. UNGER: Drs. Wilson and Flack, so safety data comes in different depths. So it's important for us to understand what you mean exactly. Are you talking about outcome trials? Are you talking about -- what kind of safety data are you talking about? What are the issues? Because that drives the size of the trials and the length.

DR. WILSON: So I think the trials that we heard about today have been conducting the chemistry profile in patient complaint types of adverse drug effect types of data, that sort of information. My concern is that let's see an aggregate of it across more than one study as best as possible so it summarizes it. And for the probably atorvastatin -- or do it by statins, especially leaning towards the statin that is likely to be one of the front leaders for development for a product. And then I think the other major issue would be probably in the elderly, and I won't define that. But I'd like to see at least a younger versus older, and then probably in
men versus women, and I don't think we've seen
that, either.

DR. LINCOFF: Dr. Temple, do you have a
comment?

DR. TEMPLE: I'm still having trouble
following this. This is to look at the effects on
lipids and blood pressure of this fixed combination
compared with the single entities used at roughly
the same doses. Is that what we want to see?
Because I already know the result of that.

DR. WILSON: Yes, it's going to be --

DR. TEMPLE: Why do I want that study?

DR. WILSON: And you have it for atorvastatin 40
in combination --

DR. TEMPLE: No. I cannot imagine a reason
why atorvastatin in the presence of, say, a
diuretic will have -- the presence of a diuretic in
the same pill will have a different response from
the presence of a diuretic taken as a separate
pill. If the bioavailability is the same, which
we're presuming, what are you -- is there any
reasonable chance you're going to find something
DR. WILSON: I think it's going to be safe, too. I agree with you. But the point is should it -- what I don't have the answer to is can you go to studies that were used in these trials or go up to other studies? If you go outside of these designed trials that we've heard about today, I think the data are relatively thinner. If you go to the literature that's published, the data's probably all in hand and is pretty safe.

DR. TEMPLE: Maybe I'm not asking the right question. I presume you're talking about looking at the effects of the antihypertensives on blood pressure, not on outcome, and of the effects of the lipid lowering drugs on lipids, not the outcome. And we will have established for the PK/PD stuff that the effects are the usual effects of these things.

What else are we looking for?

DR. WILSON: I agree with you. I think the data -- I think the products are safe. But how much for instance -- how much data is going to be
put before an advisory committee concerning
atorva 40, ASA 75, and lisinopril 10, all taken
individually or in combo for liver functions? I'm
not too concerned about the lipids. I sort of know
where those are going to be, and I think I know
where the blood pressure's going to be, rate of
rhabdomyolysis for young and old, men and women.

I think it's -- I agree with you, but I'm
not sure the data are in these trials. I think
you're going to have to go to other non-trial data
for them. But I think a committee would accept
that.

DR. TEMPLE: I guess the distinction I'm
making, it sounds to me like you're asking what
happens when you take these drugs together. I
guess I don't see how it makes any difference
whether they're in the same pill or not. So some
of those may be things we have to know before we
combine them, although they're combined all the
time.

DR. LINCOFF: So let's see if Dr. Flack has
an answer to that. Dr. DeLemos after that, and
Dr. Lewis after that.

DR. FLACK: Well, actually it was me that actually requested that. And I look at it like if you're going to combine amlodipine and valsartan and you get the PK/PD data, and you bring this up to the committee, you're going to show them blood pressure response, and you're going to show them control rates.

So I don't know why this would be any different. I don't know -- to me, it's a very low bar for them to have to get over. They're going to have to generate this data. And if I were sitting in a committee and all you brought in was PK/PD data and didn't have any blood pressure data, I'd be scratching my head, are there any physiologic data, because this would actually be a divergence from the way you've approved combination products in the past.

But I don't think you're asking people to count -- you're not asking people to count bodies. You're just asking them to show the data that they're already going to have.
Assumption is the mother of all screw-ups, and I don't necessarily know -- somebody may have a formulation that doesn't work right or there's something wrong with the formulation, and it's not that -- and so at the end of the day when they start manufacturing it, you'd want to know that, well, yes, it does lower blood pressure.

But again, I think the bar is relatively low, or lipids, I think it's relatively low. And it should be pretty perfunctory for them to provide that data.

DR. TEMPLE: Let me be clear what my question is. When we have antihypertensive combination -- Norm can correct me if I'm wrong -- they used to do these 12-grouped factorial studies. They did not make up pills that contained both drugs for each of them. They gave the diuretic as a separate pill and the dose of whatever the ACE inhibitor, whatever it was, a separate pill. And they looked for the effect of both drugs. They looked to see what the dose response was, and they did all those things.
My presumption is if people are putting two antihypertensives together, they'll have to have that information for us just the way they always would to show that it has the additive effect we expect.

What I was understanding here is that you want to see that for the fixed combination, the factorial study for the fixed combination, with formulated product as opposed to just knowing what the entities did, even if you knew that the PK was the same for both.

DR. FLACK: I think it's enough of a paradigm shift that I would like to see it. I may be in the minority. I may be by myself, but I think it is enough of a paradigm shift that I would ask for that.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: I'm fine with that, but I don't need anything beyond that. And I don't think you need a committee. I think this is -- the work for this will come after approval. A million things to figure out how to use this and where it...
should be used, but that's for health services researchers.

I think if you meet this bar and the drugs work the same in combination as we think they do, in the formulation that's actually going to be prescribed, I don't need anything else pre- or postmarket, personally. And I don't think I need to come back to a committee for it.

(Laughter.)

DR. LINCOFF: He's already put you on notice. Don't invite him back.

Dr. Lewis.

DR. LEWIS: Just to say there's a unique safety issue related to a combination that you're not addressing, right? You're not addressing the issue that patients will say I'm on a heart pill, will not know what the components are, and sort of the Lortab and Tylenol or Lortab and cold medicine thing could happen to them. Or they could go have a procedure done because they're on a heart pill, and they don't actually know it's got aspirin in it or whatever.
Now, the assumption you're all making is that the increased adherence for people who don't take their medicines or don't like taking four pills will outweigh for the population the benefit and the risks of those events to the people who have events. But there are going to be -- and you can also say that there are people who don't know their medicines even though there's four of them.

But you are introducing something novel. You're introducing something where there are four pills with completely different mechanisms, and they're not all addressing even -- it's not like, oh, I'm on some sort of blood pressure pill. I don't know the name. They're on like completely different categories of medicines all in one pill, and I think that introduces a different potential risk.

I know cardiologists order them all the time, and you think it's really, really safe, but I don't know that it's going to be safe if the patient doesn't know.

DR. TEMPLE: Dr. Lewis, that's a completely
different study from what we've been talking about. What we were talking about was what the interaction on blood pressure and stuff like that is. What you're talking about now is an outcomes study -- I'm not even sure we know how to do that. You're looking at very low event rates, presumably.

DR. LEWIS: One would certainly hope so.

DR. TEMPLE: So that's a totally different kind of study.

DR. LINCOFF: Well, so are you proposing -- the question is, what do you think they need to show? So as a clinical trialist, do you have a -- what would you like to see?

DR. LEWIS: Can I ask him a question first? Were you saying that if the combination polypill had two blood pressure medicines in it, those two blood pressure medicines would have to leap the hurdle that yesterday's drug did? They'd have to show that --

DR. TEMPLE: Yes.

DR. LEWIS: -- because I thought what we heard today is it doesn't really matter what they
do. You just take it. It doesn't matter.

DR. TEMPLE: No, no, no. We're not going to approve putting two antihypertensives together unless we know what the combined effect is. We may know already because there may be combination products that already contain these, so I don't know if there's any new data.

DR. LEWIS: All right.

DR. TEMPLE: But you always have to know what the effect of the combination is in all the dozens -- what did Norm say, 50 -- antihypertensive combinations there are. Whether you also need to see the interaction with the lipid I think is something you have to talk about. I don't think we've thought they mostly interact with lipids, but if that was a possibility, you'd want to know.

DR. LINCOFF: Dr. Sager?

DR. SAGER: I think the plan that was outlined in the FDA presentation for the PK and the PD study is sufficient. I think it would be good to have -- after this approved and being used to have some type of observational assessment to look
at safety, but also really important to look at the health benefits of this. Where we're expecting some real benefits, that'd be really nice to have that studied. But that's not part of the approval process. And --

DR. TEMPLE: But also for what it's worth, finding the benefits of the size we're talking about in observational data is challenging to say the least.

DR. SAGER: But maybe with some of the --

DR. TEMPLE: You're talking about 20 percent reductions --

DR. SAGER: -- some of the approaches now with electronic health records, maybe you'll make that --

DR. TEMPLE: That's not real possible.

DR. SAGER: And I also agree. I don't think this has to come back to an advisory committee.

DR. LINCOFF: Dr. Fried?

DR. FRIED: I actually don't think you need anything for approval, but I think for follow-up, it's going to be very hard to pick up when somebody
doesn't stop their drug for a procedure unless you get a reportable event.

The ones you might be able to follow are overlapping medications, in-use medications used on overlapping refills where you have the person has a refill in May and a refill in June, and at the same time, they have a competing medication, overlapping medication. That you can get out of electronic medical data. I mean, the Canadians have done it because they have their billing data.

But there are systems that might be able to do it. The smaller sort of GI bleed kind of sort of things are going to be much -- because someone is put on -- or has their colonoscopy when they haven't stopped their aspirin is going to be much harder for you to pick up.

DR. LINCOFF: Ms. Arkus?

MS. ARKUS: The type of information I think consumers -- more patient-centric care consumers are interested in knowing and what I would like to see looked at was if this really did benefit the patient.
As a visiting nurse for 10 years, we had patients all the time that wouldn't take their water pill if they were going grocery shopping or out to see their doctor that day. A lot of times that needs to be put aside, and they might take their blood pressure pill first thing in the morning because their blood pressure's high in the morning. So I think that there is some disadvantages to a polypill as far as having that understood.

Also, the non-adherence rate having to do with convenience, I just think that that needs to be looked at. Is it convenience or is it because of the side effects that patients experience? And if you go to PatientsLikeMe website and you see some of the data delivered by the patients themselves, I think you get the real answer of patient-centric care and where we need to start, the real reason for non-adherence.

DR. LINCOFF: Other comments? Dr. DeLemos?

DR. DELEMOS: Is it reasonable to say that because the product would not be approved for lipid
lowering but for secondary prevention that you
can -- you don't have to take any statin, that you
only evaluate statins at product in a dose that
meets the secondary prevention guidelines?

Is that something that can be done so that
you don't get the -- because we're not really
interested in the products that we've heard about
that have low-dose statins because we don't think
they'll be comparable to what best available care
is, but we would be interested in the products that
contain high-dose statins.

Is that something that, since the indication
isn't lipid lowering, we can consider?

DR. TEMPLE: Lipid lowering drugs are not
now approved for, quote, "secondary prevention."
They're approved for lowering lipids. Section 14
then lists what they've been shown to do in
particular studies, and it's actually fairly
narrow.

So the JUPITER study in the rosuvastatin
just describes how it works nicely in people whose
lipids aren't even elevated. And simvastatin says
it's for secondary prevention, and pravastatin says it's for primary prevention because WOSCOPS. But that's off in Section 14. The claim, what it's for is for lowering lipids, lowering cholesterol, LDL cholesterol.

So we would have to see what the claims for these would be. They might just be for lowering your blood pressure and lowering your lipids. We haven't thought through whether there would be any further claim or not.

DR. GRANT: I have a quick question for the committee. I've heard it sort of discussed, but I don't think anybody's explicitly discussed it. Are you more worried about us approving doses too low or too high?

Now, I've heard in discussion said atorvastatin -- sort of a lot of discussion about atorvastatin 40 milligrams, which suggests to me that because it's in secondary prevention, you're worried about a product on the market whose doses are too low. If that's true, you ought to make that explicit. I'm not quite sure you've gotten to
that.

DR. LINCOFF: Well, I think there was pretty good agreement that at minimum, these pills should include 81 milligrams of a low-dose of aspirin and 40 or 80 or perhaps both of atorvastatin, and that no combination -- since we're in the secondary prevention consideration discussion today, that no combinations using a lower dose of statin should be considered.

DR. GRANT: Okay. And for antihypertensives?

DR. LINCOFF: Well, that I think was -- I don't think that was made clear.

Dr. Kaul, did you want to --

DR. KAUL: Antihypertensives, hydrochlorothiazide if that's going to be the antihypertensive choice, you're better off using one dose, fixed-dose, which is 12.5. I've not seen any persuasive evidence of an incremental benefit by doubling the dose. If that's the -- you're going to choose.

Beta blocker is where I'm less certain. I
don't have a problem with aspirin. I don't have a problem with the statins. That one should be the dose that is in alignment with the guideline recommendations. It would look silly if we are approving a dose in a polypill which is not aligned with guideline recommendations.

So by necessity, we have to choose 40 milligrams or atorvastatin or whatever the equivalent is. If rosuvastatin becomes generic by then, so be it.

The beta blockers, I'm less certain. I think if you use altenolol, the 50-milligram dose has never been shown to be an effective dose. Maybe 100 milligram. But I'm a little bit concerned about the heart rate effects and things like that with the altenolol.

But with regards to your specific question, would we require an interaction study, pharmacodynamic with blood pressure as well as statins, I would say yes because there is a signal. I don't know whether it's real or not, but there is a signal in a polypill study, the TIPS. And we
should at least make an attempt to systematically
study it and not just attribute it to a play of
change. So that's one thing that I would
recommend.

The question I wanted to ask Dr. Temple is,
the IMPROVE-IT study results are going to be
presented in November, I believe, right, at DHA.
And if the IMPROVE-IT study results are null, would
the regulatory approval standard for lipid
modifying therapy still be based on a biomarker
when the guidelines are already moved towards a
risk-centric approach rather than a biomarker level
approach?

DR. TEMPLE: I'm not going to speak for
DMAP. Everybody's agonizing about whether drugs
other than statins all have these same effects. So
the implications of it will be figured out. It
certainly is true that every statin has had the
expected effect in every outcome study I'm aware
of.

DR. KAUL: We're talking about non-statin
lipid modifying --
DR. TEMPLE: No. I'm -- that's going to be very interesting, and I'm certainly not going to say what we're going to do. And I'm not sure we even know, but I'm not going to say.

DR. LINCOFF: Dr. Flack?

DR. FLACK: With regard to the diuretic, comment on the dose and the choice of diuretic, if you're really going to follow the evidence, then you're either going to put chlorthalidone or indapamide, not HCTZ in there, and certainly not at 12 and a half. Even HCTZ 25 without a potassium sparing diuretic has never really been shown to be that effective.

Now, I believe it probably will lower risk and maybe it's a quirk of the studies, but the data is just much more persuasive for chlorthalidone and actually even indapamide over HCTZ.

Also too, on the statin, I sure hope that people don't really proceed rapidly down the course with simvastatin because there's just too many interactions, particularly with calcium blockers. And even if you get it right, somebody else seeing
that patient is going to get them on too high a
dose of verapamil or amlodipine or diltiazem and
all. And I think it's just too dirty a drug for a
pill like this with these patients on poly
pharmacy.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: In terms of which drugs, we
haven't really talked about that, but I think we
have to remember we're talking about a post-MI
population. And I'd be a little nervous about
chlorthalidone in an unmonitored post-MI population
and the risk of hypokalemia. We're thinking we're
targeting this to people with less monitoring, and
I think other than statins that we know at high-
doses are safe and don't need monitoring, with the
blood pressure medications, we're better erring on
the lower side and the safety side because we're
anticipating these to require less monitoring.

So for me, an ACE, ARB, beta blocker
combination with a statin and aspirin meets all of
the -- every secondary prevention indication
post-MI if that's the population. I have no
problem with a low-dose thiazide. I think that would be safe.

But I think you probably should have -- if your goal is to eliminate poly pharmacy with one pill, you should have the agents that are evidence-based class 1 indications in the same pill, but they should be at relatively low doses so they don't have to be monitored.

DR. LINCOFF: Dr. Flack?

DR. FLACK: Chlorthalidone at lower dose with a RAS blocker is not going to cause that much hypokalemia. Chlorthalidone uncovered by RAS blocker, yes. But if you do what Watson Pharmaceutical did, they made a 15 milligram chlorthalidone for a while. If you put a RAS blocker with that, your issue of hypokalemia is going to be minimal. And certainly, if you use indapamide, you're not going to have much hypokalemia.

Again, we talked a lot about evidence. The evidence is just not there for 12 and a half of HCTZ. Although it's been a favorite that people
have used, it's been kind of really out there on the margins, and in a lot of patients, it's not going to do a lot of good.

I understand where you're coming from, but I think you ought to be able to handle that just with the RAS blocker.

DR. LINCOFF: Other comments?

(No response.)

DR. LINCOFF: All right. We don't have a voting question, so are there any last comments from the FDA?

DR. STOCKBRIDGE: I want to thank the committee members and guests who came from 1, 3, 5 or 11 time zones to participate in this meeting. I think we've gotten some pretty good insight and help from everybody here. So just thanks, thanks to everybody who participated in this.

Adjournment

DR. LINCOFF: If there are no other comments, we are adjourned. Thank you very much.

(Whereupon, at 4:22 p.m., the meeting was adjourned.)