DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

VOLUME II

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8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Claudia H. Kawas, M.D., Consultant and Acting Chair
Sandra Titus, Ph.D., Executive Secretary

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Michael Grundman, M.D., M.P.H.
Gustavo Roman, M.D.
Jerry S. Wolinsky, M.D.
Howard L. Weiner, M.D.

PCNS INVITED SPEAKERS

Helena Chui, M.D.
Steven DeKosky, M.D.
Ranjan Duara, M.D.
Steven Ferris, M.D.
Mary Ganguli, M.D.
Philip Gorelick, M.D.
Ronald Petersen, M.D., Ph.D.

FDA

Russell Katz, M.D.
Ranjit Mani, M.D.

PUBLIC SPEAKERS

Ray Pratt, M.D.
Andrew Satlin, M.D.
Sean Lilienfeld, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. KAWAS: Welcome this March 14 meeting of the Peripheral and Central Nervous System Advisory Committee. My name is Claudia Kawas. I am from the University of California, Irvine.

I would like to begin with introductions of the committee and, perhaps, we can start off in the corner with the FDA. Dr. Katz?

DR. KATZ: Russ Katz, Division Director, Neuropharm Drugs, FDA.

DR. MANI: Ranjit Mani, Medical Officer, Neuropharm, FDA.

DR. PENIX: LaRoy Penix, Moorehouse School of Medicine.

DR. VAN BELLE: Gerald Van Belle from the University of Washington.

DR. WEINER: Howard Weiner, Brigham and Women's Hospital, Boston.

DR. GRUNDMAN: Michael Grundman, University of California, San Diego.

DR. TITUS: Sandy Titus, FDA. I am the administrator for the committee.

DR. WOLINSKY: Jerry Wolinsky, University of Texas, Houston.

DR. ROMAN: Gustavo Roman, University of Texas, San Antonio.

DR. CHUI: Helena Chui, University of Southern California, Los Angeles.

DR. DUARA: Ranjan Duara, University of Miami School of Medicine.

DR. DeKOSKY: Steven DeKosky, University of Pittsburgh School of Medicine.

DR. GORELICK: Phil Gorelick, Rush Medical College, Chicago.

DR. KAWAS: This committee has been convened to discuss the topic of multi-infarct dementia or vascular dementia, actually. We hope to accomplish a lot today. I see many people who were here from yesterday. I am sure we will have an equally interesting day as we cover the issues of vascular dementia and the questions that we have been asked to cover by the FDA.

The format for the day is going to be invited speakers and public speakers who will have a maximum of fifteen minutes to do their presentation and five minutes for questioning. We have a timer up here. Dr. Titus does really bad things to people after the red light. You will have a two-minute yellow-light warning for the speakers up at the podium.

I want to ask everybody who does speak to please

use the microphones because it is being transcribed, and if you will introduce yourselves before you talk.

We will begin with the conflict of interest statement that will be read by Dr. Titus.

Conflict of Interest Statement

DR. TITUS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such as this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants presents no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Since the issue to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product but, rather, may have widespread implications with respect to an entire class of products, in accordance with 18 U.S.C. 208(b), each participant has been granted a waiver which permits them to participate in today's discussion.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of

Information Office, Room 12A-30, of the Parklawn Building.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Ranjan Duara would like to disclose that he is an investigator on a study entitled Validations of a Memory Screening Instrument. The study is supported by a contract from Pfizer. He also serves as a scientific advisor for Pfizer/Eisai, Novartis and Janssen.

Dr. Philip Gorelick would like to disclose that he has two NIH grants. Roche Laboratories and Bayer supplies the medication for each of the grants. In addition, he is on the speaker bureaus for Janssen/Excerpta Medica, Dupont, Roche Laboratories, Bristol Myers Squibb and Boehringer Ingelheim. Dr. Gorelick has consultant agreements with NPS, Eisai, G.D. Searle/Lorex, Roche Laboratories, Ketchum, AstraZeneca, Glaxo Wellcome, Warner-Lambert, Baxter, Rand, Solvay Pharmaceutical and Consumer Healthcare Products Association. he is also on the Thought Leader Panel which is supported by the Weinberg Group.

Finally, Dr. Helena Chui would like to disclose that the State of California (DHHS) has provided grant funding to the Alzheimer Center where she serves as a principal investigator. She is also an investigator on a

study funded by a grant from the National Institute on Aging. Additionally, she is a scientific advisor to the Alzheimer's Association.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. KAWAS: Thank you, Dr. Titus.

Now, Dr. Russell Katz, Director of the Neuropharmacological Drug Products Division is going to be giving us our mandates.

Presentations and Discussion on Vascular Dementia and Drug Development

FDA Welcome and Overview

DR. KATZ: Thank you. I would just like to welcome the committee back again. I appreciate your showing up after yesterday's intense discussion and, also, again to extend a special welcome to our invited guests who have

graciously given of their time and their effort to help us with another difficult problem.

Yesterday, as you know, we discussed the clinical entity known as mild cognitive impairment, or MCI. Today, we will ask you to deal with several similar sorts of issues with regard to the topic of vascular dementia.

Again, we bring you these questions now because a number of sponsors have come to us with proposals for studies in patients with vascular dementia. We have, of course, allowed those studies to proceed but, again, we have made no commitments to them about how data from those studies would be interpreted pending a wider discussion of the issues that I hope we will at least discuss today, if not completely resolve.

Again, many of the issues that I hope we will cover today pretty much were covered generically for MCI yesterday but I will just give you a brief rundown of the sorts of things that we would like you to discuss.

As we discussed yesterday for MCI, it is critical that we get a handle on the diagnostic criteria for the particular entity, in this case, today, vascular dementia. Again, a big point that was discussed yesterday with MCI was, even if we can identify acceptable research criteria for clinical trials that can be reliably applied by experts, how well can those criteria be applied and used out in the

community of prescribers who will actually use drugs if they are approved for this.

As you know, there are several diagnostic instruments that are available for diagnosing vascular dementia. I am sure we will hear considerably more about them today. But studies have shown that there is a considerable variability across these diagnostic instruments as far as their success in diagnosing vascular dementia.

In fact, of course, vascular dementia may not be a single entity. There have been a number of underlying vascular pathologies that have been considered to contribute to the clinical picture of vascular dementia; subcortical dementias due to small-vessel disease, cortical infarcts secondary to disease of the larger vessels. Even large single infarcts that might be located in the region of the brain are important to the genesis of dementia and maybe other pathologies may contribute to the clinical picture.

So we are very interested to know whether or not we can consider vascular dementia as a single entity, whether it consists of several different subtypes that are sufficiently different from each other so that they should be studied separately and whether or not which, if any, of the diagnostic criteria that exist currently are adequate to be able to reliably diagnose any of them.

In addition to the variability in these diagnostic

instruments in their ability to diagnose vascular dementia, they are also not particularly excellent in differentiating between vascular dementia and Alzheimer's disease. So that is an important question that we are going to want to have you address.

Of course, further complicating the picture is the considerable overlap between the pathology seen in the brains of patients diagnosed clinically with Alzheimer's disease and the vascular findings in those patients including amyloid angiopathy and abnormalities of the periventricular white matter and the findings of lesions typical for Alzheimer's disease in the brains of patients who were clinically diagnosed with vascular dementia.

So the fact that there is substantial overlap of the pathologies of each in the patients who were diagnosed clinically with one of the two specific syndromes is, I think, a complicating problem and we are very interested to hear what you think about the role of each pathology and the pathogenesis of each clinical picture.

In particular, of course, the mixed dementia is where ferreting out these issues is even more complicated. So we are very interested to know whether or not you think the diagnostic criteria that exist are reliably able to tease these matters out.

There is a particular problem which the briefing

document talks about with regard to drugs that have already been approved for Alzheimer's disease. If the diagnostic criteria are not particular good at teasing out so-called pure vascular dementia from mixed dementia, any effect that you might see in a vascular-dementia study with such a drug, a drug that has been shown to be effective for "pure" Alzheimer's, it may be difficult to know whether any effect you see in vascular-dementia patients may be just due to the anti-Alzheimer component if there is a significant Alzheimer pathology in those patients.

So that is a very important issue we would like you to talk about. Those, I think, are the main issues we want you to talk about. Again, there are questions, as there were with MCI, about design issues and whether or not you think there are specific, unique design elements that ought to be incorporated into any clinical trial to evaluate a drug for vascular dementia.

People have talked about the frontal-lobe functions being, perhaps, more important to be looked at in vascular-dementia patients than in Alzheimer's patients.

So, basically, in summary, we would like you to specifically discuss the question of the utility of the various diagnostic criteria that have been applied, their ability to reliably identify patients with vascular dementia, their ability to distinguish between subtypes of

vascular dementia, whether that is even an important concept for us to be concentrating on, can they reliably distinguish between Alzheimer's patients and pure vascular dementia and/or, in particular, mixed types of dementia and, again, critically, whether or not any diagnostic criteria that we may discuss here that may be useful in clinical trials, whether or not those criteria can reliably be applied by non-experts in the community.

Again, if there are any specific design features, whether it is control groups, whether it is duration, whether it is specific outcome measures that need to be applied in these studies as opposed to other studies in other dementing illnesses are issues that we would like you to discuss. Of course, any other relevant issue that you think would need to be brought up, we are happy to hear.

So, again, just as a brief summary of the sorts of topics we would like you to look at. I will end there and welcome you again and thank you again for your efforts.

DR. KAWAS: Thank you, Dr. Katz.

Our first speaker today is going to be Dr. Gustavo Roman from the University of Texas Health Science Center in San Antonio. He will be talking on the Critical Elements for the Diagnosis of Vascular Dementia.

For those of you who have a program, we are shifting the order today at the speakers' request to unfold

the issues and the way they were interested in showing us. So Dr. Roman will be the first speaker followed by Dr. Helena Chui.

Critical Elements for the Diagnosis of Vascular Dementia

DR. ROMAN: Thank you, Ms. Chairman.

[Slide.]

I would like to thank the FDA for this invitation to present some of these topics on a subject that has been under very intensive study for the past ten years. Indeed, in 1991, I had the privilege of organizing the workshop that addressed the topic of separating from the group of dementias those that were the result of vascular factors considering the broad range of lesions from heart failure, cardiac arrhythmias to multi-stroke infarction.

The idea was to come up with a definition that would be useful for research studies in the epidemiology field providing, then, risk factors that could, perhaps, be used to prevent this condition.

[Slide.]

As you can see, there is a wide range of investigators from several countries and continents who participated in this first attempt to come up with diagnostic criteria for this condition of vascular dementia.

In the late 1960s, early '70s, we were, so to speak, blinded by the lights of the discovery of Alzheimer's

disease as the most common cause of senile dementia. I would like you to keep this image in mind because the magnitude of the program of Alzheimer's disease has certainly influenced our thoughts on the concept of dementia and on the impact of vascular factors and other factors in the production of dementia in the elderly.

For example, it was considered that there could be no dementia without memory loss despite the fact that the clinicians at the trenches were finding patients who presented with hemiparesis, with problems with executive dysfunction, who really would not go to a memory clinic because memory was not the first and the most important complaint.

This also influenced the idea of coming up with these criteria that, in the concept of many, have been, in a way, Alzheimerized, if I can use that expression.

[Slide.]

So, with those thoughts in mind, it was decided to agree on what were the critical elements for the diagnosis of vascular dementia. Number one, it was important to have an agreement on the diagnosis of dementia because, for epidemiological studies, you need to have sort of the final pathway, the final component of the syndrome. You would not study risk factors for dysplasia of the lung. You would go for lung carcinoma to look for the risk factors.

These criteria were developed, essentially, with an epidemiological framework in the conception of the criteria.

The second point is that the patients would need to have cerebrovascular disease. By cerebrovascular disease, it was understood that it was going to be ischemic lesions, frank infarctions, hemorrhages, problems involving venous thrombosis, problems dealing with cardiac failure or problems with hypoperfusion.

It was, therefore, a fairly broad range of possible causes that were all included under the category of cerebrovascular disease. Finally, the most difficult point was to try to make a reasonable link between the dementia and the cerebrovascular disease. This is how the committee agreed to tackle the issue.

[Slide.]

Dementia was defined as a decline in memory and intellectual abilities that cause impaired function in daily living. This was an adaptation of the WHO essentially because of the need to use these criteria on an international arena, that it was equally important to define dementia in a setting that would be useful both in a developing country as in areas of the developed world.

[Slide.]

The dementia would need to be confirmed by

neuropsychological testing including impairment of memory. As I mentioned before, this is sort of a legacy of the Alzheimer's Group, that there could be no dementia without memory loss because, essentially, that is the fact, as we saw yesterday, in Alzheimer's disease.

But it would have to include two or more cognitive domains. That could be either orientation, language, visuo-spatial functions, attention. Executive functions were included there, motor control and praxis. So it is a fairly stringent criteria for the definition of dementia, having essentially three areas of cognitive impairment for a diagnosis of dementia.

[Slide.]

For the diagnosis of cerebrovascular disease, the committee felt that it was important to confirm the lesions by brain imaging essentially because those who work in the stroke field know that a significant number of patients with strokes can have a completely silent clinical course. It is the imaging that is going to show the presence, or the effects, of risk factors for vascular disease on the brain.

The committee felt that it was important to include not only the multiple large-vessel strokes, the so-called multi-infarct dementia, but there is clear evidence from the literature and from the clinical experience that a single stroke can produce an acute

dementia in a patient when it is appropriately placed; for example, in the thalamus, the so-called thalamic dementia, posterior-cerebral artery and anterior-cerebral artery territories.

The same is true for lacunar strokes. They are usually multiple, localized in the basal ganglia and in the white matter. We began to learn from the advent of CT and especially from MRI the importance of periventricular white-matter lesions in the elderly and the importance of these lesions as a cause of dementia.

This was eventually confirmed by the description of the first genetic form of vascular dementia which is called CADASIL which manifests, essentially, by the presence of extensive periventricular white-matter lesions and multiple lacunar strokes.

[Slide.]

The presence of focal neurological signs on examination was considered to be evidence of the existence of cerebrovascular lesions, especially patients with small lacunar strokes may have just very subtle focal neurological signs on examination, with or without a history of stroke because of the frequent finding of silent strokes.

The use of the Hatchinski Ischemic Scale was not recommended essentially because of the epidemiological reason that when you want to look for risk factors in a

population, you don't include those risk factors in the definition. As you know, the Hatchinski scale emphasizes a history of hypertension and a history of vascular disease and prior history of stroke.

So that was the reason for not including the Hatchinski Ischemic Scale although further studies have demonstrated that this is probably one of the most effective tools for the diagnosis of vascular dementia in particular cases.

The noninclusion of the Hatchinski scale also brought to the fore the idea that perhaps hypotension could be as important as hypertension in some cases of vascular dementia.

[Slide.]

To solve the issue of the link between vascular lesions and the presence of dementia, the committee felt that the onset of dementia within three months following the stroke could be a reasonable criteria. The second point was that those cases of dementia that presented with an abrupt onset of cognitive dysfunction were likely to be of vascular origin since this is sort of the hallmark of vascular lesions.

Also, the presence of fluctuating stepwise progression that is quite different from that seen in Alzheimer's disease was also an important element.

[Slide.]

Features inconsistent with vascular dementia were those that are usually associated with Alzheimer's disease such as a fairly profound amnesia, worsening of language, transcortical sensory aphasia, patients with pure apraxia, agnosia, absence of focal neurological signs and, especially, the imaging criteria was considered to be extremely important because, while there is not a typical lesion that would allow a radiologist to make a diagnosis of dementia, of vascular dementia, in a particular case, lack of cerebrovascular lesions in the brain in a patient with dementia is considered to be against the diagnosis of vascular disease.

[Slide.]

Clinical features consistent with vascular dementia were those that are currently included in the group of subcortical vascular or frontal-lobe subcortical lesions such as early gait disturbances, frequent falls, increased urinary frequency, personality changes, depression.

There is now in the psychiatry literature a strong trend towards the diagnosis of vascular depression, psychomotor retardation and, especially, the abnormal executive function.

There are several studies, and Dr. Helena Chui certainly will present some of the most recent data, but

from previous studies, the sensitivity and specificity of the NINDS/AIREN criteria range from 0.58 to a specificity of 0.94 which is reasonably good.

[Slide.]

The CAPA Index, the inter-observer reliability, ranges from a modest 0.46 to 0.72. Essentially because of the differences in the diagnosis of dementia, what dementia is, you can see a substantial difference in the incidence of dementia in a particular population.

[Slide.]

Part of the difficulty with a stroke and dementia and vascular lesions and dementia is that this is a necessary condition but it is not the only factor that leads to the development of dementia. This has been one of stumbling blocks, one of the difficulties in the diagnosis of this condition.

[Slide.]

I will give you an anecdotal example. You recognize Louis Pasteur. Late in life, you can see the sequelae of left hemiplegia with facial--and loss of use of the hand. Indeed, he suffered a stroke at age 46 when he was barely beginning his studies on beer and fermentation. He had a second stroke after the discovery of the rabies vaccine and the third one one year before he died.

So, as you can see, stroke is not equal to

dementia. You may not have cognitive dysfunction as a result of a stroke. That has been part of the problem.

[Slide.]

The initial approach was to say, well, it is a question of volume. The more strokes you have, the higher the chances are that you will develop dementia. Indeed, the term "multi-infarct dementia" coined by Hatchinski in '68, '70, sort of decided to take away from that group of arteriosclerotic dementia that had existed since the turn of the century, the very likely explanation.

[Slide.]

But it was also clear that this was not the only factor for dementia, that you could have, as you see in patients who suffer an acute stroke--this is the experience from Columbia University by Desmond--that the odds ratios for developing of dementia are the presence of a large-hemisphere stroke, left-sided, anterior-cerebral or post-cerebral artery.

But, certainly, the most important factor is going to be age. Patients who suffer a stroke after age 80 or older have an odds ratio almost thirteen times the risk of dementia.

[Slide.]

The second factor is that if the stroke is complicated by ischemic anoxic complications such as

seizures, cardiac arrhythmias and so on, the possibility of developing dementia is very high even when you include in the equation age, education, hypertension and other elements.

[Slide.]

So the incidence of post-stroke dementia ranges between 27 and 41 percent depending on the criteria. Let's say 25 percent of patients who suffer a stroke will develop a significant dementia making this one of the most important problems--

[Slide.]

--especially because we now have elements to prevent those, at least decrease the incidence, and there has been a substantial improvement in the prevention of cardiovascular disease in this country.

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We are going from the large vessel to small-vessel lesions--

[Slide.]

--and to lacunar strokes that can produce dementia by itself--

[Slide.]

--to the concept of Binswanger's disease where you have a substantial loss of the periventricular white matter producing sort of a disconnection of cortical function.

[Slide.]

Finally, as I mentioned, the CADASIL, the first of the genetic forms of dementia that has been essentially a model of how vascular dementia can progress.

[Slide.]

Finally, in summary, we believe that the importance of vascular factors is extremely large. Fortunately, after a decade of controversy, we are beginning to see the first results of at least clinical trials that indicate that this is, indeed, a separate population, different from Alzheimer's disease, that this is not just Alzheimer's disease with a sprinkle of lacunar lesions but that, indeed, it represents a different population.

As we will see later on today, not only the treatment but the possibility of prevention is offering one of the most exciting changes in this area.

Thank you very much.

DR. KAWAS: Thank you, Dr. Roman. The floor is now open for questions.

DR. NYENHUIS: Dan Nyenhuis from Rush Medical College. Do you think that memory should continue to be a requirement for the diagnosis of vascular dementia?

DR. ROMAN: Again, as I mentioned, the problem is with the definition of dementia, what is it that we are going to define as the dementia. We often see patients who

pass the Mini-Mental with a score of 26 who have relatively good memory. At least, they can remember two out of three objects after a few minutes.

Memory is not the main complaint, but these patients are unable to cook. They are unable to get dressed. They have major difficulties in their daily-life interactions. When you do tests for frontal executive function, you find that they are profoundly affected.

So I think this is going to require a redefinition of dementia rather than redefinition of vascular dementia. So, for the time being, again, we are sort of prisoners of the definition of dementia that resulted from the large number of patients with Alzheimer's disease.

So it will have to be in the equation and probably what we need to do is decrease the importance of memory as the main element. But this is going to require probably a complete redefinition of the problem.

DR. CHUI: Dr. Nyenhuis, may I also respond to your question about whether memory should be a requirement for vascular dementia. My response is it depends on how you define memory. I think if you define it broadly as difficulties with recall, that patients with vascular dementia will also fulfil the criteria for a memory disorder.

But these people often don't have the same type or

pattern of memory disorder. They respond better to cuing or recognition memory. So I think we could still be content to say that memory would be one of the requirements but we would have to relax how we operationally define the memory impairment. In fact, the pattern may help us in a differential diagnosis.

DR. DeKOSKY: I would like to know why memory would have to stay as a required cognitive domain for memory. As somebody from the Alzheimer's side who had nothing to do with those definitions, I am curious about someone who presents with praxis and, perhaps, language problems from a left-hemisphere lesion and the kind of executive dysfunction and, perhaps, executive memory dysfunction that Dr. Chui is describing, why would you need to have memory loss as a requirement for a significant impairment in cognitive function to meet vascular-disease criteria?

Are we still a little too attached to AD? I don't understand the logic even listening to it as an Alzheimer person.

DR. CHUI: I think it is a good debate. Actually, in the criteria that we developed in California, we dropped the requirement for memory. In the unfolding criteria for vascular or cognitive impairment, there is no requirement, really, for memory.

DR. KAWAS: I think that is Dr. Chui's way of saying it doesn't have to be part of the definition. It sounds like we have already got two definitions on the table.

DR. PENIX: As a corollary to that, what do you think the contribution of requiring memory as part of the definition for dementia has contributed to the difficulty in separating vascular dementia from Alzheimer's disease?

DR. ROMAN: I think that is an important point because what it meant was to emphasize that sort of gray area that we haven't touched of the so-called mixed dementias, patients who have what has been called pre-stroke dementia. This is a patient who has been having memory difficulties for the past three years, who is having difficulty with finding the way to the bathroom and happens to have a stroke that makes things much worse.

But that patient, and this can be as many as twelve, fifteen percent of the patients who present with so-called post-stroke dementia, are actually patients with Alzheimer's disease who happen to have a stroke because of the commonality of risk factors between the two conditions.

So I think the emphasis on memory, in a way, has given a bad name to the criteria because it says, well, what you are doing is you are including patients who actually have Alzheimer's disease and just happen to have a stroke

that triggers or makes the dementia much more evident.

That is the reason why, as I already mentioned, we are trying to give a little bit less emphasis to this memory deficit as a requirement. But ten years ago, it was an anathema.

DR. WOLINSKY: I heard a number of different ways that vascular disease can lead to this syndrome; large-vessel disease, small-vessel disease, diabetes, hypertension, CADASIL. So when we talk about treatments for this form of dementia, if it can be defined, will we always be talking about symptomatic treatments, since I can't imagine a common pathophysiology for the fifteen different types of ways we can do this with vascular disease.

DR. CHUI: I think that is a good lead-in for my talk.

DR. KAWAS: In that case--actually, though, on your way up, I would like to ask a question. Back to the discussion of two cognitive domains and whether or not memory needs to be one of them, it strikes me that defining vascular dementia with two cognitive domains and not specifying which ones does not rule out, or take out of the diagnosis, anybody who would have fallen in with memory or would have mixed dementia and would only serve to capture more people who might have been left out and, as such, that means it would increase its sensitivity for vascular

dementia if the domain of memory was not specified. Is that the case?

I think we have got two people who want to comment before Dr. Chui gets to speak. One of them is Dr. Chui, followed by Dr. Wolinsky.

DR. CHUI: I just wanted to give a nod to that interpretation. I think you are right, that if we require memory as part of the definition of vascular dementia, we are enriching the sample for Alzheimer's disease and increasing our dilemma of separating them later.

DR. KAWAS: No; I don't think you enrich. If you say two domains, and the person has a problem with memory, they will still fall into it. So you don't increase your specificity or enrich it. You actually--is that correct?

DR. CHUI: If we leave the two domains as if one could be memory, then there is no problem. It creates a larger universe. But if we specify that one of the two domains must be memory, which is the case for the DSM III criteria for dementia, and for the Alzheimer's type, then we are enriching for Alzheimer's.

DR. KAWAS: By excluding the other individuals. Okay.

DR. WOLINSKY: I see the problem of the patient who has been having progressive cognitive decline before an obvious clinical stroke. But then I have trouble with the

logic of saying that once there has been evidence of a clinical stroke, the cognitive decline can occur with or without evidence of further strokes as long as there is additional vascular disease.

So have we excluded a significant part of vascular dementia which is the most interesting part which is presenting before the stroke with these criteria?

DR. ROMAN: Part of the problem is that the data from the Nun study shows that you could make a case for what the Nordic Group of Dementia calls type 1 and type 2 Alzheimer's disease. They say Alzheimer's disease is the one described by Alzheimer with Auguste D. who was only a 50- or 51-year-old woman who developed dementia with psychotic features, if you want, and who had the typical lesions.

When you look at the pathology of those cases with early-onset Alzheimer's disease, there is really no vascular component except for amyloid deposits. But, as you grow old, and this is the case, for example, in the Nun study where the mean age of the subjects who came to postmortem was well in the '80s with a couple of centenarians in the group, it is clear that the neuropathologist cannot make a diagnosis, cannot say who was demented and who was not demented because of the presence of typical lesions of Alzheimer's disease fulfilling the neuropathology criteria

for the condition.

So what made the difference was the presence of small lacunar strokes. It seems that vascular disease seems to be the trigger, the element that sort of brings to the surface the clinical expression of the dementia, the dementia of Alzheimer's type in the clinical viewpoint.

So the idea is that, and I think Phil Gorelick will address this, perhaps we can do more, not so much for the treatment of the condition, both vascular and Alzheimer's disease, which, at the end, are essentially the final common pathway of a number of elements, but perhaps we could do something in the sense of prevention, that some of these cardiovascular risk factors could be treated to prevent the development of a dementia that, in that case, would not be that important if we call it just vascular or Alzheimer's disease.

So I think, from that viewpoint, it is extremely important to keep the separation between the two conditions. In one case, the disease in the elderly may not be enough to manifest as an Alzheimer's type dementia and that you need the vascular component.

DR. WOLINSKY: I guess my problem, and I understand the difficulties, or some of the understanding of the difficulties of what you have just described, but I thought that the working definitions you have would actually

exclude a fair number of patients with CADASIL from consideration because they would be presenting with a dementing illness before stroke.

DR. DeKOSKY: This is a place where not having to consider memory in these early slow onset by vascular determined cases would be very helpful because if you look across the group, that is, I think, one of the places where Alzheimer's disease kind of flows into the group especially those who have subcortical white-matter alterations who somehow get brought to you in that context who may have some vascular risk factors.

DR. CHUI: I think you have an excellent question. While I can't answer it, I can, perhaps, expound on it. So, if I am understanding correctly, you are saying that if we take someone that comes in with a stroke but with a history of a slowly progressing dementia before the clinical event and exclude them because we assume they have Alzheimer's disease, aren't we excluding, maybe, the most interesting part of the sample.

I agree with that. Many of us are doing that. I think, in the stroke series, about 12 percent of them have a history of slowly progressive dementia before the clinical event. Again, I think, coming from an Alzheimer's model, we assume that a slowly progressive dementia means Alzheimer's disease.

But you come the multiple-sclerosis world and you know that slowly progressive dementia could be multiple sclerosis. I think that slowly progressive dementia can also be vascular dementia.

DR. KAWAS: I guess the challenge is going to be to find it.

DR. WEINER: I just had a quick question. Is it fair to say that in somebody with a vascular type dementia there have to be abnormalities on the MRI?

DR. ROMAN: Yes; that is a requirement from the criteria.

DR. WEINER: There has to be.

DR. ROMAN: There has to be; yes. If you have a clean MRI, it has got to be something else.

DR. WEINER: What percentage of people who have Alzheimer's disease have a clean MRI?

DR. KAWAS: Age-dependent would be my answer.

DR. DeKOSKY: It also depends on where you get your cases. If you look at the centers, in our center, we code VAD cases according to whether or not they have subcortical white-matter alterations. I think we run, I would say, probably 60 percent clean when we stay below the age of 75. When we get above that, it probably decreases. But it is somewhere in the 50:50 range.

DR. WEINER: So it is an age-dependent--

DR. DeKOSKY: It is age dependent and the other comment would be that, in looking, as some of my colleagues do, at cognitive processing in normals, they clearly see this association of altered but still within the normal range and obviously slowly progressive cognitive declines, not dementia, clearly associated with subcortical white-matter alteration.

So there are ways that you can have slowly progressive changes that look like they map to some kind of alteration, at least in white matter, if we assume, like all the neuroradiologists do, that that is due to vascular disease. So there is a model for that although Alzheimer's docs don't think about it very often.

DR. DUARA: In response to your question, Dr. Weiner, when you say "clean MRI" in Alzheimer's disease, it really depends, I think, what do you mean by clean. If you consider just the periventricular area, there is a very significant increase in white-matter change in Alzheimer's disease that has been documented in multiple studies.

Although the radiologist will always read this as ischemic, they have no idea what it is and it could be a variety of different things. It could be inflammatory. It could be vascular. It could be degenerative. It could be gliosis. Who knows what it is.

So if you are just talking about that increase in

white-matter disease right around the ventricles, that is, I would say, almost universal in patients with Alzheimer's disease to a varying extent. But if you are talking about discrete infarcts, that is a different situation. I would say that it probably pretty unusual.

DR. DeKOSKY: I would have to say that has not been our experience. It may be the difference where the patients come from that Ranjan sees. Linear periventricular changes, I think, are an aging change and I excluded that from what I thought your definition of clean was.

But looking for subcortical white-matter changes, which we do both with T2s and with flares, and flares picks up a lot of things we are not sure of the origin of that we don't see on T2, we see lots of patients who are clean. But the older they get, the more likely we are to see the extensions out from the angles of the ventricles in the AD cases.

DR. GORELICK: I think one of the points here is that vascular dementia or vascular cognitive impairment is a dynamic process. The criteria that we all grew up on that came out of the psychiatric literature that this was a stepwise deterioration and then the Hatchinski score which, really, just took the old criteria and then built some weighting to it, and it heavily weights toward stepwise deterioration and vascular risk factors, may not be correct.

What we have now is the new imaging techniques which are probably going to show us--we are doing a study, Dr. Chui is doing a study. We are starting--for example, at our site, we are looking at diffusion-tensor imaging of the white matter. We are looking at the hippocampal volumes, entorrhinal cortex volumes and so on.

Dr. Chui is doing similar things. She is ahead of us by about a year. She is going to show some data. But I think the idea is that when we start looking at these things, and if we start adding diffusion and perfusion imaging at periodic times, we are probably going to find that this is a very dynamic disease and it is not just going to be the stepwise chugging along deterioration.

DR. CHUI: Coming back to your question, is the neuroimage always abnormal in vascular dementia, I would agree that our current criteria require that but that can be circular. From looking at the pathologist's end, there may be ischemic pathology with a normal MRI or CT, especially microinfarcts in the cerebral cortex.

So I view imaging as our most sensitive tool at this time but I don't think it is the end-all for detecting ischemic vascular disease.

DR. WEINER: Is there any neuropathologist seeing--you can't do that in people. So the question is is there anything more sensitive than the imaging?

DR. CHUI: Imaging is evolving all the time, so I think imaging tomorrow might be able to increase this threshold of sensitivity. But structural MRI and flare now is the best we have at this time.

DR. KAWAS: Dr. Katz?

DR. KATZ: I just sort of want to press that point a little bit. The way I hear it, there is a certain amount of sort of--I don't know, call it clinical nominalism or something--going on here. These are patients who have had strokes or something is seen on MRI. Maybe they are different clinically than Alzheimer's patients or maybe they are not, as we have already said, Alzheimer's patients who presumably have Alzheimer's and then have a stroke get worse and it is considered to be their Alzheimer's.

So there is a considerable overlap here. I am just wondering, given the clinical criteria that are applied to diagnose vascular dementia, how well does that map to the pathology? How robust is the pathologic database that supports this?

In other words, when physicians apply the vascular dementia criteria clinically and they say, "Okay; this patient has vascular dementia," what does the pathology show? There is obviously considerable overlap in the brains of patients who are diagnosed either when they were alive with vascular or Alzheimer's disease.

There is the pathology of both in the brains of these patients. I am wondering how well does the pathology, at this point, support these clinical diagnoses?

DR. CHUI: In our program project, we have about 35 autopsies at this time. We find that the pathologist sees a lot more vascular pathology than we imagined clinically.

DR. KATZ: In vascular patients, or Alzheimer's patients, or both?

DR. CHUI: In both. There are some problems in that there is an interval of time between the MRI and the autopsy. Some would argue that this difference in the magnitude of ischemic brain injury has occurred during this interval. But one of our projects is to try to get the MRI as close as possible to the autopsy.

But the sample is still very small.

DR. KATZ: But, again, it raises the question of how do you know what is causing the clinical picture. Patients who are demented and they have a vascular picture, whether it is on the MRI or clinical, you think there are vascular events. So you say, "Well, the dementia is due to the vascular events."

I am wondering, really, how, again, since sort of pathology is the gold standard, how robust the pathology is to support those clinical diagnoses?

DR. CHUI: My proposal is that we retreat from this battle because I think we have lost it. I don't think we can use pathology as a gold standard for the diagnosis of vascular dementia because pathology is mute on dementia. It tells us nothing about behavior.

Pathology can just confirm that there are ischemic brain lesions and whether or not there is Alzheimer's disease at all. So I think I am going to propose a retreat toward identifying ischemic brain disease and not worrying so much about whether it causes dementia. We should be, then, targeting our treatment at minimizing the progression of the ischemic brain injury.

DR. KATZ: But, again, to bring up the question of semantics, we have to worry about what you call these. These patients may be demented and they may have vascular disease. They may also have pathologic changes consistent with Alzheimer's disease. But we have to worry about--obviously, we all have to worry about what you call it.

I am not even talking yet about proposed treatments and prevention and symptomatic treatments. I am simply talking about what do you name these people. Can we reliably say these people have something called vascular dementia and it is different, fundamentally different, from these patients who have something called Alzheimer's

disease. That is the real question, at least at the moment, for me.

DR. KAWAS: Actually, I have a question for Dr. Chui. Of those 35 autopsies that you have, presumably of carefully diagnosed, carefully selected, individuals, what percentage of them had Alzheimer's pathology at autopsy in addition to whatever vascular you found?

DR. CHUI: Let me just talk about the first twenty-four cases because the other ten are still kind of being evaluated in our consensus process. Of the twenty-four first cases, we had twelve that were clinically diagnosed as vascular dementia.

The degree of Alzheimer pathology varied. A number of them have neurofibrillary tangles in the entorrhinal cortex and hippocampus, Braak stages 1, 2, 3 and 4. But, actually, very few of them had Braak stages 5 and 6. So there is some degree of Alzheimer pathology I think commonly taking place in the hippocampus of these individuals, but they don't have the isocortical stages of Alzheimer's disease.

A number of them have diffuse plaques in the cortex but not neuritic plaques, to complicate matters.

DR. KAWAS: Did any of them have nothing but vascular disease?

DR. CHUI: A few of them did, yes; only vascular

disease. We still say Braak 1 or 2, but these are older people.

DR. GORELICK: I just wanted to respond to Dr. Katz's question. We are fighting this age-dependent battle that Mary Ganguli called being in trenches. As people get older and older, more and more things start happening to them just as they are happening to all of us sitting around the table.

So we have a lot of confounds that we have to deal with. If you want to really get a pure case of vascular dementia, you find somebody who has lupus anticoagulant or anticardiolipin antibody and has the misfortune, at the age of 35 or 40, to have a number of infarcts, and you are probably not going to find plaques and tangles in the brain.

But, again, we keep fighting this battle that they are in the hospital for various problems. They get pneumonia. They have hypotension. They have cardiac arrhythmias and things become very, very messy for us. So I think that one of the issues is I am not sure that, in some regards, and I will try to explain that when I give my discussion, that we need to give these labels.

In certain respects, they are very important. But, in other respects, they may not be because once the brain gets wrecked, if you will, by dementia, it is wrecked. The idea is to be upstream and try to prevent that process

from happening.

I think if we start focussing upstream, we are going to be a lot better off than trying to deal with this stuff downstream when the brain is wrecked.

DR. KATZ: I agree. But, right now, I think we are sort of downstream. In other words, we have companies coming to us saying, "These patients have vascular dementia and we want to get a claim for the treatment--not necessarily prevention--just the treatment of vascular dementia."

So that is why we are here today, to figure out whether or not we have a common understanding of what that is as opposed to just calling it vascular dementia because patients are demented and they have vascular disease.

DR. CHUI: My compromise position is that the small-vessel subtype does represent one form of vascular dementia where we can label it an we can propose a pathologic gold standard because here the pathology does correlate with the severity of dementia.

DR. PENIX: I guess one of the problems is that there are no large series of neuropathological data. But is there data available to answer Dr. Katz's question through, like, the SERAD? My understanding is that SERAD is a registry for Alzheimer's disease centers and they correlate clinical data with many different things, one of which would

be neuropathological data from the multiple centers. I am not sure if that data has been put together that would give a large number.

DR. GORELICK: Generally speaking, if you look in these brain-bank studies, the diagnosis of vascular dementia is uncommon. On the other hand, you have to think about the source of the data. You have got pristine diagnoses which exclude all of the risk factors, and so on and so forth. So you are going to have a very special group of people.

DR. KAWAS: I think one of the studies that you might need to hear about is Dr. Chui's program project. So, can I introduce Dr. Helena Chui.

DR. CHUI: But I won't talk much about the program project.

DR. KAWAS: She is going to talk on Focus on Subtypes, Dementia Due to Subcortical Ischemic Vascular Disease. Dr. Chui is from the University of Southern California, Los Angeles and Ranchos Amigos in California.

Focus on Subtypes: Dementia Due to Subcortical Ischemic Vascular Disease

DR. CHUI: Dr Wolinsky, could you rephrase the question you ask about ten minutes ago? It was something about, since there are so many different pathways which lead to vascular dementia, does this mean that treatment of vascular dementia will be confined to symptomatic treatment,

because it is difficult to conceive of a treatment that could really encompass all of the different pathophysiologies.

[Slide.]

I agree, that is an excellent question. My thesis is that vascular dementia is very important for epidemiologic studies. The criteria that Dr. Roman described help us to get an idea of the overall large denominator, how big is this net.

But my thesis is that, for treatment, it is not a useful net, that we have to, then, go down to subtypes that are defined by specific pathophysiologic processes. The one that I am going to choose to illustrate today is subcortical ischemic vascular dementia.

[Slide.]

We came from a very invigorating and intense day, as you said, yesterday, talking about the early stages of Alzheimer's disease. Dr. Roman also said that most of us came from an Alzheimer background and so we are influenced very much by the model of Alzheimer's disease.

But the question is, taking a step back, and the FDA is asking us to step and ask the different questions, is Alzheimer's disease a good model for vascular dementia.

There are certain risk factors that lead to Alzheimer's disease like genetic ones in 10 percent of cases

or apolipoprotein E4. There is a common pathology, neurofibrillary tangles and neuritic plaques, and there is a common phenotype, a progressive loss of cognitive functions starting in the early stages with MCI and then progressing to dementia.

However, for vascular dementia, if we start here and go backwards, there are a whole host of risk factors; hypertension, diabetes, hyperlipidemia, atrial fibrillation, CADASIL, hypotension, et cetera; many types of cerebrovascular disease, atherosclerosis, arteriosclerosis, amyloid angiopathy, which is seen in Alzheimer's disease and thus makes Alzheimer's disease a vascular dementia.

Hypotension, changes in the blood-brain barrier leading to several types of brain injury; hemorrhages; ischemia, ischemia due to occlusion, due to hypoperfusion, leading to many syndromes; hemiparesis, hemisensory loss; visual-field defects; akinetic mutism; neglect; constructional apraxia dementia.

[Slide.]

Vascular dementia is not a disease. It is only one possible phenotypic expression of vascular brain injury, among others, focal deficits. Sometimes, there is no observable phenotypic expression. We see, in MRI, evidence of brain injury and there is no history of a clinical event.

Cerebrovascular disease sometimes leads to

dementia. Alzheimer's disease, arguably, does so invariably. Unlike Alzheimer's disease, we already know a lot about vascular risk factors and how to treat them so focussing on vascular dementia is an arbitrary and late choice.

[Slide.]

The FDA's questions, can vascular dementia be clearly defined in a clinical setting; I believe it can, yes. We just defined dementia, cerebrovascular disease and that there is a relationship between the two. But my question is is this useful, given its heterogeneity for treatment? Is this useful for treatment, given its heterogeneity?

Are there valid criteria for the diagnosis of vascular dementia? Not if pathology is the gold standard because, unlike Alzheimer's disease, the severity of the pathology does not correlate strongly with the severity of vascular dementia. The volume of infarcts may vary from 1 centimeter to 1 cubic centimeter or milliliter to 230 in Erkinjuntti's paper.

Can vascular dementia be distinguished from Alzheimer's disease and other causes of dementia? We can define the vascular brain injury. We cannot rule out concomitant Alzheimer's disease. That is a weakness of the diagnosis of Alzheimer's disease. It is really not a

vascular-dementia problem. It is a problem with Alzheimer's disease.

But my question is does this matter? Can't we just treat the vascular injury and then treat the Alzheimer's separately, two separate things. We have separate independent markers for two processes.

[Slide.]

So my position is that vascular dementia is an important diagnosis for epidemiologic studies but it is not a useful concept for treatment. This is Dr. Wolinsky's question. It is too broad. It is akin to trying to treat neurodegenerative dementias as one group; Alzheimer's disease, frontal-temporal dementia, dementia of the Lewy body. We can treat them symptomatically.

[Slide.]

There are too many types of cerebrovascular disease and too many pathophysiologic mechanisms.

[Slide.]

There are too many clinical phenotypes, major hemispheral syndromes, lacunar state and variations in the clinical course, abrupt onset, stepwise progression and slowly progressive decline as we see in Binswanger's subtype.

[Slide.]

There is a problem with the clinical criteria.

They are not interchangeable and, as I mentioned, there is no gold standard for vascular dementia.

[Slide.]

Here are several criteria for vascular dementia that we studied in the State of California. We took twenty-five vignettes and sent them around to seven centers and asked them to check coding sheets for each of these criteria; the Hatchinski Ischemic Score, the Diagnostic and Statistical Manual, the California Alzheimer's Disease Diagnostic and Treatment Center Vascular Dementia and the NINDS/AIREN criteria that Dr. Roman described in great detail.

Left off this list is the ICD10 which we didn't study. Of these twenty-five cases, the autopsy showed vascular pathology in 24 percent. The DSM IV criteria picked up most of these cases. So did the Hatchinski Ischemic Scale modified. The ADDTC and the Hatchinski Original picked up about a half. The NINDS/AIREN criteria picked up about a fifth of the cases.

So there is a great difference in the sensitivity of the criteria using just the presence of vascular pathology as the gold standard.

Internally, actually the Hatchinski scale has the greatest inter-rater reliability. The kappa scores were the highest, 0.6. For DSM IV and ADDTC and NINDS, there was a

moderate degree of internal consistency.

[Slide.]

Why do we have such difference in the sensitivity of the these criteria? The way I conceptualize the issues, it is very similar to what Dr. Roman laid out. We have dementia and we have vascular disease in the title, the nominal labeling. The challenge is how do we demonstrate this causal relationship.

The criteria vary in what they consider to be necessary clinical signs and symptoms. For example, do you require focal signs, neurologic signs and symptoms. The NINDS/AIREN do. The California criteria do not. What do we require about the cognitive impairment; that it have an abrupt onset? Do we require structural imaging? The Hatchinski Ischemic Scale does not.

What other factors do we consider to be a causal relationship? The ADDTC criteria and the NINDS/AIREN criteria require some sort of a causal relationship between a clinical event, a stroke, and the cognitive impairment. That really narrows their sensitivity.

So this kind of variable way of putting together these pieces of the puzzle explains, in my mind, why there is so much variability in the criteria.

[Slide.]

One solution for treatment is to focus on

subtypes, to take the perennial--go from a lumper to a splitter. So here we are taking the splitter strategy. My shorthand for this is subcortical ischemic vascular D. And the D could stand for dementia or it could stand for disease. Disease is more the pathophysiologic process and dementia is one phenotype.

[Slide.]

The small vessels that we are speaking of are 100 to 600 microns in diameter. These are arterioles that have no internal elastic lamina and they are within the brain substance. They are within the cortical mantle as short arterioles but then a number of them called long medullary articles perfuse the deep and periventricular white matter. These small arterioles also feed the subcortical grey matter in the basal ganglia and thalamus.

[Slide.]

So let's take a look at this cascade of events within this subtype. Here we have hypertension and diabetes mellitus as the most common risk factors. CADASIL would go in here, too. They lead to small-vessel pathology, SIVD, using one form of the label, leading to ischemic brain injury. Of course, hypertension also leads to hemorrhagic brain injury.

This leads to a syndrome of dementia due to SIVD as well as gait disturbance, urinary incontinence, and so

forth. So SIVD is a term that can be used to describe either the subtype of the vascular disease or the dementia syndrome. I prefer to say dementia due to SIVD to clarify that ambiguity.

SIVD represents a more homogenous clinical pathological entity and, therefore, I believe will be a more useful target for treatment. I am going to abbreviate this paradigm shift, the splitting, the focussing on subtypes, as drilling down. This is supposed to be an arrow pointing down.

By using neuroimaging, finding a surrogate marker for ischemic brain injury here, we can shift the focus of treatment to here, earlier in the disease process. So, while we can look at dementia as one of the outcome measures, my suggestion is that we really focus on this as the primary outcome measure, shift left earlier in the disease process.

So this paradigm shift I am going to refer to with the abbreviation, shifting left. This is supposed to be an arrow to the left.

So, really, the take-home message from my talk this morning is that we should drill down and shift left.

[Slide.]

So the FDA criteria can be reframed; delete vascular dementia, replace SIVD.

[Slide.]

There are two pathophysiologic mechanisms for SIVD. One is occlusive. This leads to lacunes and to lacunar states. The other pathophysiologic mechanism has been much more controversial. It is hypoperfusion leading to deep white-matter lesions and Binswanger syndrome. I put this in parenthesis because, clinically, Binswanger syndrome, I believe, is only the tip of the iceberg of the disease.

With MRI and CT, to some extent, we can detect this well before there is clinical Binswanger syndrome.

[Slide.]

So the two pathophysiologic mechanisms are occlusion of one of these small vessels which will give rise to lacunar infarcts in the grey matter, subcortical grey matter, or in the subcortical white matter. The hypoperfusion mechanism leads to incomplete infarction, not cystic or complete infarction but incomplete infarction, in the end zones of the long penetrating medullary arteries.

These are long, high-resistance vessels. When there is a diffuse small-vessel disease picking up every one of these, the perfusion pressure head will be lowest here and this, I believe, is manifest as white-matter lesions on MR or CT as leukoaraiosis.

[Slide.]

Just briefly, because these are in your handout now and I think you have noticed I changed my talk and am now just entering what you have in front of you, these lesions are like--the lacunes and the white-matter lesions are readily seen on MRI and, to somewhat a lesser extent, on CT.

So lacunes are bright on proton-density MR with a few rare exceptions. Cystic lacunes is the exception. They must be distinguished from perivascular spaces which are bright on T2 but not brighter than CSF on proton density.

I won't go into these details, as I said.

[Slide.]

For the hypoperfusive mechanism, the deep white-matter lesions, we have, on MRI, various degrees of white-matter lesions. This slide came from the Cardiovascular Health Study of, I think, about 26,000 or 33,000--I forget--community-dwelling elderly. There is some correlation with neurobehavior once the lesions are rated greater than 5.

[Slide.]

So how do we conceptualize the diagnosis of subcortical ischemic vascular dementia? We have dementia, and here there is a more or less homogenous behavioral syndrome. It is the frontal dysexecutive syndrome. There are memory problems but the pattern is that, while there are

difficulties with recall, recognition memory is better spared.

There are certain clinical signs and, on the MRI, multiple or strategic lacunar infarcts and confluent white-matter lesions. Treatment can be symptomatic at the dementia stage or it can be aimed at preventing ischemic brain injury, shifting left.

[Slide.]

There are criteria published for subcortical vascular dementia by Erkinjuntti et al. in the Journal of Neural Transmission, 2000. This encapsulates this--

[Slide.]

--with the MRI criteria or--

[Slide.]

--CT criteria.

[Slide.]

For clinical trials of SIVD, the subtype, we would want to add cognitive measures that are sensitive for frontal dysexecutive function, working memory, retrieval deficits in memory, and speed of processing.

[Slide.]

For the clinical trials, structural imaging will be paramount. MRI would be preferred. The imaging could be used qualitatively for the diagnostic or the entry criteria and quantitatively as an outcome measure or a surrogate

marker for progression of ischemic brain injury.

[Slide.]

So, in summary, can SIVD be clearly defined in the clinical setting? Yes. And it may be more meaningful for treatment drilling down. Are there valid criteria for the diagnosis of SIVD? They are published but not yet validated. Pathologically, I feel we should aim at confirming the ischemic vascular injury in excluding Alzheimer's disease but not necessarily try to confirm that the dementia was due to vascular disease.

Can SIVD be distinguished from AD and other causes of dementia? Yes; we can define the vascular injury. But the question is we know we can't rule out concomitant Alzheimer's disease. The question is, does this matter? Why not treat both processes independently?

What outcome measures should be used? Add executive and recognition memory. What features should be included in the clinical design? Structural neuroimaging.

Thank you.

DR. KAWAS: Thank you, Dr. Chui. Actually, I would like to ask you a question. In the drill-down and shift-left model, it seems to me that what you were proposing was that we needed to put as a treatment for this the prevention of additional vascular injury as opposed to the prevention of vascular dementia, per se.

In that paradigm, to my mind, then, drugs that would be appropriate would be decided in the traditional model of what drugs are useful for stroke rather than what drugs are useful for dementia that is related to stroke.

Is that the case?

DR. CHUI: I think, in general, I agree. But I would point out that I think stroke neurologists, at this time, are focusing their effort on preventing the damage--preventing occlusion. They are focusing on the model of occlusion, preventing occlusion or minimizing the damage once occlusion has occurred.

There is, in my mind, a neglect of the importance and the possible effects of hypoperfusion. So I think the designs would be the same but there has to be a broadening of the concept. Vascular dementia--we see patients that we believe have vascular dementia, and, on autopsy, they have vascular dementia, they have a slowly progressive dementia with--maybe they have had one clinical stroke but they have many more ischemic vascular lesions on their imaging than clinical events.

They have a slowly progressive history. On pathology, they have some Alzheimer's changes in the hippocampus but not throughout the cortex. How, why are they slowly progressing? One hypothesis is it is this generalized stenosis and this hypoperfusion. There is where

we need to place our emphasis.

It is not just the prevention of stroke, a clinical, dramatic event, but a prevention of a more progressive subclinical incomplete infarction.

DR. KAWAS: You feel fairly convinced that that exists and that those gradual decliners are not doing it with another pathology, like Alzheimer's, that if we treated hypoperfusion, we would make a difference in some clinical way, if we had a treatment for hypoperfusion of some sort?

DR. CHUI: I do. I think you can tell that I do. I appreciate hearing other voices on that.

DR. GORELICK: I would get back to the issue that I have the strong suspicion this is a dynamic process. Unless we have serial MR technology going on these cases, we are not going to know for sure because a lot of these patients who wake up in the morning and feel a little clouded and feel they have the flu or it is their rheumatism, they may have just had an ischemic event, whether it is the pathology event or it is a physiologic block, uncertain.

Again, with more MR imaging that could be employed, we could probably see some dynamic changes. I think that is what Helena is referring to.

DR. DUARA: Maybe Dr. Chui should respond to that. I was going to ask a different question.

DR. CHUI: Dr. Kawas, another reason I believe is that is that in our program project, we do quantitative MR imaging. To our surprise, there is a lot of brain atrophy. The best correlate of the severity of dementia and vascular dementia is the degree of hippocampal and cerebral-cortical atrophy.

DR. KAWAS: Does the degree of hippocampal atrophy correlate with the degree of Alzheimer concurrent pathology?

DR. CHUI: No. If you go back--we saw that. It doesn't. There is something else going on in vascular dementia of this SIVD type, because that is the focus of our program project, that leads to a diffuse atrophy of the hippocampus and cerebral cortex and it is not explained by cortical neurofibrillary tangles and neuritic plaques.

DR. DUARA: Actually, that was the question I was going to ask you. If you look back at the old data on vascular dementia, there was a study done by Miller-Fisher published in The Lancet in 1962 where he looked at people, about 300 autopsies that had been done at Mass General Hospital.

These people had been evaluated by neurologists at Mass General within six months before they died, and they were considered not to be demented, whatever that meant at that time. The average number of lacunes in their brain of these 300 or so people was 3.2 lacunes. He had specified

that the size of the lacunes could be up to 2 centimeters in diameter.

So the question is how many--you showed a number of images today, Dr. Chui. Some of those looked like they were infarcts. Some of them looked like they were nonspecific white-matter hyperintensities, those relating to small-vessel ischemic vascular dementia.

Is there a way of optimizing--I guess that was my question and I think you partly answered that. But, if you look at T1 and T2-weighted images, if there is a cyst-like formation, a true lacune, rather than just a hyperintensity, does that increase your specificity of knowing that this is a vascular event? Perhaps, you could elaborate also on the question about hippocampal changes that you see.

Should the hippocampal change be on the same side as the vascular event that has occurred, or the major vascular event? Is there any relation there, the asymmetry of it, to understanding the pathophysiologic of that infarct in some region of the cortex or subcortical region?

DR. CHUI: I guess there were several questions there. Regarding increasing the specificity in the imaging for a vascular event and whether using T1 and T2 and proton density would improve the specificity, I don't think so. I do think that, as the T1 gets darker, it probably correlates with greater tissue injury so it might indicate the severity

of the ischemic injury but I don't think it helps us saying it is ischemic versus demyelating or something like that.

I guess your last question was does the syndrome--is it related to the side of the lesion or the location of lesion. I mean, that is a good question, and people have proposed a lacunar hypothesis, that it is a lacune in, say, a frontal subcortical loop, the head of the caudate as opposed to the putamen, the anterior limb of the internal capsule as opposed to the posterior limb, the genu instead of the posterior limb, the anterior or dorsal-medial thalamus as opposed to the posterior-lateral thalamus, or the ventricle-anterior thalamus.

Those proposed important locations that would increase the likelihood of a cognitive impairment. I think that is still a plausible hypothesis. But, in our program project, we haven't addressed that fully. We haven't broken down location to that degree yet.

But we didn't find a good correlation between the number of lacunes, like 3.5 lacunes, and the severity of the dementia. The best predictor of the severity of dementia was hippocampal and cerebral-cortical atrophy.

The cortical atrophy correlates with the white-matter lesions. The volume of the white-matter lesions correlates with the severity of cerebral-cortical atrophy, the ribbon. But the white-matter lesion volume

doesn't contribute a lot by itself to the dementia severity.

So I think the white-matter lesion is a good marker for ischemic vascular injury, once you take out MS and HIV and progressive multifocal leukoencephalopathy by clinical circumstances and so forth. Once you take that apart, I think it is a good marker for this second model, for the hypoperfusive mechanism. So I think it is a good marker for that, but it is not a great marker for the severity of cognitive impairment because it is mainly affecting the cabling, the white-matter tracks.

It starts with demyelation. It is going to cause slowing. Later it is going to cause axonal loss. So we are going to see, first, some declines in speed, declines in executive function, but we don't see a severe dementia until the white-matter lesion becomes all over the place. At that point, there is severe cerebral-cortical atrophy.

Again, I think I sound a lot like multiple sclerosis.

DR. KAWAS: I think you sound provocative enough that Dr. Gorelick, followed by Dr. DeKosky, is dying to have the floor. Dr. Katz, would you like to respond first and then we will move around the room?

DR. KATZ: I am still sort of troubled by the equation with the causality in the middle and trying to sort of tease that out, the lack of correlation between the

white-matter disease and the degree, or perhaps the presence, of dementia is troubling from the point of view of causality, not that a great correlation would prove causality either, but it would be stronger evidence that it was causative.

You said that, for this particular SIVD subtype, that there is a stronger or more homogenous clinical pathologic correlation than for other types, presumably of so-called vascular dementia. But you are suggesting now that, at least from the point of view of the white-matter disease, there really isn't much of a correlation.

How robust is the clinical pathology correlation in this particular subtype? Is there a wealth of data that shows that they are correlated? Again, these things suggest that they maybe they aren't very well correlated. I would just ask that question.

DR. CHUI: I think they are better correlated than if you take vascular dementia as just a whole and try to correlate the vascular lesions. In this subtype, the lacunes tend to fall first in subcortical white matter and gray matter, and they tend to fall in the frontal lobe more than the posterior lobe.

I think when you finally do volume all the lacunes pathologically--and somehow, we have to get some kind of a pathologic measure of what is going on in the cortex, what

is causing the atrophy there may be. But, at this point, I don't have data to say how strong that correlation is.

DR. KATZ: Maybe as a follow up, you also said that there was a relatively specific clinical picture with a frontal dysexecutive syndrome. I am wondering how specific is that. Do you see that in other types of dementia? Do you not see other sorts of typical dementing symptoms in this SIVD population?

I am really trying to get a handle on how specific this thing really is and how well we understand it both pathologically and clinically. So, from the clinical point of view, how good is the data on that?

DR. CHUI: I think if you showed the neuropsychological testing blindly to some neuropsychologists, they may not be able to say this is SIVD versus Parkinson's disease or progressive supernuclear palsy or normal-pressure hydrocephalus or even multiple sclerosis. But I think when the clinician has the imaging as well as this picture, it becomes pretty specific.

DR. GORELICK: I missed some of Dr. Katz's comments; I'm sorry. But I just wanted to indicate that there may be a unifying hypothesis for all of this. If you shift the paradigm over a little further to the left and really become radical, what you end up seeing is that hypertension, in mid-life, leads to cognitive impairment

later in life.

If you look at the MRI scans, for example, in the NHLBI Twin Study, what you find is the brains are smaller in the twin that had hypertension as opposed to the twin who did not have hypertension.

If you look at some of the other MR imaging studies, what you are finding is that there are areas in the brain where you might see accentuation of the loss of tissue. One of the areas that Strausberger has pointed to has been the hippocampus and the thalamus.

So this issue that you had first raised before I had to step out about why sometimes you see the white-matter lesions and it is correlated and sometimes you don't, what happens with hypertension over time is you are going to get, one, shrinkage of the brain. Two, you are going to have white-matter disease. Three, you are going to get lacunes. It depends where you are on that spectrum as to what is going to pop up at that particular time.

Again, there is a fair amount of cohort data from mid-life following out to later life that shows this.

DR. DeKOSKY: We made advances in Alzheimer's disease by stopping viewing dementia as global and saying the pattern of cognitive impairment is, in fact, the way you can make a diagnosis of inclusion. The dysexecutive symptoms that show up with the interruption of these frontal

subcortical loops, predominantly anteriorly, I think are one of the major markers for what makes clinicians look at patients and say, "This looks like a cognitive vascular impairment."

The problem, I think, listening to Helena and to the old history of lacunes is lacunes can cause problems or not, cognitively, depending on where they are. I think the next step may well be trying to correlate where they are, which is difficult but, with imaging, can be done with the clinical syndromes that they present.

Listening to the hippocampal shrinkage data, for which there are pathological reasons that it occurs, I thought of the same thing I suspect other people did. There is the lurking undiagnosed Alzheimer's disease in these cases that is causing this.

It would be one of the reasons why I think it would be extraordinarily helpful to look at cases who may have had an executive memory problem, the forgetting to remember, but who don't have the primary problem. If they did, and if their hippocampi were the ones that shrank, then I think you would have clear evidence that you could have a vascular syndrome that caused those sorts of atrophies that might, in fact, make it more helpful to diagnose but that would not have this specter of Alzheimer's disease being the real cause of the atrophy.

Until we have removal of that, either by quantitation of how much amyloid is in the brains of these cases or by removing what we would regard as sina qua non Alzheimer's symptoms, there will still be this doubt that Dr. Katz is trying to dissect his way through.

DR. PENIX: Dr. Chui, I like your approach in separating the cortical infarcts from the subcortical. I think, clearly, cortical infarcts are very different clinically and as far as etiology is concerned. I think that, by framing this this way, you are giving us an analogous picture of brain ischemia that is similar to ischemic heart disease.

We know that congestive heart failure is due to small-vessel disease and accumulation of small-vessel disease that can lead to left ventricular failure. So this gives us an idea that accumulation of this small-vessel disease in the brain can lead to a dementing process.

I think that, as far as the mechanism of hypoperfusion, that still needs to be shown. That is somewhat controversial. But, also, by separating it, separating this stroke syndrome, if you can look at it that way, creates another problem.

I still have problems interacting with primary-care physicians and calling all strokes CVAs. Therefore, we are asking them to--I have difficulty making

them understand that ischemic strokes are different from hemorrhagic strokes and now we are going to really press them to try to subcategorize ischemic strokes even more so. So I think that could present a little difficulty.

DR. VAN BELLE: I am trying to figure out what is the mix of your SIVD in terms of the total panoply of vascular dementia however defined. Secondly, you indicated that vascular dementia, that particular definition, is not useful for treatment. Is your definition useful for treatment, your SIVD?

DR. CHUI: I guess the first question is how important is SIVD for the overall mix of vascular dementia. I have tried to approach that question in two ways, one looking at hospital series of stroke patients, how many of them have lacunar strokes. It is about 10 to 30 percent, more common among African-Americans and Asian-Americans than Anglo-Americans.

The explanation there I think is because there is greater prevalence of hypertension in African-Americans and Asian-Americans.

Another way to look at your first question is, among people with vascular dementia, how many of them have this SIVD variant. That is the more direct question. The data there is more meager. In epidemiologic studies, we are just struggling with trying to find a common definition for

vascular dementia and although subtypes are outlined in the NINDS/AIREN, epidemiologic studies don't usually include neuroimaging studies which we required to do this separation.

So most epidemiologic studies are noninformative on your question. I think the exception to that would be, like, the Honolulu Heart Study, the Honolulu Asia Aging Study, where there is imaging.

In hospital samples, or in memory clinic samples, of vascular dementia, how many have SIVD. Phil, I would think of your study there. There it is pretty high. It is up to 50 percent.

DR. GORELICK: Right. We have looked at consecutive stroke patients since about 1987. We find, in our subgroups, that about 50 to 60 percent--and, again, this is largely in African-American population with a high prevalence of hypertension and other cardiovascular risk factors--it is about 50 to 60 percent. This is not population-based data. This is all comers to the hospital with a stroke.

DR. CHUI: Your second question is how useful is this definition for treatment, which is the hypothesis. I think that that is yet to be seen. But I think it is more promising than this larger one. I think the question is treating hypertension. Hypertension is this--so how

effective is treating mid-life hypertension and preventing this? I will leave that for Phil.

DR. ROMAN: Could I add just one more comment. The results of the factor of recruitment of patients; when you concentrate your efforts on post-stroke dementia patients, number one, you are dealing with a very old population with a high rate of mortality. So the number of patients who complete the study decreases very quickly.

As a matter of fact, dementia is a risk factor for poor prognosis for poor survival. So, by sort of veering away from this group, the multi-stroke dementia that would be sort of the most obvious for controlled clinical trials, you sort of improve the chances of completing the trial and demonstrating an effect.

The rate of failure to complete the study is very high when you just use multistroke dementia patients.

DR. WOLINSKY: Sitting here, just as you say, you feel like you are talking about MS. I look and have always expected that probably the advances that we need in multiple sclerosis for neuroprotective agents were going to come from your field because it is not sexy to do that in MS but it is in Alzheimer's disease and stroke.

And we have learned something lately, that we have some correlation with the findings that we can quantitate with our portal to the pathology of MRI. But our lesions

look the same as yours and our correlations are probably going to be no better, or maybe worse. Global changes are probably more important than focal changes and we are getting around to understanding what we don't know and how we do have fairly good insight but we still don't test specificity with this tool, which creates a problem.

But one of the things I think we have learned recently was to add a cognitive dimension to our global assessment of patients with MS and it adds something to understanding how drugs are working.

What I have heard, with your model for small-vessel vascular disease, is an overconcentration on dementia when the other dimensions of destructive processes in the brain must be included. Alzheimer's, you can forget about it because they happen so late they are not useful.

It is a dementing illness primarily from the beginning to end. But vascular disease is not. So, again, I worry about, as I think you have told us, the treatment paradigms being focussed just on dementia when the other things may give you a marker earlier.

DR. GRUNDMAN: In the definition of dementia, you have both neuroimaging and a cognitive syndrome. How much SIVD do you actually need on your MRI in order to have SIVD?

DR. CHUI: When you are using the "D" there, do you mean dementia or do you mean disease?

DR. GRUNDMAN: How much change on your scan do you need in order to say that you have enough there to correlate it with the clinical syndrome to say that you have dementia due to that entity?

DR. CHUI: It is a good question and I think I must go back and present the data. The thing I would want to show is the atrophy, actually, how much atrophy is needed before you start to see--what is the slope between the brain volume and, say, cortical gray matter and the whatever cognitive variable we use on that.

I can't tell you that. We have that data, but it is going to be a continuum.

DR. GRUNDMAN: So it is not the white matter, itself. It is this sort of corollary measure?

DR. CHUI: Yes; I think there is something going on here that we don't understand. The white matter and the lacunes are, in my mind, a marker that there is an ischemic mechanism but the route to the behavior is through this atrophy. And we don't understand that route, yet. It is circuitous.

DR. GRUNDMAN: Getting back to the question of how you would apply that in a community setting, I would assume that the idea would be that people would look at the scans and look at the white matter, not the atrophy.

DR. CHUI: Yes. I have just finished writing an

article for primary-care physicians on SIVD. What I recommend for the practicing person is to use the Cardiovascular Health Study and err on the conservative side. Their data showed that you could detect a relationship between cognitive function on, say, the modified Mini-Mental or on certain way scores or on the trails.

Once the rating exceeded 4, greater than or equal to 5, you could see the step-off occurring. So erring on the conservative side, I tell people, if you are seeing them as demented and you want to ascribe it to white-matter disease, to incomplete infarction, to SIVD, then expect to see greater than or equal to 7 on this which is confluence and extending partly way out into the centrum semiovales.

So I think there is a practical way of using the severity of the white-matter lesions.

DR. PENIX: Could you repeat that please? 4 indicated--you mentioned 4 and 7. I missed the 4.

DR. KAWAS: Would you like to put the slide back and maybe do it that way?

DR. CHUI: Okay; yes.

DR. KAWAS: In the meantime, Dr. Katz and then Dr. Grundman.

DR. KATZ: Again, it is the lack of correlation between the white-matter disease and the dementia and this

presumed correlation of the hippocampal and cortical atrophy with the severity of the dementia. We haven't seen that data, the correlation between the atrophy data and the degree of dementia.

I don't know how robust that database is, but, for argument sake, let's assume that that is very well correlated. I think, ultimately, we would have to sort of see that data but, again, let's assume that is what is correlated.

That is the link, as you say, between the white-matter disease--the vascular pathology and the atrophy is at the moment conjecture. It is hypothetical. We have no idea what the link is. It may not be through a vascular route at all. They may just be coincident findings.

But when we use a term like vascular dementia, the implication is that there is causative relationship between the two, that it is a specific pathophysiology and pathogenesis of the dementia. That is what I am trying to get my hands on. I am trying to learn what the evidence is that that really is what is causing the dementia.

Your question is a fair one. Does it matter whether you call it vascular dementia, or do you call it Alzheimer's dementia. It is a fair one sort of generically, but, for us, it is a critical question. So I am still trying to get a better handle on these correlations and the

causative nature of the vascular disease.

DR. ROMAN: We were in the same difficulty until CADASIL was described. Fortunately, we have here sort of a natural model of a disease that is characterized by small-vessel changes, that is a granular deposition in the vessels not only in the brain but in the skin and the muscle. This is a condition characterized by recurrent multiple lacunes and then by extensive white-matter lesions.

When you do MRIs on the relatives on patients with CADASIL, people who are affected, who carry the same gene, you find that they could be either asymptomatic--they could start having executive function. They could have problems with depression. Or, they finally start showing up the symptoms later on as the disease progresses of an acute stroke or the vascular-dementia picture. And they all end up with vascular dementia, essentially.

So we have here a very good model that can tell us--and there are very good correlations made on is it the number of lacunar strokes, is it the extent of the white-matter lesions, that defines the presence of the dementia.

But, indeed, I think we need to look at this problem as a continuum that starts with just a couple of lacunar strokes, a little bit of periventricular lesions and extends to the point where the symptoms become obvious, even

to the primary-care physician.

Part of the difficulty has been, also, that if we continue to use our paradigm of dementia emphasizing just an Alzheimer's disease type, we are not going to make the diagnosis because these patients will go to the urologist complaining of excessive difficulty with nocturia.

They may have frequent falls and show up with the orthopods. They have a hip fracture and then become acutely demented after the hip is fixed. So I think we need to emphasize that there is, indeed, a continuum that behaves completely different from Alzheimer's disease and that this is a separate population in terms of the way they progress.

Again, until we had CADASIL, we were just presuming that that was the reason. But now we have a marker that allows you to see, in this natural model of the disease, the CADASIL, how you go from one lacune to two and then the extensive white-matter lesions until you finally reach the stage of dementia.

DR. GRUNDMAN: Along the lines of shifting left, probably SIVD, the risk factors for this are hypertension, diabetes. But these are also risk factors for larger strokes. So I guess I would wonder--you know, with Alzheimer's disease there is sort of a natural history or a course that one might expect. You go through these various stages. We are arguing about where it begins and where it

ends, but, in this case, it seems to me like SIVD could become large multi-infarct dementia at some point.

So I am wondering how you are going to deal with that in your nosology.

DR. CHUI: Mixed. I call it LIVD and SIVD. Actually, I thought this would be a nice pattern. But when we are looking at the pathology, we see a mixture, actually. There is arteriosclerosis and atherosclerosis. It is not going to come out this neatly. There is going to be mixed vascular Alzheimer's. There is going to be mixed SIVD, LIVD.

DR. GRUNDMAN: That is what I suspected. Do you know the proportions of each? I guess, within the context of a trial or the trials that we are talking about, would you be thinking just about doing short-term trials so that the trial would be over before they might have had a larger stroke?

DR. KAWAS: I am not sure that is a question easily answered in this context. You can defer and go to the--

DR. CHUI: I think the SIVD patient is at risk for LIVD, too, at risk for both a small stroke and a large stroke, absolutely. If we use the surrogate markers like MRI and some of these other measures, we hope we can follow them before they are censored by a large stroke and then

their cognitive testing is not going to be meaningful.

DR. GRUNDMAN: So would this model work more for, like, a symptomatic treatment than for long-term prevention treatment or do you just use different markers as your endpoint, like larger strokes and worsening dementia or a combination of both.

Have you thought about those sorts of outcomes for the different types of agents that might be used?

DR. KAWAS: Am I overstepping to say maybe this is something we can take care of in the larger context?

DR. CHUI: Later on; yes.

DR. KAWAS: Later on.

DR. CHUI: I appreciate that.

DR. KAWAS: Maybe if you would like to show Dr. Penix the 5 or greater, and then we will have a break, which I think will relieve a lot of people in multiple ways.

DR. CHUI: Thank you.

[Slide.]

This is taken from Longstreth et al., the Cardiovascular Health Study. This is their visual method for rating the severity of white-matter lesions. There is also 0 and 9, but they are not shown here because 0 is defined as less than 1 and 9 is defined as greater than 8.

So if you look at 8, you can start there, the periventricular white-matter lesions are well out into the

centrum semiovale which looks black there. 7 is described as confluent and extending partly through the centrum semiovale. 6 is confluence around, I guess, the caps there. 5, you certainly have a periventricular rim that is extending out, I don't know, at least 10 millimeters or something like that.

[Slide.]

Then the next slide shows how it is related to cognition. On the X axis is the rating scale. This was a community-dwelling sample so most of these elderly had very little in the way of white-matter lesions. Actually, I don't show the distribution there. Then, on the Y, it is the mean modified mental-state score which is the 3MSSE. It is out of a total of 100 points.

And then the two different hatchmarks are for men and women. So you see around 3, you don't really see too much. Once you come down to 4 and 5, you start to see the dropoff. And then 7. So it depends on how you want to cut that.

But we were saying, to the family practitioner, if the person is demented, which would be a modified mental-state score of usually about 84, you see it correlates with about a 7. That is how he picked that number.

DR. KAWAS: Did you get your question answered,

Dr. Penix?

DR. PENIX: Yes.

DR. GRUNDMAN: Assuming that you have the white-matter changes and that they correlate with the Mini-Mental score or some other cognitive measure, do you have a predicted rate of progression that you might expect to see in these patients?

DR. CHUI: We are just working on that now. In the program project, we are starting to get into that longitudinal phase.

Coming back to the issue of the correlation, the hippocampal and cortical atrophy explain about 40 to 50 percent of the variance in the overall severity of dementia if you use the CDR. If you use neuropsychological testing, it is about the same.

If you do a multiple regression analysis, the white-matter lesions don't add much more above that. But if you do a different type of stepwise multiple regression and you put white-matter lesions in first, you will see the correlation between the white-matter lesions and the severity of dementia as well.

The white-matter lesions correlate with the degree of cortical atrophy so that they are probably linked in steps. So I think the white-matter lesions is part of the thing that is driving this overall process. But the

stronger predictor is the atrophy.

DR. DUARA: Helena, could I ask you, these were not pathologically proven to be free of Alzheimer's disease, these cases that were--

DR. CHUI: No; that's correct.

DR. DUARA: There relationship between cognition here and the white-matter changes that you show could be related to all kinds of diseases; is that true?

DR. KAWAS: Unless I am mistaken, those people weren't necessarily demented. Those were just examples from the CHS study, I believe.

DR. DUARA: But you did show the relationship to cognition. So I am just saying that that relationship that you are seeing to cognition in those cases does not necessarily reflect the effect of the white-matter changes that we see on cognition. It can reflect multiple other pathologies.

DR. DUARA: That is the point I was trying to make.

DR. ROMAN: There is a strong correlation with age. With aging, you see an increase in the prevalence of this white-matter diseases.

DR. DUARA: As a follow-up to that, if I can just elaborate on the gradings that you have there. In our brain bank, for the patients that were evaluated with MRI and

where MRI was graded, if I just loosely use that scoring system, patients were diagnosed to have Alzheimer's disease, they may have had a small vascular component. There are very few--well, there are some, but a relatively small number of people who had pure Alzheimer's disease with nothing in the brain.

But patients who had predominant Alzheimer's disease, only about 10 percent would have gone into grade 1. 90 percent would have at least grade 2 and some of them would have gone right up to grade 8, without significant vascular disease. There would be a vascular component, presumably, but it was predominant Alzheimer's disease.

DR. KAWAS: The mean age of your sample?

DR. DUARA: In the mid-seventies.

DR. CHUI: We had a case that I thought was vascular dementia because it had grade 8 white-matter lesions and, on pathology, showed Alzheimer's disease and amyloid angiopathy.

DR. KAWAS: On that note, I think we will take a break until 10:30. We will reconvene then. Thank you, all the speakers and panelists.

[Break.]

DR. KAWAS: Welcome back to the Peripheral and Central Nervous System Drugs Advisory Committee. Our next invited presentation is Dr. Ranjan Duara from Mt. Sinai in

Miami Beach, Florida. He will be talking to us on White-Matter Disease and in Progressive Dementias; is it Vascular or Degenerative.

Vascular Dementia: Factors Influencing Diagnostic Accuracy

DR. DUARA: Actually, there has been a change in the title of my talk.

[Slide.]

I think I have said quite enough about white-matter disease so I am planning to address, in this talk, factors influencing diagnostic accuracy for vascular dementia. It is a question that Dr. Katz has asked virtually nonstop this morning.

DR. KAWAS: He is worried he is not going to get an answer, either. So I am glad you are going to give it a shot.

DR. KATZ: I hate to be a noodge, but that is why they pay me.

[Slide.]

Amongst my collaborators, I would like to point out the one listed at the bottom, Dennis Dickson, who is the pathologist who did the pathology on all the cases that I am going to be describing. If you don't know Dr. Dickson, he is basically a dementia pathologist, Alzheimer's disease and Lewy-body disease I guess are the areas that he has worked in most.

I was just asking Dr. Roman if there was somebody who was considered a world-wide expert in the pathology of vascular dementia. I am not sure that there are in the way that we associate with Alzheimer's disease, whether there is a pathologist that stands out at this point.

But, in any case, I would say that, amongst people who look at dementia from a pathological standpoint, that Dennis Dickson is quite prominent in the field and every person that looks at dementia has to evaluate the possibility that this is vascular and try to exclude it or include it, as the case may be.

[Slide.]

What I am going to describe to you is the data that we have accumulated over the past ten years or so in the State of Florida Brain Bank. Dr. Dickson became the pathologist for this around 1995, so I am only going to be describing the cases that he has personally evaluated and graded in terms of whether they have Alzheimer's or vascular dementia or any other type of pathology.

As an overview, you can see here that the frequency of Alzheimer's and vascular dementia are quite different, as you might expect, and there is very little change amongst the different age groups here, listed below 60 and so forth. For Alzheimer's disease, it is pretty constant. It is about 75 percent.

For vascular dementia, those below the age of 60 had only 6 percent vascular dementia. And then it increases up into the seventies and then there seems to be a slight decline. But these are not significant changes except for the early versus the--below 70 and above 70, there is a difference in frequency for vascular dementia.

The total number of cases of vascular dementia that we have in this study is 52. Of those, only fifteen had what was considered pure vascular dementia in the parenthesis. So--yes?

DR. KATZ: I'm sorry; I just have a question, a clarification question. When you say Alzheimer's dementia or vascular dementia, you mean that was a clinical diagnosis or that is a pathological diagnosis?

DR. DUARA: No, no; I'm sorry. I should have specified. This is the pathological diagnosis.

DR. KATZ: What were these people diagnosed as in life?

DR. DUARA: I will be coming to that.

[Slide.]

The postmortem diagnosis of Alzheimer's disease, there was a gender difference in this group. In the older age groups, there was a predominance of women, females to males. In Lewy-body dementia, there was a predominance of males both below the age of 70 and above the age of 70.

But, for vascular dementia, there was not, actually, any significant age difference. But that may also be related, in part, to the numbers.

[Slide.]

I am just reviewing here some of the largest studies, postmortem studies, brain-bank studies, if you will, on dementia. What was found in terms of the frequency of vascular dementia--and you can see that it varies tremendously. I think, as we discussed yesterday with the different causes of mild cognitive impairment, it really depends on your referral population, what your setting it, what the frequency of the dementias, of the different etiologies of dementia, is going to be.

For example, Brun, in his study, 70 percent of his cases had mainly vascular dementia and 34 percent were pure. In our study, only 16 percent. In Galasko's study from the Alzheimer's Disease Research Centers show a 9 percent frequency of vascular dementia and only 2 percent were pure vascular dementia.

So there is a very varying frequency.

[Slide.]

The accuracy of the clinical diagnosis depends on how the clinical diagnosis was made. I am showing you different types of studies. The specificity, in general, is very high for vascular dementia. The problem is the

sensitivity which is not high.

In the study at the bottom that you show that we looked at, and this is not really published at this point, only 9 percent were diagnosed premortem to have vascular dementia. But this was not--and I specify this was not--a diagnosis made by neurologists, necessarily. This was what a community physician or neurologist or psychiatrist, whoever had followed that patient and whose records we had, had labeled this patient to have.

I included this only to show you what the community diagnoses, at least in Florida, as vascular, how frequently they diagnosis vascular dementia and what their hit rate is, so to speak, for this entity.

Gold, for instance, used different criteria and those are the accuracies, the sensitivities and specificities. So I think, in answer to some of Dr. Katz's questions, you could look at the different criteria, the Alzheimer's Disease, the Research Centers, the Hatchinski Ischemic Score and the NINDS/AIREN criteria.

There, again, you see, in general, the specificity is high but the sensitivity is relatively low.

DR. KAWAS: Dr. Duara, can I ask you--I mean, when you get this 9 percent, it is presumably 9 percent of whatever the gold standard was detected.

DR. DUARA: Right.

DR. KAWAS: The gold standard is pathology. But how much pathology did it take to fall into that denominator? If a brain has one lacune? Five lacunes? What was the pathology criteria for calling this vascular?

DR. DUARA: I have asked Dr. Dickson what his criteria are. They have been pretty constant throughout the evaluation period. He requires, basically, the lack of other pathologies and what he calls major vascular disease, or disease affecting crucial areas including the thalamus, basal ganglia structures.

If I try to get more specific about it, I really can't because he is making the diagnosis partly by the exclusion of other pathologies, or relatively little other pathologies, what he considers is a significant load of vascular disease. This might be microvascular as well as overt lacunar infarcts or large-vessel infarcts.

DR. KAWAS: That means that, with his definition of pathology, 91 percent of people who have no other significant pathology other than vascular disease were missed by the clinicians?

DR. DUARA: Right.

DR. KAWAS: Thanks.

DR. CHUI: May I, while we are on this slide, Ranjan, just point out that the Gold paper, in 1997, didn't include neuroimaging in 80 percent of the cases. Or, to say

it the other way, there was only neuroimaging in 20 percent. So it is really not a fair test of the ADDTC or the AIREN criteria which require imaging.

The title of the paper is correct. It says something about the possible vascular dementia, which doesn't require imaging.

DR. DUARA: Thanks for pointing that out.

[Slide.]

In our brain bank, you can see the mixtures of different pathologies. I think this might address, in part, what you were asking about how the diagnosis was made, but not really fully. Mixed pathology in the two dementias, you can see that about 64 percent in patients who were diagnosed to have Alzheimer's disease pathologically, 64 percent were pure.

Diffuse Lewy-body disease was coexistent in 21 percent. Vascular dementia, or vascular disease, was coexistent in 13 percent. And then there were other pathologies including hippocampal sclerosis.

In the vascular group, 63 percent had coexisting Alzheimer's disease and only 27 percent were pure and then 10 percent had other pathologies. So this is the problem with the diagnosis of vascular dementia. Most of the time, it is not pure whereas, in the majority of the Alzheimer's cases, the disease was considered to be pure Alzheimer's

disease.

[Slide.]

Again, trying to answer the question that Dr. Katz has addressed, what are the problems that we are faced with with trying to make this diagnosis of vascular dementia? When we look at sensitivity, we are looking at the proportion of people who are affected, how many people are detected by the test in the total population of affected individuals.

With specificity, we are looking at the proportion of unaffected people, the negative test. Probably the best indication of how a criterion or a test works is the positive predictive value, which is the proportion of patients--which is the clinical question that we all want to ask--the proportion of patients with a positive test who are found to be affected with that disease that the test is supposed to positive for.

[Slide.]

Here is the problem that we are faced with. With Alzheimer's disease, in red, the sensitivity of the diagnosis is about 90 percent. The specificity is 60 percent. It is not a very good specificity. But it is not that much of the problem in the overall accuracy, the positive predictive value, for Alzheimer's disease because the prevalence of Alzheimer's disease is high.

So one has to factor in the positive predictive value. Prevalence of the illness becomes a factor in that equation. So, for Alzheimer's disease, because the prevalence is high, at least in the United States and probably most of the Western world, the positive predictive value is around 85 to 90 percent.

For vascular dementia, the specificity is high. The sensitivity is not high. Actually, the curve goes above because the specificity drives this more than the sensitivity. The curve is actually above the Alzheimer curve. However, the problem is the prevalence. The prevalence is low and so the overall positive predictive value goes down to about 50 percent. That is the problem we are dealing with.

DR. KAWAS: This data is with which criteria for vascular dementia?

DR. DUARA: This is whatever criteria you use. We are just using means of different studies looking at the overall sensitivity and specificity for the two diagnoses and seeing how that plays out in the real world. When you make the diagnosis, what is the predictive value.

DR. VAN BELLE: I think you are going to have define prevalence a little bit more carefully. You don't mean prevalence in the general population.

DR. DUARA: No; excuse me.

DR. VAN BELLE: You must mean prevalence in some kind of a clinical series that you get.

DR. DUARA: It is a relative prevalence; excuse me. I should have specified that.

DR. VAN BELLE: Because, for example, if the prevalence of Alzheimer's is, say, 1 in 10, which is very high--that is not realistic--now, you are way down on the left-hand side of your graph there. If the vascular dementias are still lower, probably by a factor of another 10, then you basically have zero predictive value of a positive test.

DR. KAWAS: I am not sure prevalence is the term you mean. Perhaps, you mean the proportion of demented subjects with each diagnosis.

DR. DUARA: Right; if you looked at, for example, the series that we looked at in this brain bank, the relative proportion of--yes; I think you right. The relative proportion of Alzheimer's versus vascular dementia that one would normally see.

Thank you very much.

DR. KAWAS: Thank you. The floor is now continuing to be open for questions. Dr. Katz?

DR. KATZ: If we could just see the first slide again. I am just trying to get a sense of this prevalence question. Again, the prevalence of a particular disorder

will depend on not only the sample but the diagnostic criteria, whether you are talking about pathology or clinical diagnosis.

[Slide.]

These are all the brains that came to the brain bank?

DR. DUARA: Yes. I think it is a fair question, in what context were these autopsies done. We have a State of Florida Brain Bank for dementia. It is not for Alzheimer's disease specifically. It is funded by the state and there is a recruitment program. There are currently thirteen memory-disorder clinics that are funded by the State of Florida all over the state.

Each memory-disorder clinic has a mandate, as part of their funding, to recruit patients for autopsy regardless of diagnosis as long as they have a diagnosis of dementia. So this is in the context in which we accumulated these cases.

In addition to that, private practitioners mainly in larger metropolitan areas become aware of the presence of the brain bank, perhaps through autopsy done on one of their other patients, and then refer patients directly. So there are patients that are not necessarily directly from the memory-disorder clinic.

But the large majority come from the

memory-disorder clinics. It is not an Alzheimer program. It is a dementia program. I just want to specify that.

DR. KAWAS: Perhaps this is an extension to that question. All of these studies of frequency in a brain bank or frequency of diagnosis in a nursing home are interesting, but they have a lot of variability and none of them speak to the true question of prevalence; that is, how common is vascular dementia out in the population.

Do we have any epistudies or what are our best estimates from community-based samples that, perhaps, someone on the panel can tell us?

DR. GORELICK: One of the issues is your age. So if you look at elderly people in Sweden, the Goteborg study, you get a very high prevalence of a vascular component to dementia whether it is mixed or pure. That overtakes Alzheimer's disease.

In some of the older studies from Asia, although these things are changing now, it would be more common to find what they were calling vascular dementia than it was Alzheimer's disease. So I think this is going to be very much age-dependent, dependent on what region of the world you are dealing with and then the underlying assumption is that, if you have populations at very high risk for strokes that you are going to start seeing more vascular dementia.

But it does vary. These are the real epi--well,

you are going to get about 50 percent or more in 85-year-old Swedish men, just to give you an idea from Skoog's study, if you put together the patients who have pure and mixed, what they thought were pure and mixed cases.

Again, there is going to be a majority--there had been publications of a majority in the Asian countries of vascular dementia at a time. Again, there are questions of how that data was adjudicated. There were all kinds of biases that may have gotten into the adjudication.

If you talk to Lon White about what goes on in the Honolulu Asia Aging Study, which was the Honolulu Heart Program, and getting the pathologists to agree that this wasn't vascular dementia because it was more of an honor to die of a brain death from vascular dementia than other things.

There are all kinds of factors like that that get mixed in there. So I think the good epidemiologic studies--if you look at the Eurodem experience, for prevalence, it very mirrors what you are seeing here and hearing about here, that you have a lot more Alzheimer's disease in Eurodem than you did have vascular dementia. It makes up a small proportion of the prevalence.

But then there may be certain target populations that are at high risk.

DR. KATZ: The prevalence numbers that you said,

those are all pathology diagnoses, or clinical?

DR. GORELICK: These are epidemiologic studies so this is population-based data or cohort-based data and, generally, they are not backed by pathology.

DR. KAWAS: In fact, if I am not mistaken, the studies that have the highest estimates, like the Skoog study, basically rely on making a clinical diagnosis because there was some evidence of vascular disease on an imaging procedure. The individuals in the Skoog study were over the age of 85. Since we know there is a strong correlation, it is not clear to me that all those individuals really should have been considered as vascular dementia as much as demented and had some lesions on CT, potentially.

Another thing that was notable in the slides that were put up was that almost--I mean, I usually use the estimate one-half of vascular dementia cases have Alzheimer's pathology. But, actually, we were shown even higher numbers from the brain bank in Florida. It was more like three-quarters of the vascular-dementia cases had Alzheimer's pathology.

DR. DUARA: 64 percent.

DR. KAWAS: Which is two-thirds. So, when we identify three people with vascular dementia, two of them have concurrent Alzheimer's disease and one of them doesn't is roughly the statistics from your site, at any rate.

DR. GRUNDMAN: Just following up on that, if I understood you correctly, when you showed the curve with the positive predictive value, so when you called the person vascular dementia, there was a 50 percent chance that you were right; is that correct?

DR. DUARA: That's right; yes.

DR. GRUNDMAN: Of the cases that you were wrong, how many of those had vascular pathology in addition to their Alzheimer pathology?

DR. DUARA: I can't really answer that question. I think if you look at just the overall rates of what patients were with Alzheimer's disease, in terms of vascular pathology, that should give you some sort of idea.

DR. GRUNDMAN: So probably--

DR. DUARA: About 25 percent.

DR. GRUNDMAN: So, in 75 percent of the cases where you called a person vascular dementia, they actually had either pure vascular dementia or mixed?

DR. DUARA: Right.

DR. GRUNDMAN: That is not too bad. That is getting close to the 80 percent that we were looking at with Alzheimer's disease. So the question is what sort of criteria were you using for vascular dementia when you made your diagnoses.

DR. DUARA: The slide that I showed you was a

hypothetical slide. We haven't actually done a clinical pathological correlation study as such. What I showed you for the 9 percent was just the referral diagnosis, what the referring physician had said he or she thought was the diagnosis.

DR. GRUNDMAN: Okay. So we don't actually know what the criteria were for--

DR. KAWAS: No.

Our next invited presenter is Dr. Philip Gorelick who will be talking to us about Background and Potential Strategies for Prevention of Vascular Dementia. He is from Rush Medical College.

Background and Potential Strategies
for Prevention of Vascular Dementia

DR. GORELICK: I want to thank the committee for inviting me today. My background is in preventive neurology. I am the upstream person. I want to be where all the damage is just beginning to start. I don't like to be downstream where all the wrecks are. I have proven that to myself over time.

[Slide.]

I am going to be talking about cardiovascular risk factors and their prevention, and the prevention of vascular causes of cognitive impairment.

[Slide.]

Just as a review, I just want to remind you that stroke is the second leading cause of death in the world. It is estimated there are about one-third of the stroke mortalities in the developed countries and about two-thirds in the developing countries. So this is a huge problem not only in developed countries but in developing countries.

[Slide.]

We clearly have modifiable risk factors for stroke. They are both medical and life-style, and you can see some of them listed such as hypertension, atrial fibrillation, smoking, heavy alcohol consumption and diet.

[Slide.]

I made some calculations a number of years ago about the population attributable risk; that is, what percentage of stroke would be explained by these modifiable risk factors. Clearly, as you can see here, up to about 49 percent of stroke is explained by hypertension, making hypertension the crown jewel of the modifiable risk factors.

Interestingly enough, if you look at cardiovascular risk factors, even though we have identified all these risk factors, we only explain about 50 percent of the variance. So there is about another 50 percent of cardiovascular disease we need to explain.

[Slide.]

If you are looking for the fountain of youth,

there may be some signals from the Honolulu Asia Aging Program which we have all been alluding to. Those men who lived I guess a healthy lifestyle and ended up being free of physical and cognitive impairment in older age didn't have high blood pressure, didn't have high glucose, weren't smokers and weren't obese. So there may be a lesson here of a signal that may be important to us.

[Slide.]

I certainly acknowledge there is skepticism of vascular dementia. I am bringing coals to Newcastle after we have heard all these discussions. But, clearly, stroke could unmake latent Alzheimer's, as we heard. AD brain pathology is common in the elderly. The cases may be mixed and some have claimed that vascular dementia is overdiagnosed.

[Slide.]

We have also heard that there may be preexistent dementia. Again, this gets into this overlap or mixed issue. This happens to be one study that showed about one-sixth of the cases had preexisting dementia. Most of these would have been Alzheimer cases.

[Slide.]

On the other hand, I don't think we can ignore vascular dementia, or the vascular cognitive impairment or vascular component. This is from the Finnish data. You

have seen some of this already. If you look at the Finnish data and some of the other studies such as Desmond and Tatemichi's work, what you find is that about 25 to 30 percent of these patients have dementia associated with the stroke.

[Slide.]

Furthering the theme, the Nun study, which you heard about, and the Nun study showed that those who had AD neuropathology, and, again, these are individuals who had special life styles. They had the same diet and so forth and many of them lived to older age.

What you see is that, if they had AD neuropathology and brain infarcts, they had poorer cognitive function and an increased prevalence of dementia. Dr. Roman has reviewed that. On the other hand, those who didn't have AD neuropathology and had infarcts, there was only a weak association with poor cognition.

Clearly, if you start developing atherosclerosis of the circle of Willis, you are more likely to get infarcts. So this, again, emphasizes the importance of vascular changes in the brain and dementia.

[Slide.]

Are there any links between Alzheimer's disease and vascular changes. The answer is yes. There have been a number of publications that are showing such things, of

course, as cerebral amyloid angiopathy, as we have all heard of. There is degeneration in the endothelium and there are possible effects of amyloid on the endothelial vessels, and so on and so forth.

[Slide.]

So there are some changes, vascular changes, that you do see in Alzheimer's disease. Then, one of the question is how is that possibly leading to--these vascular changes leading to changes in the brain of the Alzheimer patients. While there have been a number of hypotheses that have been offered, one of is that ischemia accelerates AD by formation of free radicals and that beta amyloid may do the same thing.

A very interesting one has to do with angiotensin II, that this may impair learning. It may be higher in Alzheimer's brains. That would certainly be another vascular factor that could contribute to cognitive impairment and decline in Alzheimer patients.

[Slide.]

I did an evidence-based review in 1997 about possible risk factors for vascular dementia. Clearly, certain factors kept popping up in the available studies. Again, some of these studies were--there were rather few studies at the time and things like age, race and sex and education level.

But if you looked at the potentially modifiable factors, the ones that you would see as stroke risk factors also came up as risk factors for these patients who had what was called vascular dementia. So, hypertension, cigarette smoking, myocardial infarction, diabetes, high cholesterol, heavy alcohol consumption and so on.

[Slide.]

What is also very interesting to me, as one who is in preventive neurology, is that these same risk factors are starting to rear their heads in the Alzheimer studies. For example, this is from the Rotterdam study. What they found is that diabetes, atrial fibrillation, smoking and carotid plaques were associated with Alzheimer's disease. They later showed that hypertension is another factor that has been associated.

[Slide.]

To turn to this idea of redefining vascular dementia, I am certainly in the Hatchinski camp on this. I think that we really should be talking about dementia associated with stroke and, specifically, vascular cognitive impairment because this whole idea of vascular dementia may be too generic and too restrictive.

I think we have to be a little more open-minded about all of this. Vascular cognitive impairment really leaves the idea that there is a spectrum. You could have

very mild cognitive impairment. You can go on to full-blown cognitive impairment.

[Slide.]

I wanted to focus now on one of the risk factors because I think there is a possibility for a unifying hypothesis here. Again, this is being very, very upstream. I want to show some slides about hypertension because it may be very important in the dementia process.

This is data from Sweden. This was actually a population-based cohort, but you are seeing cross-sectional data here. These were people at age 70. They were men who had 24-hour ambulatory blood pressure in various metabolic studies and then they had some cognitive testing done as well.

Basically, what happened here is that there were predictors of impaired cognitive performance in this group which included high diastolic blood pressure, high 24-hour blood pressures, non-dipping and insulin-resistance in diabetes.

So what you are seeing here is people who have these risk factors, the traditional cardiovascular risk factors, may be at risk of having cognitive impairment. If you are wondering what non-dipping is, as you go to sleep, your blood pressure is supposed to drop some. Those who have hypertension, it may not drop at night. The normal

nocturnal dip may not be there. These are the people who think are going to get in trouble, as I will show you shortly.

The other group is people who have an exaggerated dip at nighttime and those are your hypoperfusers that you have been hearing about.

[Slide.]

The studies go on. This is the Goteborg study by Skoog. What was interesting, if you look at age 70 at elevations in blood pressure, whether it is systolic or diastolic blood pressure, it predicted dementia in 79 to 85-year-olds. If you looked at increase in diastolic blood pressure at age 70, by 75, it predicted both AD and the vascular form of dementia.

Of course, the increase in blood pressure increased the white-matter lesions. If you look at some of the other studies, you find the same thing in some of these cohorts over time, that specifically blood pressure and some of the other cardiovascular risk factors are predictors or cognitive decline later on.

[Slide.]

Very interesting to me is what we are all doing in mid-life. This is from the NHLBI Twins Study. What they did here was took monozygotic twins at about age 45 or so, followed them out 25, 30 years. What they showed by very

sophisticated MR technology, and Charlie DeCarli has been heading up this effort, there were low brain volumes in the twin that had elevated systolic blood pressure at baseline.

When they did these studies some twenty-five years later, they found that the brain volumes were smaller in the twin that had elevated blood pressure, coronary heart disease and some of these other factors, and that white-matter hyperintensities were being predicted by elevation in systolic blood pressure and such other factors as glucose intolerance and low HDL.

[Slide.]

If you track these people in the study, what you find is that, over time, they start developing cognitive changes and there is reduced verbal learning and memory. So, as time is going on, and you have hypertension, it appears that it may be eating away at the brain, so to speak.

[Slide.]

What is very, very interesting is the Syst-Eur Trial that was conducted in Europe. This is a study that used a long-acting calcium channel blocker called nitrendipine. What you see here is that people were followed with Mini-Mental-State exams. If they had significant changes, they would be followed into a protocol where the DSM IIIR criteria was used.

What was very interesting in this small number of outcome events was that, in the placebo group, there were twenty-one cases of dementia and in the treatment group, there were eleven cases of dementia. So, what basically happened, there was a reduction of about 50 percent of the dementia.

Interestingly enough, when you looked at the subtyping of the dementia cases, according to DSM IIIR, most of these cases that were spared were Alzheimer's disease cases.

[Slide.]

I have done some population attributable-risk calculations for some of these risk factors as they related to vascular dementia. I would be happy to share them with the committee if you would like. I have got an overhead and, if anybody wants to see it--but, basically, what it shows with the population attributable-risk data is what you might expect from hypertension. It is about 67 percent or so of the attributable risk.

So it is much higher than all the factors. The other factor that came in in the number-two position was hypercholesterolemia, specifically LDL. That was about 33 or 36 percent.

[Slide.]

I want to bring up the PROGRESS Trial because that

is a trial that is out there and adds to this whole theme of prevention of cognitive impairment. This is a case that is enriched. This is a study that is going on predominantly in Europe, the Asian-Pacific rim, AustralAsia are. They are looking at an ACE inhibitor, perindopril.

It is an enriched study because they have patients who have TIA and strokes, ischemic strokes. They are not only randomizing people with hypertension to the ACE-inhibitor treatment but they are also taking people who don't have hypertension.

That study is going to be--the results are going to be announced in June. So I think this is going to be an important study that may give us an idea of an enriched sample of people at high risk, what might be our calculations, our power calculations, for subsequent studies.

I want you to keep in mind that the ACE inhibitors not only lower blood pressure but they probably protect the vascular endothelium. So they have more than one effect which might be very important, especially if the angiotensin 2 is really elevated in a number of those patients with dementia.

[Slide.]

So my bottom line here is that I think we ought to be really trying to get at the source of where these

problems occur. The source starts when you start developing the risk factors. I think that shifting the paradigm over to the left even a bit more than Helena has done might be useful.

So I think that one of the focuses should be hypertension and its treatment and I do think we have testable hypotheses based on the Syst-Eur Trial and what is going to come out in the progress study.

[Slide.]

Then, finally, there is another exciting possibility with cholesterol-lowing agents, specifically the statins. We are now seeing some observational type of data that suggests that people who are on statins may have lower risk of developing dementia. Again, this would also be a testable hypothesis.

What is very exciting about this is that this is another drug that has more than one function. It not only lowers cholesterol, this calls of drugs, but it also serves in other capacities and that would be to reduce inflammation, stabilize the endothelium and so on. So this may be another exciting possibility.

Finally, I think that if we are going to be doing these studies, we are going to have to high-powered neuroimaging that Dr. Chui is doing in her study that we are doing in one of ours. I think that is going to be very,

very important so it is going to help us sort out what some of the mechanisms are and what some of the underlying disease is.

Thank you.

DR. KAWAS: Thank you, Dr. Gorelick.

The floor is now open for questions.

DR. KATZ: Just a clarification. On the Syst-Eur study, 21 patients develop dementia on placebo and 11 on drug. From a clinical point of view, what was the nature of those dementias? Were they Alzheimer's? Were they vascular?

DR. GORELICK: These cases were largely Alzheimer patients when they came to final adjudication. They were adjudicated by specialty neurologists, according to the paper, or specialty physicians in dementia. It is a savings of about 19 per 1000 over five years. That is what the difference has boiled down to.

But, interesting enough, they were predominantly Alzheimer cases.

DR. PENIX: Did they look at just conversion to dementia or did they look at cognitive scales as well?

DR. GORELICK: This is a study that used the Mini-Mental State exam as a screen. Once you dropped below the magical cut point of 24 or 23, then you were shunted into another protocol and the physicians had to put them

through studies including imaging and to meet DSM IIIR criteria to establish a diagnosis.

Again, this was a pre-planned substudy that was done and organized at the inception.

DR. KAWAS: Dr. Gorelick, every time somebody shows us risk factors for vascular dementia, they put up a list that is, to my mind, risk factors for cerebrovascular disease, period. Has there been any indication in the literature of the difference in those two risk-factor sets? Is there any risk factor that is more indicative, or more related, or more potent in making somebody develop dementia with vascular or just--

DR. GORELICK: I think so. I think that the two that keep popping up, and, again, this area has been relatively understudied compared to Alzheimer's disease. There are not many of us out there that are doing the studies. But, certainly, hypertension and diabetes, those keep popping up.

I can show you the population attributable-risk data if you are interested.

DR. KAWAS: You think hypertension and diabetes is more related to dementia with vascular disease than just vascular disease alone?

DR. GORELICK: Oh, no, no, no. My interest in this whole area began in the 80s when the Dean of the School

of Public Health sat down with me and said, "I don't think there is anything such as vascular dementia." Of course, I nearly fell off my chair because I had just got done training with Lou Kaplan. We learned our neurology stroke by stroke.

So, as I am falling off the chair and gagging and gasping for air, he is telling me there is no vascular dementia and challenged me to do a study. That is how I got involved in my first case-control study on this topic.

So your question, again?

DR. KAWAS: Actually, my very first abstract in my career was on risk factors for vascular dementia. They were no different than the risk factors for stroke.

DR. GORELICK: What Jacob Brody set me on to at the time was to go look at some information that was being published out of the UK. The assumption was that if you had risk factors for stroke, they would be the same risk factors for vascular dementia.

So I generally assumed that that would be the case. And then Brody said, "What is the data out there?" and I said, "There is very little." So he said, "Prove it." So that is how we got started.

Again, if you look at the Honolulu Asia Aging Study, some of the Canadian cooperative studies, the studies that we have done, Tatemichi's studies and Desmond's studies

and all the rest, and, again, it is only basically one or two handsful, the things that keep popping up are the traditional cardiovascular disease risk factors.

I am not sure we can say that it is more important in general stroke as compared to vascular dementia.

DR. KAWAS: So, does that mean that in drug development and treatment paradigms, every time everyone tells us we need to shift to the left, they are talking about the therapies that we already have been promoting for cerebrovascular disease and there is really nothing any different.

DR. GORELICK: Right. These are therapies that are not being utilized very well in the population. If you believe the NHAINES data, for example, only about 27 percent of hypertensives are well controlled. If you look at the curves that NHAINES is showing now, as we got into the '90s, the curves are starting to go in the wrong direction in that we are seeing a drop-off of awareness, treatment and control.

The problem I have is that if you start treating blood pressure in mid-life, which you need to do on an individual basis, that is a very, very expensive proposition. I think the exciting thing is that there may be this unifying hypothesis between what we are calling vascular cognitive impairment and vascular dementia and

Alzheimer's disease.

If that is truly the case, then the control of blood pressure, whether it is on an individual high-risk-strategy basis or if it is on a mass basis in the population might be very effective down the road.

DR. PENIX: I support that. I think that is a missing area in what I thought was in regards to vascular dementia. It may actually also serve to decrease the incidence or conversion to Alzheimer's disease.

But in our clinic, we begin to look at the data in our memory-assessment clinic at Grady in Atlanta, and 65 percent of our patients come in with uncontrolled hypertension, and 24 percent of the patients have stage II and stage III which is an advanced hypertension.

So, clearly, it is a problem. I think if we can get a handle on that, we may be able to decrease the dementia in general. The question is whether we are treating Alzheimer or vascular dementia.

DR. GORELICK: I want to make one other comment about this. I think you have to be careful in terms of this whole blood-pressure issue because if you look at prevalence studies, you see that the blood pressures are actually low. I think they are low because you get the prevalence incidence bias and that these are burned-out cases and they are going to have lower blood pressure because the brain has

already been damaged.

So I think there is a false sense that the blood pressures are actually low once the people get disease and that has been shown in some of the general dementia and Alzheimer's disease studies, that the pressures are actually low. But, when you look at the incidence data, it is clear that they are high before this all happens.

The other thing I want to caution everybody on is that once you have so-called vascular dementia, it may be that you actually need your blood pressure elevated a little bit. If you look at John Sterling-Meyer's data from a long time ago, the people who did the best, who he defined as having vascular dementia which, I believe, met DSM III criteria at the time, if I am not mistaken, they had systolics of 135 to 150. The people who were under that did worse.

In our case-control study, we found something similar, that as the blood pressures were dropping, these people were doing worse and the ones who actually had higher absolute blood pressures did a little better once the frank disorder had set in.

DR. ROMAN: I would like to bring your attention to a population that is Mexican-American in South Texas with an extremely high prevalence of diabetes mellitus. There has been a long-standing concern of why is it that we see so

many complications of diabetes, beginning with renal failure, blindness, peripheral neuropathy and, of course, stroke and dementia.

There is some very interesting data pointing out to the very high frequency of executive dysfunction in these patients who have difficulty controlling their diabetes. You go into a circle where the use of the insulin and the oral hypoglycemic agents becomes more and more complex and the patient has less and less capacity to follow the instructions, ending up not only with the vascular impact but also with the effects of hypoglycemia, and so on.

So it seems that that could be a particularly severe factor for certain populations, particularly Mexican-Americans where, as Helena mentioned, small-vessel disease is quite significant. We see small-vessel disease and lacunar strokes quite often.

DR. GORELICK: There is some data suggesting that there may be a problem with insulin signalling in the brain, insulin-receptor resistance and that, once you develop diabetes, you may be developing brain as an end-organ complication of diabetes. It may even have to do with phosphorylation of tau. There is a pathway there that the insulin receptor may be influencing.

DR. KATZ: Just an observation. Your unifying hypothesis, as well as some of the data, would suggest that

there is a correlation between risk factors for cardiovascular and the incidence of Alzheimer's disease. Even the results of the Syst-Eur study, they all sort of suggest, to me, and maybe I will ask it in the form of a question, do they suggest to you sort of a blurring between the distinction between Alzheimer's and vascular dementia?

DR. GORELICK: Thank you. That is the point. I think that there is a blurring. I agree with you. I think we have to be very careful here. I don't think we want to recreate what we did with neuroprotectants and stroke. We probably spent a billion or more dollars, or industry did, and we made this great leap of faith and didn't really have the right data to make the jump to where we needed to be, and now we are paying for it.

So I think there is this blurring and I think we have to decide where our target is going to be. If we can ferret out the cases who have strokes and Alzheimer's disease together, we have a clear target. If we can't do that, then we have got to step even further to the left and say, "Well, let's start looking at this possibility of a unifying hypothesis, and what we need to do here, and get an enriched sample of people who are high risk and see where we can take it."

I think that these modifiable risk factors do have a lot of advantages because we know they are safe and

effective therapy and people know how to use the agents in the community because they have been out there for a long time and it does have some advantages.

DR. PENIX: I would just like to reiterate that one of the problems, I think, with the neuroprotective studies in stroke is that we have lumped all ischemic stroke together, particularly including small-vessel lacunar subcortical strokes with large-vessel strokes which are probably very different.

I think, there, if they were separated, there is a possibility that some of those studies may have been positive.

DR. GORELICK: That was a point that we made in the Stroke Therapy Academic Industrial Roundtable, or STAIR, Project which was a meeting between industry and academia to sit down and say, why did this go wrong, why have we spent about a billion dollars and don't have a positive result.

Certainly, that was one of the issues of the patient selection was poor. The issue was had we used diffusion perfusion imaging that we would have gotten rid of the smaller-vessel infarcts and we would have had the right target population. Some of the preliminary work on this has shown that if you had the right target population, you have enriched your sample and you really don't need that many patients relative to what we have looked at and what we have

spent.

But the are other issues, too, of course. One of them is going from rodent models and skipping primates and going right to the human studies and making this big leap of faith.

DR. CHUI: Dr. Kawas, could I come back to your tantalizing question, is there any difference between the vascular risk factors for stroke versus vascular dementia. I would say that maybe we haven't really answered that question fully.

I want to pose the idea that vascular dementia has--there are different natural histories and we know a very little bit about them. There may be the large-vessel strokes that cause more of a static or abrupt onset, plateau and then to the next step.

And then there may be more slowly progressive ones. The question may be are there differences in vascular risk factors leading to the static versus the slowly progressive vascular dementia. There, my hypothesis would be that it would be hypertension and diabetes that have a greater exaggerated impact on the slowly progressive dementias.

We can see that in some of the epidemiologic studies like the Honolulu Heart Study that the mid-life hypertension is associated with cognitive decline in late

life without any history of clinical stroke. In the Erick study, the atherosclerosis risk in community, the article by David Knopman, I guess this January, also showed that hypertension and diabetes were risk factors for cognitive impairment.

DR. KAWAS: This concludes the invited speakers. We have several public speakers. I would like to fit at least some of them in before lunch. Our first public speaker is Ray Pratt. Dr. Pratt is the Senior Director of CNS and Internal Medicine for Eisai/Pfizer. He will be talking to us about Diagnostic Criteria, Proposed Outcome Measures and Experiences to Date.

Public Speakers

Diagnostic Criteria, Proposed Outcome Measures and Experiences to Date

DR. PRATT: Thank you very much. It is a pleasure to be able to speak before such an audience, particularly coming after Dr. Gorelick here and his comments about prevention. I think that the prevention of dementia probably should be our gold standard of developing drugs to be able to do that.

However, once dementia actually occurs, then we are faced with what do we have to actually about it in the clinic.

[Slide.]

I would like to begin my commentary by stating that when we started our studies with Aricept in the population of dementia with cerebrovascular disease, it was in 1996 and 1997. I was particularly impressed by the dates of all the articles that people were discussing at the round table this morning, the tremendous amount of information that has occurred and has been published since 1997 concerning this issue of vascular dementia, what is it, how do we classify it and where do we go.

However, at the time we actually were conceiving our studies in dementia with cerebrovascular diseases, the only thing we really had to go on at the time was the clinical diagnosis by the Alzheimer's criteria, the ADRDA criteria, for probable and possible Alzheimer's disease as well as the two criteria that were suggested for vascular dementia, the AIREN criteria and the California criteria.

Furthermore, we also had directives from both the--draft directives from the U.S. FDA as well as the European regulatory authorities concerning the types of outcome measures that would be necessary in development of anti-dementia drug products.

So, at that point, we took the look at decided that we were going to focus our clinical studies in a patient population that would not have been included in our previous trials with Alzheimer's disease with Aricept. And

we chose to actually focus on the specific population as defined by the NINDS/AIREN criteria which included, at the time, again, the definition of dementia which was predominantly a memory component of loss plus at least two other cognitive domains of impairment and was identifiable by both clinical and radiological criteria.

Particularly the cerebrovascular disease had to be documented by neuroimaging studies and that vascular risk factors had to be a prominent component of the patient population and particularly, perhaps, more prominent than they were in our Alzheimer studies.

Additionally, we made a decision also that we were going to try to exclude, as best as we possibly could, patients who had previous documented diagnoses of Alzheimer's disease. The studies, just briefly, to recapitulate as to what we did is that they are parallel group design studies. They are 24 weeks in duration. They are double-blind placebo-controlled and we have we have open-label extensions following.

[Slide.]

We believe that this actually defines a clinically relevant population. We chose to include both patients with possible and probable dementia with cerebrovascular disease as defined by the AIREN criteria. Particularly, we were encouraged to look for patients with stroke, intracranial

hemorrhage and, particularly, extensive white-matter disease on neuroimaging studies.

We wanted to include patients, particularly with diabetes mellitus, insulin-dependent type of diabetes mellitus, hypertension, atherosclerosis and cardiovascular disease which, again, were excluded or limited in some of the probable AD studies that led to the approval of Aricept.

Importantly, the question we wanted to end up with was to get to a patient who was evaluated for the first time, so can this be helpful in terms of generating labeling for the physicians and the community. What do I do with a patient who presents to me with dementia? I work them up and I find that they have evidence of cerebrovascular disease. They don't quite fit into the Alzheimer's criteria. We thought that this type of study would actually get to the point of doing that, so we encouraged patients who had not been treated with anything before and who were evaluated with dementia for the first time who met the criteria for enrollment to be included in the study.

[Slide.]

I would like to take a few minutes to go through this slide because I think this explains our thought process in terms of just looking at the continuum between the probable AD group of patients as well as the probable vascular dementia group of patients.

Again, we have the probable AD group of patients defined by the ADRDA criteria. We are all very familiar with the criteria that this used including the dementia with gradual onset, continuous progression and, particularly, neuroimaging was negative for cerebrovascular disease.

The neuroimaging that actually we are looking for would be cortical infarcts, subcortical infarcts, multiple lacunes and extensive white-matter disease.

In the pivotal trials for Aricept in probable Alzheimer's disease, the neuroimaging studies were over 95 percent totally negative for any additional intracranial pathology. So this was a very highly selective population that really did truly meet criteria for probable AD. Again, there was no significant comorbidity that was appreciably present. There were some patients in the studies who went on to have strokes, who went on to have heart attacks and who had evidence of peripheral vascular disease. However, these were very, very few patients.

Moving over to the other end, there, if we take the NINDS/AIREN criteria as the criteria defining inclusion into our studies, the definition of dementia remains the same across all three of these. In other words, we are stuck with the memory prominence plus two other domains that have to be involved. Therefore, we are at least enriching a population that does have one commonality across all three

of the clinical populations that we are looking at.

However, again, the temporal relationships have to be there, onset within approximately three months of a recognized clinical stroke, a stepwise progression, something which we all generally understand but which we found to be extremely difficult to document in the clinical settings and particularly reviewing charts and asking people to document how did you make a determination that patients were stepwise deteriorating, focal neurologic findings correlating with the residuals from cerebrovascular events that occurred and, again, neuroimaging being positive for cerebrovascular disease.

The group that actually falls in between there, what we are calling the possible VAD group by the AIREN criteria--and, again, I am not certain that we need to know--that possible VAD, probable VAD, may be the best terminology that we use. We actually called our studies studies of dementia with cerebrovascular disease not necessarily vascular dementia because of the issues that we are discussing today.

Again, patients had to have dementia but the CVA, a clinical stroke was not really required to put them into that temporal aspect. The onset and progression by clinical history could be very variable and comorbidities, in terms of hypertension, cardiovascular disease, diabetes may or may

not be present.

We made one minor deviation from the real AIREN criteria in that possible VAD by that criteria does not require neuroimaging to be positive to make a diagnosis of possible vascular dementia. However, for purposes of our research studies, we actually required all patients who were enrolled in these studies to really have positive neuroimaging to some degree for each of the--to be included in the study with possible or probable VDA.

The investigators were left up to make the determination on their best clinical judgment as to where these patients fell based on the actual criteria that was there.

One other thing I would like to point out also is that where did we actually find the patients to enroll in these studies. I think it is a very useful commentary here. For the probable AD populations in our pivotal trials, we actually had a significant number of memory clinics specializing in Alzheimer's disease which form the basis of our investigator cohort for this.

We found that those same memory clinics performed very poorly in finding patients who met criteria for vascular dementia. The best performers actually were either academic clinics or sites that actually had large relationships with the community physicians, physicians in

internal medicine, family practice, cardiology, endocrinology and particularly diabetes clinics were a very useful part of finding patients to enroll in the studies.

So, again, we believe that these criteria actually form a clinically relevant clinical criteria for actually describing the population that we are going on to study.

[Slide.]

I would like to turn for a few minutes and talk about the outcome measures. The outcome measures that we chose for our clinical trials, again, are very similar to the ones that we have used in our Alzheimer's clinical trials.

We have a cognitive domain, a global status and a functional domain. These were chosen to comply with recommendations from both the U.S. and the European regulatory authorities for the development of anti-dementia drugs. Again, the ADAS-Cog which we chose as our primary cognitive outcome measure is administered to the patient. We have a patient and caregiver interview for our CIBIC-Plus as well as a caregiver assessment of the functional status that is rated by a clinician or psychometrician.

We all know that all three of these endpoints have been extensively validated in the Alzheimer's population. However, in the vascular-dementia population, only the ADAS-Cog has been used in previous studies of this

population.

However, there is no reason to suspect that the global assessment or the functional assessment would not be equally valid in a population enriched for patients with cerebrovascular disease as opposed to probable Alzheimer's disease.

Finally, all of the outcome measures that we chose actually are sensitive to drug effects in placebo-controlled trials, I think a very important aspect when looking at outcome measures in terms of whether we can actually detect differences in drug-treated versus placebo and, in some cases, also show negative studies where treatments that wouldn't be expected to work also don't show any effects on the outcome measures.

[Slide.]

We have gotten into a lot of discussion on cognitive domains and which are important and which are not. I think just the important aspect to hit on this slide is that there are very few domains, at least in studies that have been retrospectively looked at, that are prevalent in vascular dementia as opposed to Alzheimer's disease with the exception, again, of the front executive function.

Unfortunately, the ADAS-Cog does not really have a good functional executive dysfunctional test as part of it and so that is one thing that we will be lacking in our

clinical studies is an assessment of this modality.

[Slide.]

Finally, I think the usefulness of the NINDS/AIREN as a criteria for enrolling patients in clinical trials also helps to tell us who doesn't get into our trials. So what was the reason that we actually excluded these patients from our clinical studies. We had approximately 600 screen failures to date in our clinical studies, and approximately 22 percent of them just had no evidence for cerebrovascular disease despite extensive prescreening and assessments by our investigators to try to maximize the number of patients who had cerebrovascular disease to be enrolled into the study.

The largest group of patients who are excluded gets into this condition that I think we were actually talking about a little bit with Dr. Gorelick was the issue of unstable conditions. The clinical study was a six-month study and we actually wanted to enroll patients who had a reasonable probability of actually being able to make it through the study successfully.

Therefore, we put a few conditions up front that defined what we believe, in our best judgment, to be medical stability. Typically, we wanted patients at least out of the hospital for three months. We wanted their medical treatment regimens to be stable for three months. That

turns out to be a very, very difficult task to achieve sometimes in this population.

Finally, the issue of the MSSE. The MSSE was used as our primary screening test again because of the memory prominence of the component there. It is a very simple test and would have wide utility in the primary-care arena. We found that 15 percent of our patients were excluded on the basis of MSSE, particularly scores in the 27 to 29 range, despite the fact that they may have had multiple impairments on their ADAS-Cog or on their CDR rating that would otherwise have included them into the study. However, they did not have this criteria and were, therefore, excluded from the study.

[Slide.]

I would like to conclude by making the statement that I believe the NINDS/AIREN criteria, as we used in our study, really does select a different population from the probable AD group and particularly the clinical characteristics are different from the AD population.

On respect, in particular, that we have focused on is that the neuroimaging is all abnormal. The outcome measures that we have chosen, the ADAS-Cog and CIBIC-Plus are appropriate because we believe the cognitive deficits in both of these groups that we have actually studied are similar.

Importantly, we believe that this is a clinically relevant population for labeling purposes because it can reasonably be identified by clinicians pursuing a dementia workup.

Thank you very much.

DR. KAWAS: Thank you.

The floor is now open for questions. I thank you, Dr. Pratt. I think that is important data for us to see. When do you expect to have the entire study completed?

DR. PRATT: We are still finishing up the last patients in the clinical cohort so, soon, we hope.

DR. PENIX: The screen-failure slide, the patients who were excluded with no evidence of cerebrovascular disease, they were all made by neuroimaging?

DR. PRATT: Yes.

DR. ROMAN: Would you like to comment on the Mini-Mental as a screening instrument? I think that brings us back to the definition of dementia.

DR. PRATT: I think that it is a very important one. We chose it because of the definition and the utility that it had in our Alzheimer's population. Clearly, we were unexpected that so many patients would be screen-failed simply on that basis alone, and I think that is something we would like to go back and examine on those patients.

But I agree that it does not actually test some of

the areas that we actually are knowing, that we have patients with deficits in, particularly the frontal executive dysfunction is totally ignored in the MSSE. So the MSSE, I think, was not, at least for the purpose of this research study, maybe the best tool to use as the screener.

Again, I am not certain what other tool we would use in the community to be able to pick up these patients more frequently.

DR. CHUI: A suggestion; some simple test for executive function could be verbal fluency, like FAS or animal fluency, trails A or B.

DR. KAWAS: Do you think you would get the 90/10 separation on those tests when compared to Alzheimer patients?

DR. CHUI: Oh, no; not specific. Sensitive. More sensitive, not specific.

DR. KAWAS: Thank you very much.

Our next public speaker is Dr. Andrew Satlin who is Director of Clinical Research at Novartis. He will be speaking to us on Issues Related to the Development of Drugs for the Treatment of Patients with Vascular Dementia.

Issues Related to the Development of Drugs for the Treatment of Patients with Vascular Dementia

DR. SATLIN: Thank you very much for the opportunity to present to the committee.

[Slide.]

I am going to propose some answers to the questions that were raised by the FDA and I hope to suggest, through the answers to our questions, that we are ready to do clinical trials in vascular dementia at this time, good clinical trials. This is important because we know that drugs such as the cholinesterase inhibitors, which have been approved for treatment in Alzheimer's disease, are being used empirically and in clinical trials already to treat patients with vascular dementia and it is really incumbent on us to test definitively whether these drugs and others work and, if so, to provide them to the populations that need them.

[Technical difficulties with slide projection.]

DR. KAWAS: While we are waiting, does anyone want the floor?

DR. CHUI: Dr. Kawas, may I ask Dr. Pratt, are you able to divide your sample by subtype, vascular-dementia subtype? I might have missed that. I was out of the room for a while.

DR. PRATT: We will ultimately be able to subtype them. We have actually tried to collect as much information as we can to be able to classify by stroke location, type of neuroimaging findings and we have designed the studies, actually, so that the two of them can actually be put

together, so we will have a very large cohort in which to actually look at individual subtypes at the end of the trial.

DR. KAWAS: I think we are set for Dr. Satlin.

[Slide.]

DR. SATLIN: Thank you. The first question is whether vascular dementia is a clearly definable entity clinically. I would suggest that, of course, we need to first determine which criteria we are going to use in defining the diagnosis and that the NINDS/AIREN criteria are probably the best at this point, at least for use in clinical trials.

No criteria, obviously, are definitive. What we want to do is to find criteria that will allow us to maximize validity and reliability. By requiring a combination of focal signs on examination, neuroimaging evidence and a causal relationship between the two in addition to the presence of dementia, these criteria are probably the most rigorous that could be used in order to define a specific population.

So they really establish the highest burden of proof. In fact, several studies including one by Dr. Chui, suggest that the criteria are conservative when they are compared to other diagnostic criteria for vascular dementia.

In other words, while they may be less sensitive

and will pick up a smaller population available for a trial, they are likely to yield a more homogenous population. And that is probably important because a key issue in designing trials in vascular dementia that are specifically looking at the effect of a drug on vascular dementia is to exclude other diagnoses, in particular Alzheimer's disease.

From Gold's study, looking at the neuropathology, patients classified by the NINDS criteria were only misclassified as having Alzheimer's disease in 9 percent of the cases and misclassified as having mixed dementia, vascular plus Alzheimer's disease, in 29 percent of the cases.

Finally, the criteria in several studies have been shown to have moderate reliability with kappas in the range of 0.4 to 0.7.

[Slide.]

In order to apply the NINDS criteria, at least for diagnosis of probable vascular disease, neuroimaging evidence was required. So we believe, of course, studies should include, as a screening tool, MRI imaging in order to make the imaging diagnosis.

However, we would propose eliminating the requirement for a temporal relationship in cases of pure subcortical vascular disease by MRI criteria. Why would we do this? First, of course, there is a practical

consideration in those patients who have pure subcortical vascular disease, as we heard this morning.

Very often, there is no evidence clinically of stroke and it is very difficult to determine a temporal relationship between the clinical stroke and the onset of dementia as there would be with other forms of vascular disease. So that is a practical consideration.

We also think that, in terms of establishing a population for study that will be clinically relevant and will be relevant to the population that would be treated out in the community. But this is also an important consideration, the reason being that one can imagine that, in the community, those patients who have classic clinical features of vascular dementia will be identified and possibly treated without neuroimaging.

But, in those cases where the clinical course and the other clinical features are not classic, neuroimaging might be used and then one would find that you would identify those vascular-dementia patients predominantly with subcortical disease. So the subcortical population will be pulled in by the imaging criteria.

Finally, of course, the application of the criteria need to be reliable among different investigators in the study and so training in the use of the criteria and an investigator meeting would be essential.

[Slide.]

The next question is whether vascular dementia, of course, is distinguishable from Alzheimer's disease. Clearly, as everyone has mentioned this morning, there is a great deal of overlap between Alzheimer's disease and vascular dementia and probably more than is expected by chance.

It is variously estimated that about a third of patients with vascular disease will have neuropathology consistent with Alzheimer's disease and the same in the opposite direction. Of course, we don't know which pathology in any individual patient is contributing the most to the clinical symptoms of dementia.

However, as I have already suggested, the NINDS/AIREN criteria are relatively specific for the exclusion of vascular dementia and, as Dr. Chui pointed out this morning, the Gold study actually included very few patients who had neuroimaging criteria so, in fact, these figures may be conservative. One could imagine that if imaging had been done on all of these patients that you would be selecting for a population that was even more weighted toward vascular dementia and away from Alzheimer's disease.

There is other evidence that suggests that the dementia in patients with vascular dementia, even in those

patients whose dementia is due to subcortical vascular disease does not simply indicate the presence of Alzheimer's disease pathology. This has been pointed out by Fein in his study where, for example, hippocampal and cortical atrophy associated with cognitive impairment were found on autopsy in patients with subcortical ischemic vascular disease without Alzheimer's pathology and also the patterns of association between the imaging changes and the cognitive impairment was different in patients who had lacunar disease from patients who had Alzheimer's disease.

So this evidence further suggests that vascular dementia is a separate clinical entity from Alzheimer's disease as well as different on neuroimaging.

Finally, quite apart from the question of whether vascular disease and Alzheimer's dementia can be distinguished, in a clinical trial, the requirement for a statistical and clinically relevant effect in the vascular-dementia treatment arm will preclude the possibility that the effects are entirely due to treatment with Alzheimer's disease so long as the proportion of patients with Alzheimer's disease is low enough. And we think that it can be kept low enough using the NINDS/AIREN with the minor modification that I discussed before.

[Slide.]

So, turning to outcome measures, clearly with

vascular dementia as with Alzheimer's disease, two primary outcome measures in any study would be essential, one looking at the primary symptomatic domain which is cognitive and the other looking at a global measure in order to validate the clinical relevance of the cognitive change.

Several researchers have suggested that vascular dementia has a predominance compared with Alzheimer's disease of deficits in front-lobe function. So it seems to make sense to use a cognitive measure that includes those items standard for evaluation of Alzheimer's patients, as in the ADAS-Cog, with some additional items that would be weighted toward frontal-lobe function including attention and concentration, executive function, verbal fluency, working memory and psychomotor speed.

There are a number of tests, obviously, that could be chosen to meet these areas. Several of them have been recommended by an expert committee including a maze test, a verbal-fluency test looking at generation of words. While these additional items are not individually validated in vascular dementia, each has been found validated in Alzheimer's disease patients and, certainly, because of the association with the frontal-lobe functioning, they have face validity in vascular disease.

Then, finally, of course, any of a number of methodologies for doing a global rating would be appropriate

such as the ADCS-CGIC.

[Slide.]

Finally, I would suggest that trials need to be at least comparable in length to trials of Alzheimer's disease. Several studies have suggested that both Alzheimer's disease and vascular disease progress as relatively similar rates but, in the absence of any pilot data or available data regarding possible symptomatic treatments of drugs such as the cholinesterase inhibitors, in vascular-dementia patients, there is a need to treat long enough, as we do in Alzheimer's disease trials, in order to insure that we could see a drug-placebo difference based on a presumed decline in the placebo patients over the course of the study.

Also, of course, a longer duration will provide more safety data in this population. This is, clinically, a different population from Alzheimer's disease because of the risk factors which lead to additional medical disability and, therefore, a need to look at the safety of these drugs over a longer period of time.

I would also suggest that an important component of trials in vascular dementia is to monitor for the changes in vascular risk factors, especially over a long trial, since these, as well, could have an impact presumably that would be similar in the drug and placebo arms of the trial but at least one should look at hypertension, smoking,

hyperlipidemia and diabetes over the course of the trial.

[Slide.]

To conclude, a properly designed clinical trial in vascular dementia should select as homogeneous a population as possible in order to insure that the overall effect of the drug is driven by the population of interest. We think that the NINDS/AIREN criteria are, at this point, best to do that.

[Slide.]

The study must use outcome measures with demonstrated validity and reliability or at least reliable measures that have demonstrated validity in dementia and that, on the face, seem appropriate to use in patients with vascular disease and frontal-lobe dysfunction. Finally, the study must be of adequate duration, comparable to studies in Alzheimer's disease.

So, again, in conclusion, we think that these trials can be done now, that the NINDS/AIREN criteria are most appropriate, acceptable and usable by a group of investigators in order to define the population, that this population further is clinically relevant and that, with the modifications we have made in the criteria, could be applied easily in a community setting and give us an opportunity to test these treatments definitively so that they can be used in this population.

Thanks very much.

DR. KAWAS: Thank you, Dr. Satlin.

The floor is now open for questions.

DR. GRUNDMAN: You mentioned that we needed to do longer-duration studies to insure decline in the placebo group. I was wondering about what sort of natural-history data you actually have on these patients considering their heterogeneity. We see patients with stroke and, often, within the weeks after the stroke, they improve. Now, in your cases, some of these strokes were within three months; right?

DR. SATLIN: We don't actually have patients enrolled in a study as of yet. These are proposed solutions to some of these problems. I agree with you that there is a great deal of variability in the progression. I would think that any study would need to exclude people who were immediately post-stroke, at least until they were stable.

DR. GRUNDMAN: But some patients can show improvement over the months following a stroke.

DR. SATLIN: That is what I mean. Until one is clear that there is stability, that further improvement from the acute stroke is not occurring.

DR. GRUNDMAN: On the other hand, some of the patients with the subcortical variety may actually progress differently than patients of the multi-infarct variety. So

I was just trying to figure out, depending on your patient mix, you might have variability in the rate of decline that you are postulating.

DR. SATLIN: I agree. I think that is another argument in favor of doing a longer trial because the variability may be reduced, at least if you look much further out, than if you try to look at--

DR. GRUNDMAN: But then they might have more strokes, too.

DR. SATLIN: That is certainly true. You have to do a large enough trial to insure that at least these things are going to be balanced, if possible.

DR. KAWAS: Actually, I have a question about one of your thoughts, that if you had a trial, that the treatment effect could not be driven by Alzheimer patients. You keep referring to the 91 percent of Alzheimer's disease patients that get excluded by this criteria.

But that exclusion rate, if I am not mistaken, is for excluding pure Alzheimer's disease.

DR. SATLIN: Yes; that's right.

DR. KAWAS: Since we have seen data today that tells us that easily the majority of people who get a diagnosis of vascular dementia are likely to have Alzheimer's pathology, generally, the majority is potentially enough to drive an effect, I would have thought.

DR. SATLIN: I think there are different data that suggest different things. In the Gold study, for example, the 9 percent, you are right, is for Alzheimer's disease pure. But the figure for mixed was only 29 percent. So the question, then, would become first would it be even lower if Gold clinically had used not just NINDS/AIREN for possible vascular dementia but for probable excluding people by imaging criteria.

Then, in other series, the question becomes which criteria were used and you need to know that in order to be able to assess the weights, the comparability with the rates of pathology.

As Dr. Chui mentioned this morning, also, in her autopsy series, I guess you mentioned twelve patients with vascular dementia who had very little in the way of any Alzheimer's pathology.

DR. CHUI: They had a spectrum of Alzheimer's pathology but only two of them had Braak Stage 5 and 6, isocortical stages of Alzheimer's. But it was a very small sample.

DR. DUARA: I guess my question relates to--it is addressed to you and also to Dr. Katz and the FDA, in general. We now have criteria for vascular dementia that we can use, and you have shown--and the previous speaker has also shown how we could use these studies. We know that

using these criteria, the likelihood is that we are going to have a substantial number of patients with Alzheimer's disease.

The fact is, though, that, under the current FDA indication for the cholinesterase inhibitors that have been available, these patients would not normally have the indication for these drugs at this point. They would be patients--I mean, you could use it off-label, of course, but you are diagnosing these patients as vascular dementia.

So, if you, then, do a trial on these patients who are excluded, basically, because they don't have, as far as you can clinically detect Alzheimer's disease, wouldn't that be a fair trial to conduct, regardless of what the actual cause of the improvement is, whether it is because it is helping coexisting Alzheimer's disease or not?

The fact is that these people are actually excluded from, as far as the FDA is concerned, these trials.

DR. KATZ: I guess the short answer is sure. There is nothing wrong with studying people who have dementia. Who knows what the underlying etiology is in showing an effect of a drug. That would, presumably, be useful information, important information.

The question is how do you identify these people, what do you call them in labeling. Are they different from Alzheimer's patients? For example, there may be Alzheimer's

patients with vascular disease. That may be a more accurate description of who these people are.

That is different from saying these people have something called vascular dementia. One of the purposes of today's meeting is to sort of hash this out, what should we call them, how do we describe them. So, sure; it would be good to study them, it seems to me. And I don't know that they are excluded--companies may choose to exclude the Alzheimer's patients who have evidence of vascular disease on, let's say, imaging in their studies, but I don't know that there is a requirement that they do so.

But, nonetheless, obviously, people are always trying to identify homogenous populations for study so I suppose most of those patients were excluded.

But, yes; the question is how do you describe it.

DR. GRUNDMAN: Just, again, on the issue of the duration of the trials, I guess it sort of depends on what it is that you are trying to accomplish. I guess I am not really sure. On the one hand, it sounds like you want to insure that they decline, but we don't really know how quickly or what their natural history is.

So it seems to me like if we are trying to develop drugs in this area, if we are looking at a symptomatic agent, they wouldn't need to be a year long, unless you just want to document that the improvement persists over a longer

period of time.

DR. SATLIN: That is absolutely right. It is really analogous to the situation with Alzheimer's disease. I am suggesting that it is at least analogous and, maybe for one or two reasons, might be--

DR. GRUNDMAN: So we are talking about symptomatic drugs.

DR. SATLIN: Oh, yes.

DR. GRUNDMAN: We are not talking about disease-modifying drugs as we were would talk about in Alzheimer's disease, necessarily, or the types of drugs that Dr. Gorelick was discussing earlier.

DR. SATLIN: I think it would depend on the drug that was being tested, obviously, what you would look for. But if one was testing cholinesterase inhibitors, for example, in vascular dementia, using the same rationale as treatment in Alzheimer's disease, namely the cholinergic deficit, yes, one would look for a symptomatic effect.

DR. CHUI: I thought you framed that trying to exclude that Alzheimer's disease might be driving a positive effect very nicely. Have you thought about how you might randomize the vascular group with the mix with the Alzheimer's between your treatment and placebo arms so that they would be balanced?

DR. SATLIN: I think what we would be trying to do

is to select a single population that would be as exclusive of Alzheimer's disease as possible and then--obviously, we won't have the neuropathology on the patient--and then just randomizing them to the treatment. So I am not sure if there is something else you are suggesting.

DR. CHUI: I am just thinking aloud, but maybe on the degree of memory loss or the pattern of memory loss, that there would be the same type of pattern. The Alzheimer pattern would be equal between the treatment and the placebo group.

DR. SATLIN: I suppose it would something that could be tried, although, again, that would influence a number of factors including the size of the trial and could you really make those distinctions just clinically, might be difficult to do.

DR. CHUI: A related question. Have you thought about randomizing between the subtype of vascular dementia, between the placebo and the treatment arm?

DR. SATLIN: That is a very good point. I think at least one would want to look at the data afterward to look at subpopulations, whether you stratified patients or not at the beginning. Absolutely.

DR. KAWAS: Thank you very much.

Our final speaker in the public form is Dr. Sean Lilienfeld. Dr. Lilienfeld is the Director of Global

Clinical Research Development, CNS, Janssen Research Foundation. He will be speaking to us on the Overview of Design and Results in the Placebo Groups from Trial with Galantamine in the Treatment of Vascular and Mixed Dementia.

Overview of Design and Results in the Placebo Groups from Trial with Galantamine in the Treatment of Vascular and Mixed Dementia

DR. LILIENFELD: Thank you very much for the opportunity to address you.

[Slide.]

I hope that some of the data that I will share with you will answer some of the questions that have been posed in the last forty-five minutes. We performed a study in Europe, Canada and Israel and Poland involving some 600 patients using the criteria that have been discussed this morning. We have some interesting placebo data to share with you.

[Slide.]

Obviously, the problem that we faced was nicely described by Dr. Pratt earlier. We had studied galantamine in patients who met the criteria for probable Alzheimer's dementia and as best we could exclude patients who had any other disease, so this was done.

However, the reality is that there may have been some patients in the study who had vascular disease. By use

of radiology, in particular, as has been mentioned, we tried to exclude these patients but the reality is somewhat illustrated here, and this slide was kindly leant to me by Dr. Erkinjuntti.

It is really quite unclear, particularly in a natural population, but even in a trial population, how large that mixed patient population is. We may have, and we hope to have studied the patients who are illustrated on the right-hand side in green early and excluded the blue and mixture patients, but we may not have done.

However, in order to address the considerations which were mentioned earlier, and, in particularly, does the mixed population affect the efficacy of these drugs and, more so, was there any safety consideration, we decided to perform a study which would evaluate, hopefully, both populations.

In order to do that, we used the NINDS/AIREN criteria and the standard Alzheimer's criteria in the fashion that I will describe to you.

We allowed the inclusion of, really, two groups of vascular patients, those who had a diagnosis of probable vascular dementia as defined by NINDS/AIREN criteria who should have been, then, the group of clinically pure patients.

We also allowed patients who would have been in

that middle group, the mixed group. They would ADRDA criteria for possible Alzheimer's disease, possible because their radiology would make it impossible for them to meet the diagnosis of probable.

They also would have had to meeting the AIREN criteria radiologically for vascular dementia so they fitted into that group's possible vascular dementia and, hence, we called them mixed dementia. The other screening criteria were similar to those you have heard earlier today and, again, in both groups, the probable and the mixed group, we insisted that the radiology was positive and the radiological criteria that we applied I will highlight for you in a minute, but they were the AIREN criteria.

[Slide.]

A few subtle modifications, and I will only point the modifications out to you, you don't need to concentrate on the whole slide. It was suggested earlier that, perhaps, Dr. Roman's criteria were very strict in that they required memory to be present. Dr. Chui's criteria did not. So we modified the NINDS/AIREN slightly in that we required deficits in two or more areas of cognition but we did not specify that one had to be memory.

However, when we reviewed this protocol with Dr. Erkinjuntti and he was our external advisor, he felt that we probably would have every patient having a memory deficit

because the first criterion required the standard diagnosis of dementia. So it is likely that most patients did, in fact, have memory but it was not an absolute requirement.

[Slide.]

The cerebrovascular disease criteria were applied in this standard format.

[Slide.]

For the group who had probable vascular dementia, we did stick to the strict criteria in that the temporal relationship, abrupt deterioration of fluctuating stepwise deterioration had to be present.

[Slide.]

For the patients who fitted into the mixed group, we used the ADRDA criteria for the establishment of dementia so they all had a memory impairment.

[Slide.]

But they also all had to have positive radiology. These have been discussed several times. I won't eat into your lunch time by going over these criteria again.

[Slide.]

There were several exclusion criteria, the highlights of which are here. So we attempted, as best as we clinically possible, to exclude other causes of neurodegenerative disease. In particular in the patients who were included as having probable vascular dementia, that

meant that Alzheimer's disease had to be excluded as well and relevant medical conditions were also exclusion criteria.

[Slide.]

These are the radiologic criteria and you have seen these several times. I would just like to make one point here and that is we do have the results of these studies in house. I will discuss those that I am at liberty to with you now. Clearly, these have been submitted to several large peer-reviewed organizations and so some of the data I cannot share with you because we don't want to jeopardize the publication thereof.

But looking at these criteria, one interesting thing that we did notice is that very few patients had a radiology report which suggested that they fitted only into one of these. More than two-thirds of patients had at least two of these diagnoses present.

Whether that is a function of the way that radiologists look at scans or whether, in fact, it is reality is debatable, but just using radiology, it is going to be quite difficult to end up with the smaller subgroups that Dr. Chui suggested because the radiologists are either overinterpreting the scans or patients have got mixed types of vascular disease.

[Slide.]

These are the results from the study. You can see there are almost 600 patients in total. I will point out a few highlights here. Physicians were asked to diagnose the patients into the two groups I have discussed, either having probable vascular dementia or mixed dementia.

You can see that, fortuitously for us because we didn't stratify, that we ended up with about 50 percent of patients in each group having mixed dementia and about 40 percent in each group having pure vascular dementia.

Where are the other 10 percent? They probably have mixed dementia but the physicians were able to state that they felt they couldn't determine clearly between these two and they didn't want to commit, and so there are 10 percent of patients who are, in fact, in one of these two groups but not represented in either group.

When I show you the breakdown in the groups, then these 10 percent of patients are, in fact, excluded.

[Slide.]

These are the placebo results of the six months. I think there are a number of highlights. In each stage, I will show you a slide like this and then remove--the blue line represents all the placebo patients including those 10 percent of unclassified patients.

The yellow line in each graph will represent the patients who had a diagnosis of mixed dementia and the red

line those who had a diagnosis of probable vascular dementia.

[Slide.]

I think what is interesting, if you remove the combined group, is the deterioration--this is the ADAS-Cog over six months. We see that the patients who had mixed dementia--in other words, who probably had a component of Alzheimer's disease--deteriorated as has been seen in most Alzheimer's studies by about two points over six months.

A very interesting finding, of course, is that the patients who had probable vascular dementia did not deteriorate at all over the course of six months. This is post hoc analysis. The idea was not to compare these groups but I think it is relevant given the focus of this meeting. These two subgroups of placebo patients separated by 2.2 points on the ADAS over six months and that was statistically significant.

[Slide.]

These patients were also rated with the Neuropsychiatric Inventory, again with the combined group in the middle in blue.

[Slide.]

Here you see that the direction of shift is the same as you saw for the ADAS-Cog in that patients with the mixed dementia have deteriorated more than patients with the

probable vascular dementia but they have not separated over six months.

[Slide.]

This shows the disability assessment for dementia. This is Serge Gautier's Functional Scale. Again, you see similar trends.

[Slide.]

Patients who have mixed dementia have deteriorated in the same order as we have seen in our Alzheimer's studies by about 6 percent over the six-month period whereas patients who had probable vascular dementia have not deteriorated nearly as much, again, a 5 percent difference which is statistically significant at six months.

[Slide.]

I would like to show you all the results and the p-values but, for reasons that I have pointed out, I cannot do so. I was also hoping that both Dr. Ferris and Dr. DeKosky would remain here because they have seen these results and they were going to be my--at least someone can verify what I am telling you. Well, they have both left. However, within the next ten weeks, at a very important congress in Philadelphia, you will able to see these results yourself and you can see if these, in fact, were the case.

The reason I want to show you these results are these, because one of the questions that has been raised is

what are suitable efficacy tools. In fact, all of these tools were able to detect clinically relevant and statistically significant differences.

[Slide.]

What we would like to conclude from these limited data that I have shared with you is that, using the NINDS/AIREN criteria, physicians in nine countries were able to differentiate patients with probable vascular dementia from those who had Alzheimer's disease with cerebrovascular disease.

Taking these two subgroups of patients and observing several scales, a cognitive scale, a neuropsychiatric scale and a functional scale, the two groups deteriorate at different rates over a six-month period suggesting, at least in the clinical trial, that they do represent different populations, identifiable populations.

[Slide.]

Asking you to believe in the limited data I have showed you, the currently used tools are sensitive, that patients who have mixed dementia deteriorate at a rate equivalent to that we have previously seen in patients who have Alzheimer's disease whereas patients who had probable vascular dementia, using these tools, were relatively stable over six months. I think that is not completely surprising.

[Slide.]

These tools that we have applied are, in fact, suitable in that they are able to detect both clinically relevant and statistically significant differences between patients who received an active drug and patients who received placebo over six months.

Thank you very much.

DR. KAWAS: Thank you very much.

The floor is not open for questions.

DR. GRUNDMAN: I don't know if you can actually answer this question, but you brought up that the results were positive. Given the different rates, do you mean that the results are positive for the comparison groups as a whole or for the pure placebo, the pure VAD group and the mixed VAD.

DR. LILIENFELD: The study was powered for the groups combined but, in fact, that slide is appropriate for--

DR. GRUNDMAN: Both subgroups.

DR. LILIENFELD: For both--however you want to define it.

DR. GRUNDMAN: Placebo treatment comparison results.

DR. LILIENFELD: I cannot--

DR. GRUNDMAN: You can't; right. But the reason I

am bringing it up is because there wasn't really much of a decline. So, basically, in this sort of a treatment modality, you would actually have to show an improvement, which gets back to the questions I was raising to the previous speaker.

DR. KAWAS: Dr. Lilienfeld, may I ask you--the people were classified as mixed or pure by the clinicians.

DR. LILIENFELD: Yes.

DR. KAWAS: Did you go back and look at what baseline characteristics distinguish these two groups? What, basically, was the clinician using to separate these two foci?

DR. LILIENFELD: They applied the NINDS/AIREN criteria, at least if they met the diagnosis of probable vascular dementia, then they labeled those patients probable vascular dementia. If they did not, that usually meant that there was no temporal relationship between the vascular disease and the onset of dementia, usually the subcortical patients.

They ran into the problem that I think the speaker before me--

DR. KAWAS: But there wasn't a particular part of the criteria.

DR. LILIENFELD: No.

DR. KAWAS: For example, sometimes the difference

between possible is neuroimaging. But that wouldn't be the case here because you used neuroimaging in both groups.

DR. LILIENFELD: Yes.

DR. KAWAS: But if you looked at the baseline characteristics of the two groups after the clinicians separate them, nothing stands out.

DR. LILIENFELD: Very subtle differences. They are not statistically significant. The ADAS-Cog scores differed by 1.2 points at baseline, 22 point and 23 point, something. I don't remember exactly. But the groups are statistically not differentiable in baseline characteristics, MMAC scores, ADAS-Cog scores, that type of feature. They were differentiated on the NINDS/AIREN criteria.

DR. KAWAS: Whatever they did, to my mind, they did an interesting and good job of separating them into something. Hopefully, what they separated them into is mixed and pure. If that is the case, the mixed group, in every single parameter, clearly shows a much more rapid rate of decline.

DR. LILIENFELD: Yes.

DR. KAWAS: The mixed group, in every parameter, looked almost like Alzheimer patients, as you point out.

DR. LILIENFELD: Yes.

DR. KAWAS: So, certainly, for that group, the

effect conceivably could be mediated via Alzheimer's pathology rather than the other.

DR. LILIENFELD: But not for the other--if the other group does not have Alzheimer's disease, then--

DR. KAWAS: It would have to show an effect, also.

DR. LILIENFELD: Yes.

DR. PENIX: One point of clarification; you did, for your probable vascular-dementia group, modify the NINDS/AIREN criteria.

DR. LILIENFELD: That's correct; probably not requiring memory.

DR. LILIENFELD: That's correct.

DR. PENIX: Did you require memory for the mixed dementia group?

DR. LILIENFELD: Yes.

DR. CHUI: I think it is very encouraging, like a break in the sky, that there is evidence that we can diagnose mixed. That is very, very encouraging. It is amazing because the mantra for so many years has been that we were stuck.

I think, maybe, I can venture, it is maybe the neuroimaging now that is helping. If I can pursue your questioning a little bit more to try to find really what was the clinical characteristic that helped the clinicians separate the mixed from the pure, could it have been a

history of slowly progressive dementia, that if that was present, they would automatically go into a mixed?

DR. LILIENFELD: It is difficult for me to be certain about what is was that led to the difference. In terms of the data that we have collected which is, obviously, limited compared to what the clinician has at his disposal, the baseline characteristics of the two population groups look the same. The diagnosis is different.

The only difference, by the protocol, is the inclusion criterion. One meets the criterion for probable vascular dementia and the other meets the criterion for possible vascular dementia. So we didn't do an epidemiologic study. We said, apply the criteria and they either have probable vascular dementia or possible.

They applied them and they look different.

DR. CHUI: I understand.

DR. LILIENFELD: But I can't tell you what it is.

DR. CHUI: We want a psychoanalysis of the clinician. But, a related question, would apolipoprotein E4--how did it--

DR. LILIENFELD: We have these data, but I don't have them--

DR. CHUI: Would that have helped with the mixed.

DR. LILIENFELD: We have these data but I don't have them available at the moment.

DR. LILIENFELD: One last comment about the radiology findings. You had them divided into four different categories; multiple cortical, strategic, multiple lacunes and white matter. You said that at least two-thirds of the patients with the vascular or mixed fell into one or more of those four categories so that it would be difficult to separate into the subtypes.

But, actually, I just wanted to mention that, of those four, actually, the multiple cortical could be considered large-vessel. The strategic would be subdivided by large and small. Then the multiple lacunes and white matter would be small, so that you really can take those and divide them--the four can be grouped as two, lumped as two.

DR. LILIENFELD: Yes.

DR. CHUI: Then you might be able to have a subtype.

DR. DUARA: Helena, I just wanted to ask you about a comment that you made. You said, "At last we have data that shows us that we can identify mixed dementia." But my interpretation of what was shown was, actually, that you can't distinguish between mixed and Alzheimer's disease.

What you may be able to distinguish is between what was called probable vascular dementia or, perhaps, pure vascular dementia and that the characteristic is just that they deteriorate at different rates, which may only mean

that they have less of Alzheimer pathology than the mixed group has.

DR. KAWAS: But I think our point is that they were identified prospectively and, no matter what the underlying groups are, they separated into two groups by course, the course of the two individuals.

DR. DUARA: The probable did, but not the mixed group. The mixed group were identical to the Alzheimer group.

DR. CHUI: No; I agree with you. I think there are two boundaries between mixed. One is mixed versus AD and the other is mixed versus pure vascular. If I am understanding correctly, there is no good distinction between mixed versus Alzheimer, but there was a distinction between mixed versus pure vascular.

DR. LILIENFELD: Obviously, in this particular study, there is no group that was prospectively identified to have probable Alzheimer's. The comment that I made was that it is comparable to previous studies we have done. The real comparison here can only be between mixed and probable.

I suspect that your argument is completely correct, but that comparison we didn't do in this study.

DR. CHUI: You don't have pure Alzheimer's in this study?

DR. LILIENFELD: In this particular study.

DR. CHUI: Oh; I see.

DR. VAN BELLE: I don't know the patient population, but could it be the case that the mixed group is sicker in some sense than the pure vascular dementia? I don't know. I am thinking--I tend to be a continuum person rather than a splitter. So are we really talking about two distinct clinical entities or are we talking about a continuum and you just have picked out one piece of the continuum versus the other?

Do you know whether the mixed group is sicker than the other group?

DR. LILIENFELD: I don't believe, in terms of the tolerability--it is clearly not the ideal way to study this, but in terms of the adverse events seen and tolerability, the groups were different. That is the only data I can give you from a clinical trial, obviously. The cardiovascular risk factors appear to be more or less the same between the two groups.

As I say, at baseline, we were not able to differentiate the two groups on any demographic-type data we collected, including use of antihypertensives, previous myocardial infarctions, this type of thing.

DR. GRUNDMAN: My question is actually along the same lines. Claudia pointed out that the two groups seem to separate, and it seems like the validity of this is based on

their subsequent course. But, again, getting back to the point that was just raised as to whether or not there were some baseline factors that may have been different between the groups, such as their baseline Mini-Mental scores or their demographic, education, those sorts of factors, that might have influenced the rate of progression.

DR. LILIENFELD: Those factors--the two you have mentioned--were not dissimilar between the groups. So the standard dementia variables are matched.

DR. GRUNDMAN: So both the pure and the mixed were all about 20 on their Mini-Mental, the pure weren't, like, higher Mini-Mental scores?

DR. KAWAS: I think we have asked Dr. Lilienfeld this question, three people, three times, and the answer is no.

Do we have any more questions for Dr. Lilienfeld?

DR. KATZ: It is an interesting finding. Are you planning on repeating it?

DR. LILIENFELD: We have planned studies excluding the mixed population on the basis of discussions with your organization.

DR. WOLINSKY: I suppose it is a sort of related question because, at least in my mind, if you are viewing dementia as a symptom with multiple diseases contributing to it, and you have been able to have symptomatic therapy that

overcomes some aspect of the target symptom in a relatively defined but still mixed patient population, why wouldn't you repeat the study, if you need to repeat it, across dementia and then worry about how the subgroups fall out later on, especially if the issue is symptomatic versus disease-related therapy which, it seems to me, is frequently going to be the base in patients defined for dementia as the target treatment.

DR. LILIENFELD: I think, from the industry perspective, if the label was able to reflect a broad dementia population, we would be encouraged to study that population. The current labels clearly indicate not even the whole Alzheimer's population but a defined subset of the Alzheimer's population.

Up until now, the direction has been that we would need to specify the subgroup of demented patients we were studying. And so we have followed that direction and tried to be splitters rather than lumpers. But the question is clearly valid if the indication of dementia, all comers, is acceptable, we could study it.

If I was going to argue from Dr. Katz's seat, I would say you put in 97 percent Alzheimer's patients and you can be assured or your outcome and you call it dementia.

DR. KAWAS: Dr. Katz, would you like to comment?

DR. KATZ: Yes. Certainly, up until this point,

we have encouraged sponsors, or sort of the tradition has been that you study a particular dementia and it has always been Alzheimer's disease because, right or wrong, the field believes, the community believes, that that is a dementia that is specific to a specific pathology, and we have not, to date, considered dementia as a global symptom that is sort of homogenous and cuts across a whole series of underlying pathologies.

It is an intriguing idea that, perhaps, someday, maybe someday soon, we will consider it that way. We have not to date and I think today's discussion is very important toward the end of deciding, sort of maybe in a global sense, what is dementia, if there really is a blurred distinction between vascular and Alzheimer's dementia.

Maybe one outcome is we ought to be looking at dementia as a symptom. But, again, the question here today was is vascular dementia a specific syndrome analogous to Alzheimer's dementia being a specific syndrome. This is what I would like to hear people discuss--after lunch.

DR. KAWAS: I second that. I think we have had an excellent morning and we have got a lot of things to discuss this afternoon. We will reconvene at 1:45.

[Whereupon, at 12:35 p.m., the proceedings were recessed to be resumed at 1:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:50 p.m.]

DR. KAWAS: Welcome back to the Peripheral and Central Nervous System Drugs Advisory Committee. We had an interesting morning of presentations of the topic of vascular dementia. We have been given some questions which I would like the committee to turn to, specifically, and also if, at any point, we can ask Dr. Katz or anyone else who needs to guide the work of the committee.

I think we heard a lot of very excellent information. Hopefully, in the next hour or so, we will try to synthesize that and respond to each of the questions. Beginning with the first question--I think, actually, the first two questions maybe, in some ways, get lumped together in the discussion.

Dr. Katz asked us essentially about the utility of the diagnostic criteria, the ability to identify vascular dementia, to distinguish it from vascular dementia in combination with AD and other pathologies, and the use of the criteria by non-experts in the community environment.

I think these issues all center around the first two questions which we were asked, which are, can vascular dementia be clearly defined in a clinical setting and are there valid criteria for the diagnosis of vascular dementia.

I will start by summarizing and saying that my

ears heard a lot of different criteria proposed for vascular dementia, both this morning and over the years. But it seems to me that, increasingly, people were favoring one particular criteria and that was NINDS/AIREN criteria.

We also heard several times during the course of the morning about the usefulness of adding or including imaging to the diagnosis criteria as a means of improving particularly specificity and sensitivity. We also had, to my mind, a rather astonishing demonstration of at least physicians in one study, a large group of physicians in Europe, apparently had the ability to divide vascular-dementia patients into two categories, those with pure vascular disease and those with Alzheimer's or other processes, potentially, in a mixed form of vascular dementia.

We were never, overall, allowed to get an opportunity to see the construct validity of these criteria. For the most part, as Dr. Katz asked us repeatedly, I think we heard that there are not excellent clinical pathological correlations, if that were to be the gold standard or one way of determining validity. But, still, in the context of that study, I think it was notable that there was some predictive validity of the two groups that were divided by the clinicians in the study, presumably reflecting two different pathologies of some sort.

So, if I could open the floor for a discussion on the first two questions of the validity of criteria for the diagnosis of vascular dementia, and I will throw in mixed here, also, and whether or not these criteria could be taken out into the community.

DR. PENIX: I think that I agree. There seemed to be agreement that the NINDS/AIREN criteria were the ones that are used more frequently. Again, there are a number of discussion points that emphasize that the requirement that memory be included as one of the diagnostic criteria may confound or may actually increase the number of Alzheimer's patients that are included in those studies.

Certainly, again, there are only discussions about it. Dr. Roman indicated that, certainly, they used the requirement for memory because they were modeling the Alzheimer's disease criteria but clearly mentioned that there probably is a need to revise that.

Certainly, the Janssen study indicates that when they used that revision, it clearly showed that there was a difference in, I guess, the pure vascular dementia from the mixed group. So I think that my concern is using memory as a requirement--and it is unfortunate that there is very little data about neuropathological correlation with the original criteria and there certainly is none on a modification.

But I think that we should consider whether we should include the requirement for memory.

DR. KAWAS: Do any of our invited speakers want to comment on making that change?

DR. GORELICK: Just one quick comment. The criteria that some people are proposing for vascular cognitive impairment doesn't have the memory requirement in there, necessarily, and Helena's criteria doesn't have it in there.

I agree with you. I think that you are enriching, or you have the chance of enriching, to group of Alzheimer's patients by doing that.

DR. KAWAS: So, in answer to the first question, can vascular dementia be clearly defined in a clinical setting. Can we take those criteria out into the clinical setting, in the opinion of the people around the table and from what they have heard today?

DR. DUARA: I think you can make a diagnosis of vascular dementia and expect there to be vascular lesions in the brain. If one uses the strict criteria, the NINDS/AIREN criteria, I think you are not going to avoid there being coexisting Alzheimer's disease or, perhaps, some other pathology like Lewy-body disease being there.

But to a slightly lesser extent, or to a somewhat lesser extent, the same is the problem with Alzheimer's

disease. So it is just a question of degree. With Alzheimer's disease, we know there are going to be infarcts. There is going to be Lewy-body disease there and there may be hippocampal sclerosis, which is not related to Alzheimer's disease.

So we are dealing with the same issues. It is just a question of, in this situation, you are probably dealing with more. From the data that we have, that is what it suggests. But I think you can still make that diagnosis and expect that pathology to be the predominant one.

DR. KAWAS: I don't want to put Dr. Helena Chui on the spot, but since she brought up an important issue, in your presentation, you suggested that, whether or not we have criteria for vascular dementia, that it lacks utility in the therapeutic arena and that subclassifications were the approach that you would encourage people to take.

I think there is some merit to that that maybe needs to be brought back up in this discussion now.

DR. CHUI: But I think that maybe I should modify my position a little bit because I think I agree that vascular dementia can be labeled in a clinical setting. It is broad. I think it could be useful for symptomatic treatment of vascular dementia but, based on its heterogeneity and pathophysiology, I think, for future, more disease-modifying treatments, that it would be good to look

at more homogeneous subtypes.

DR. KATZ: I will just throw this out. It seems to me that there is the potential for a certain amount of circularity here in the absence of good, underlying clinical pathologic correlations because you can set up diagnostic criteria for patients who have dementia and evidence somewhere of vascular disease, whether it is by history or on some imaging study.

It is almost circular that you would be able to distinguish, on clinical grounds, patients with what you are then calling vascular dementia from patients with Alzheimer's disease or other dementing illness because you have defined it that way.

You said, "I am going to call people who have dementia and vascular disease vascular dementia." So it is not surprising that you should be able to distinguish patients with vascular disease and dementia and patients with dementia without vascular disease.

Obviously, I have said it before, but in the absence of strong pathologic correlation with these clinical criteria, to be able to say, "Well, we know we can diagnose vascular dementia on clinical grounds," seems almost circular. Anyway, I will throw that out and see what people think.

DR. GRUNDMAN: We are getting into one of these

little semantic arguments. Would it make more sense to just call it cognitive impairment in the presence of strokes? Would that satisfy the problem?

DR. KATZ: I don't know if it would satisfy the problem. I think it would be more descriptive and less--again, I think the term vascular dementia implies that there is a causal relationship between the underlying vascular disease and the dementia whereas to say dementia with associated vascular disease, I think, is potentially more accurate.

On the other hand, I am not sure it is terribly useful. You can find people with dementia and red hair. I don't know that it is a critical distinction. What I am trying to find out is what is the evidence that there is a critical link.

DR. GRUNDMAN: It might depend on each drug that might come forward but, in the case that we looked at before, if you classify dementia with stroke or dementia in the presence of stroke, it didn't seem to matter which group you were in, whether you were in the mixed group or the other group. In this particular case, the drug also works in Alzheimer's disease, so I think you have got all your bases covered.

DR. KATZ: I don't think it is a drug-specific question. At least, I am trying not to make it to be a

drug-specific question. I am simply asking a question about how do you describe the clinical entity. I don't think it depends on whether or not you have a treatment for it or not.

I am just trying to figure out what is an accurate way to describe these patients.

DR. GRUNDMAN: It probably would be more accurate to say that it is dementia in the presence of stroke because then you are not making any assumptions about the causality. But that is what you are observing empirically.

DR. CHUI: I think the construct validity, the question of construct validity, the pathologic gold standard for vascular dementia, is illusive. Maybe there are other ways of getting at the causality.

I think, for vascular dementia, what we can do is you can see most of the pathology on the MRI and then, at pathology, at the autopsy, you confirm that those lesions are there and they are ischemic. At autopsy, we really don't have any more information than we have from the MRI about their causal relationship, so we can't really look for the pathology to inform us more about the causality.

So we mustn't expect the same of the pathology for construct validity of vascular dementia as we do for Alzheimer's disease. So I think we should look for alternative ways for defining construct validity. I think

that we can confirm that they are ischemic lesions but not confirm that they had a causal relationship.

DR. KAWAS: Can you suggest some alternative ways for construct validity?

DR. CHUI: One is the absence of Alzheimer pathology so no other explanation, kind of like the NINDS criteria for Alzheimer's disease, exclusion of other pathologic explanations for the dementia. And then you have the vascular pathology.

We do have enough evidence that the lesions were in the right location that are important for behavior. There is a whole database on that. The causal relationship between the stroke--the temporal relationship, rather--between the stroke and the cognitive decline is causal evidence, circumstantial to some extent, but it is causal evidence. The NINDS criteria are conservative, but that is what they require.

So those are other ways of trying to garner evidence for causality.

DR. KATZ: I agree that you can't establish causality based on the pathologic picture. You can't do it for Alzheimer's disease, either, I suppose. You can say there is a stereotypical picture, a pathologic picture of Alzheimer's disease. It is hard to know whether or not what you are looking at is causative of the disease.

But, again, I am sort of struck by your own data which suggested that there isn't very good correlation between the white-matter lesions and the degree of dementia, or, perhaps, the presence, even of dementia although you suggest the atrophy of various structures. Hippocampal atrophy and cortical atrophy are better correlated.

But if it were the case that, routinely, there was a very good correlation with the degree of white-matter disease or the lack of Alzheimer's-like findings in the brains of patients who were diagnosed in life with vascular dementia, even though that wouldn't be proof of casualty, it would be stronger evidence, it seems to me, than what we have now which suggests that lots of patients who are diagnosed with vascular dementia have a fair degree of pathology findings that are consistent with Alzheimer's disease.

So I agree, you can't establish causality, but there could be stronger correlations, let's say, or cleaner or purer. I know it is hard to get those, of course.

But the other thing that maybe we can address, also, with regard to this question has to do with the clinical picture. How well-established would you say it is, and how good is the evidence, that the clinical picture of vascular dementia, sort of typical clinical picture, whatever that is, of vascular dementia is really very

distinct on clinical grounds from Alzheimer's disease.

People are talking about this sort of executive dysfunction in patients with the diagnosis of vascular dementia. Is there sort of good evidence establishing that that is relatively specific for the clinical diagnosis? People have been talking about these various frontal lobes. Has that been documented or is it something that people sort of, in their experience, think they see?

DR. PENIX: Jeff Cummings has written about the front executive abnormalities in vascular dementia and--

DR. KAWAS: And in Alzheimer's dementia.

DR. PENIX: Exactly; sure. And I wanted to make another point; in regards to a gold standard, there is no pathological gold standard for diagnosis of vascular dementia. That was one of the discussion points that was raised in the NINDS/AIREN study, that we needed to establish a pathological criteria for vascular dementia.

There are several that are available for Alzheimer's disease. So part of the problem is that we don't have an agreed-upon standard neuropathological criteria. Therefore, I think we have to rely on surrogates. It looks like the MRI or imaging data is probably the best that we have.

DR. KATZ: Perhaps the lack of pathologic correlation is part of the problem. I suppose one doesn't

have to rely on something else. You can be at various stages in the development of a particular diagnosis. Sometimes, you are not there yet. You are not there at the point where you have a good idea of how to define this because you are lacking a critical piece of the puzzle.

Maybe that is the case here. I am just raising that as a possibility. I know people want to make the diagnosis. The question is are we at a point, is the field at a point, where they can confidently say yes, these are the criteria to be able to diagnose vascular dementia and we know that the vascular component is what is responsible for the dementia for the following reasons.

If there is a big hole in that list of reasons, a critical absence of data, maybe you just have to say we don't know yet.

DR. KAWAS: Would anybody else like to answer Dr. Katz' question about the role or the prevalence of executive dysfunction in vascular dementia versus Alzheimer's?

DR. GORELICK: I don't think it is specific. Don Royale, who is one of Gustavo Roman's colleagues, has published a lot on this. They have an interview that is geared toward detecting executive dysfunction. What they are now saying is that this may be an early sign in dementia. So we are talking about Alzheimer's, as you have alluded to, Claudia. We are talking about vascular

dementia.

Because of the cutoff or disconnection syndromes that occur, if you will, because of small, deep infarcts and, often times they are in the frontal white matter, that is why you may tend to see a lot of that in so-called vascular dementia. But I don't think it is specific.

The other comment that I wanted to make is I agree with what Michael said. We have continued to use the term dementia associated with stroke, which is basically similar to what you are saying over the years. The reason why we use vascular dementia or vascular cognitive impairment or whatever we are talking about is because people have accepted those terms, but I think there still is a murkiness about this. That is why we have had more of a broad net, dementia associated with stroke, in our publications.

DR. KAWAS: Which one of you wants to talk about the executive dysfunction part first and then we will go on.

DR. DUARA: There was a paper in Neurology, either earlier this year at the end of last year, that addressed the frontal subtype of Alzheimer's disease. I don't know if any of you are aware of that paper, but basically they looked at people who had basically a frontal-lobe syndrome.

If you look at the tests that they used to establish that, they were all the executive-function tests that one would use, plus others. So there is an executive

dysfunction that occurs in Alzheimer's disease. There is a subtype of Alzheimer's disease that presents with primary frontal-lobe pathology.

That is what they showed in the paper, that those patients, on pathology, had primarily frontal-lobe lesions, plaques and tangles. So I agree that you can't really distinguish patients with vascular dementia from Alzheimer's disease based on executive dysfunction.

DR. KAWAS: Not to be too naive about it, I know I went to school and spent a lot of money to learn this, but can somebody tell me if the frontal dysfunction in vascular dementia is anything more than the frontal lobes in terms of brain tissue is about equal to all the rest of the brain put together.

Even in strokes that only happened randomly, you would expect more "frontal" signs than you would occipital or whatever. Are we sure it is even more than that, the observation that people are making about frequent frontal dysfunction in these people?

DR. CHUI: I think that the notion that frontal-lobe dysfunction is greater in vascular really comes from the subcortical subtype because if you have a left middle cerebral-artery stroke, you know that is aphasia. If you have a right middle cerebral-artery, you know that is neglect. That is not a frontal predominant syndrome.

I think that this notion is coming from the subcortical subtype. The distribution of lacunes in subcortical gray matter and white matter is predominantly in the frontal lobes. This was a paper written by Ishi--I showed the slide--1986 in Neurology. Why does frontal-lobe symptomatology predominate in vascular dementia. He was talking about lacunes, this SIVD subtype.

He has a nice diagram there showing the map of all the hits in the cases. You wouldn't confuse the front from the back. The front was top-heavy, full of lacunes. He never really answered why, why are those vascular. Those are the areas that have the frontal subcortical loops, this notion.

So I think there is as clinical pathologic correlation explaining why there is as predominant frontal executive dysfunction syndrome in SIVD.

I think your question, Dr. Katz, about the clinical path correlation--it is a real challenge to us in neurobehavior. I think the answer is no, we cannot do it now, just the frank answer. We certainly can't do it by taking a single domain and saying that this pattern is specific.

Maybe as we have more information, technology, and so forth, we are going to be able to address this in multidimensional ways. For example, just to take it to two

dimensions, it could be that the Alzheimer pattern is a greater loss of recall and an equal loss of recognition memory with a greater loss of animal fluency than letter fluency, and this SIVD pattern is better recognition memory and equal involvement of animal versus FAS but worse than the Alzheimer when you control for overall severity of dementia.

So I think that, in the future, maybe we will be able to get looking at the lesion distribution, whether we are looking at imaging MR or pathology. I think they are the same thing. We are just looking at the distribution of lesions and saying, based on what we understand about the networks, the cognitive networks in the brain, predict the behavior, then take the patient, measure the behavior with neuropsychological testing and say, how close is this fit.

But, right now, when we do an evidenced-based search of the literature and say how good are neuropsychological tests in predicting the subtype of dementia, they are not very good right now.

DR. KAWAS: Helena, right now, all the criteria are basically driven by nonpsychometric properties. You were just suggesting sort of a new approach. If we were to have criteria developed with psychometric testing, could you envision that being taken out into the clinical setting?

DR. CHUI: When computers rule, out in the

clinical setting, maybe. It is too much data.

DR. KAWAS: Can I maybe summarize? I think that we, as a committee, have said that we can define vascular dementia in actually any number of ways. But the validity of what we are defining is not completely established yet, either through psychometric, pathologic or other measures.

We believe that, for the most part, we can distinguish Question No. 3, distinguish Alzheimer's disease and pull them out of these patients at least to some extent. How well is yet to be determined. Could vascular dementia be defined in the clinical setting would depend on which criteria we ask clinicians to use.

It strikes me that, in part, the language of stroke is already familiar to physicians, unlike yesterday where we were talking about a language that physicians have not been trained in, to recognize. A lot of the impact and a lot of things that people on the committee said have to do with reverting back to the language of stroke--i.e., the risk factors of stroke and treating them, or the way we categorize stroke.

So we actually have a physician base out in the clinical arena, I think, that is a little further along in getting to criteria than maybe they would be to the type of thing we discussed yesterday. But that is because of all the work that has been done in stroke, primarily, and not

the work in vascular dementia, it seems to me.

I would like to sort of move us to Question No. 4, what outcome measures are appropriate to use in clinical drug trials conducted in vascular dementia. None? Let me at least give you two choices. Let's talk in general outcome measures. Do we think that, in vascular dementia studies, the most likely thing to be useful would be time to another event, time to more severe dementia or onset of dementia, change in cognition over time?

Do we think that the instruments and outcome measures that we have been using for Alzheimer's pathology should just be rolled over into vascular? That is where I see most of the heads nodding.

DR. CHUI: With a few additions, as I think there was convergence saying that the ADAS-Cog, for example, doesn't really cover frontal executive functions very well so we certainly would need some additions.

DR. KAWAS: So you would use the ADAS-Cog plus additions or something instead of?

DR. CHUI: ADAS-Cog plus additions.

DR. KAWAS: Plus? Are there other additions that people want to tell before Dr. Katz asks us what he really wants to know?

DR. DUARA: I would just go with the ADAS-Cog. If we are going to do a clinical trial, everybody is geared up

to using the ADAS-Cog. If you can show improvement on that, then you have got a significant finding, whatever that finding means.

DR. KAWAS: So the same instruments plus some executive function, so far.

DR. KATZ: I just wanted to ask--we don't have much of the committee left as I look around the table. I guess you are the only two members. I will ask a question which, in effect, I suppose you have been answering but just to get it explicitly out, I will ask the same question I asked yesterday which is are we ready to have drugs be developed and approved for so-called vascular dementia at this point given the questions that remain and given the uncertainties about the pathophysiology and that sort of thing.

I just want to hear someone say yes or no, we are ready. I mean, we are talking about trial design already so, before we sort of get into that, it just might be useful for us to hear whether or not we think we are there and we are at the point where we can approve a drug for the indication of vascular dementia.

What I heard today, there were two different ways to approach therapies for vascular dementia that were implied by our speakers and the discussions. The ones that were "potentially disease modifying," to my mind, had no

specificity at all towards vascular dementia. They were specific towards preventing the accumulation of additional vascular events of whatever sort, full-fledged strokes or more hypoperfusion or whatever.

So, to my mind, the ones that were looking at changing the underlying basis of the disease were synonymous in many ways to the changing recurrent stroke.

The other treatments or gestalts that were discussed I thought were symptomatic in many cases. We launched into the discussion of should we be talking about symptoms for dementia, then, and not worrying about these individual differences between dementia diagnoses.

So it wasn't clear to me, personally, that I heard anything that says that there is something unique about vascular dementia as an indication for drug therapy but rather that we know a lot about it, both from what we have studied, other dementias as well as what we know about stroke, that give us an opportunity to potentially make some therapeutic proposals.

Does that answer your question from my opinion? Then you will get Dr. Wolinksy's.

DR. KATZ: Maybe the answer is no. Do you think that we should be in the business now of approving drugs for vascular dementia or, perhaps, dementia with vascular disease or should we just be worried about approving drugs

for dementia independent of the presumed pathology? Again, companies have come to us, as you have heard. Some have already performed their studies. They are looking for a claim for the treatment of vascular dementia.

Right now, we have only permitted claims for the treatment of Alzheimer's disease. They want to know whether or not we can grant them a claim for vascular dementia, let's say symptomatic treatment. Is that something that we are ready to do, in your view?

DR. WOLINSKY: My own bias is that, given what I have heard over the last two days, there is dementia which is a cardinal and long and important manifestation of Alzheimer's disease and, depending upon the length of the study and the design of the study, one could look at drugs which were treating the cardinal symptom or using the cardinal symptom as an indication of treating the underlying pathophysiologic process.

Those two studies have slightly different designs and substantially different time tables. What I have heard about dementia, which is a symptom of a variety of diseases, the two main diseases of which are Alzheimer's disease and whatever vascular dementia is, is that one could envision studies that are designed for the symptomatic treatment of dementia which would not necessarily have to differentiate which of those two or mixed disorders one had accumulated

for those studies.

They probably will have to show some measure of improvement and not just holding the common ground so that they really are a beneficial symptomatic therapy. But they will not be able to very easily make any inference about whether or not they are affecting the natural history of the disease, almost no matter how long they are, unless they have been able to differentiate those component patients that are contributing to the data in a long-term study.

DR. KAWAS: I am not sure I am going to answer any better than before, but at the beginning of the day, I think I felt differently. At this point, maybe because I had lunch with Dr. Wolinsky, I actually am coming around to that notion, too.

I, personally, have never seen data that suggests that individuals who are given a diagnosis of vascular dementia by one of these criteria would improve when given, for example, a cholinergic agent. However, if that data were to come out, it seems like, on some level, we need to allow to the prescribing community the idea that these drugs do have potential in these individuals in spite of their diagnosis, however it was made.

I guess this reflects my bias, that I don't think the indication, personally, is for vascular dementia, per se, because I am not sure what we have identified in these

individuals who have a vascular component and dementia.

On the other hand, I think there needs to be some way to express that individuals who have a vascular component and dementia may respond, if they do, indeed. So that brings us back to maybe we should be thinking more in terms of a syndrome and symptomatic treatment no matter what the perceived etiology is.

Then the criteria becomes a lot less crucial, as long as individuals are demented and as long as the trial can show symptomatic improvement of that dementia and as long as retrospective analyses don't suggest that there was a subgroup that did not respond and that subgroup was characterized specifically by the vascular pathology, then, perhaps, the indication of dementia for symptomatic trials is not as far-flung as I thought it was this morning.

Do we have comments from the other invited--

DR. CHUI: I just want to be sure, though, that when you are suggesting that we might just drop the etiologic label from dementia, we are not opening it too far, we are not suggesting that a symptomatic treatment would be also for frontal-temporal dementia or dementia of the Lewy-body type; we are talking specifically about Alzheimer's, vascular and the mixed and putting those two together.

DR. KAWAS: I would argue why do you think that a

particular drug that helps those two won't help frontal-temporal dementia. I would argue you don't know until you try.

DR. CHUI: Yes; you can try, but the data would have to, again, support that. You would have to know that you had frontal-temporal-dementia patients in there and see if they improved. There is anecdotal data that actually anti-cholinesterase worsens the symptoms of frontal-temporal dementia.

DR. WOLINSKY: The greatest difficulty in this kind of thing would be the potential for losing first principles and not excluding hypothyroidism and B-12 deficiency and chronic anemia and underlying liver disease. But I don't think any of us are suggesting that.

DR. DUARA: There is also anecdotal data, in fact, studies, that show that patients with diffuse Lewy-body disease respond very well to cholinesterase inhibitors. So why wouldn't we use it for those individuals?

But I think Lewy-body dementia is also a sort of an example here. If you look at the pathology studies that I presented earlier this morning, Lewy-body dementia was more common than vascular dementia and yet you are saying, Dr. Katz, that people are coming to you for improving an indication for vascular dementia. Why aren't they coming for Lewy-body dementia?

I just wonder about that question because there is already much better data showing that Lewy-body dementia does respond to these drugs.

Of course, if somebody tried to do that, they would have an even bigger problem than they have with vascular dementia because it is going to be almost impossible to try to distinguish between those two entities. So maybe that is why they asked for that indication.

The reason they are asking for vascular dementia is that they think they have a fair chance here of separating the two. What you have asked, over and over again, is can we really say that we are really talking about vascular dementia.

I am not quite sure where to go, given all the data that we have. But my leaning is certainly to say that, with the criteria, with the strictest criteria we have--and that will really exclude a lot of patients who may be categorized as vascular dementia by various other criteria, obviously--so it would be a rather small subset of patients. But, in those patients, we have a pretty good indication that we are dealing with patients that have a lot of vascular pathology.

It may be that the mix of having a vascular pathology with Alzheimer's pathology or diffuse Lewy-body dementia pathology, that is a separate indication, maybe. I

don't know. But I think we should think about it in those terms. I would be in favor of distinguishing vascular dementia as an entity and seeing if there is an indication for it.

DR. KAWAS: Other comments? Dr. Katz? Shall we go on to, should clinical drug trials in vascular dementia incorporate any special features in their design?

DR. GORELICK: I think we have got to make sure we know what the target is. I know this is not a specific issue you want to hear, but given all the published data on clinical trials in vascular dementia, or what we are calling vascular dementia, we have struck out every time.

I don't think we have gotten to first base. We certainly haven't hit a home run. Of course, that is excluding what we heard here today. There may be very promising data that is in pipeline that will be coming out from the speakers we heard from, but I guess we have got to go back to square zero.

Right now, the trend in vascular dementia is that we are hoping that the subcortical form that Helena has talked about is going to save the day and we are going to be able to define that and that we are going to be able to jump from there because if that doesn't happen, we've got a big problem.

I think people are going to have to take a very

careful look at that subcortical form, understand a little bit more about the natural history of it, or as best we can tell, the natural history, these placebo groups that we are seeing in these studies and correlate it with imaging studies from these specific trials are going to be very, very important.

But, again, I get back to that same issue with neuroprotectants. We have struck out there and I think we made a leap of faith and we jumped from one stage in development all the way to the final stage and I don't want to see that happen in vascular dementia, as we call it.

DR. KAWAS: Good point. I am not sure that we have helped very much. Have we confused very much?

DR. KATZ: Yes; but sometimes that is helpful. Yes; it is a tough issue, obviously, but I think it has been very helpful.

DR. KAWAS: I really do feel like an extension of what we have been hearing. It really is important to separate out whether you are talking about therapies that are going to affect the underlying pathology versus therapies that, in some way, whether we know the mechanism or not, are symptomatically affecting the process.

To my mind, if it is affecting the underlying process, I don't think there is an indication. The indication is the indication of stroke and preventing

stroke, not dementia, per se, or vascular dementia, per se, either.

I don't personally think that we have anything for underlying process in the pipeline other than what we have already in our anti-stroke armamentarium. So, in that sense, I, personally, do not see it as an indication.

But I am concerned about the possibility that cases that someone, somehow, has decided are vascular dementia might respond to these therapies and how to insure that they would get included in the fold is of concern.

DR. KATZ: Again, I agree. We talked about it a little before. If there is a group of patients in whom appropriate treatments are not yet indicated and yet it works in those people, it is useful to have those out there and they need to be somehow--again, I think most of what we have been grappling with here is how to describe that, how best to describe it.

That is very important from our point of view for various reasons. But, obviously, if the drug helps people who haven't been studied before, that would be very useful to know and we will have to decide how best to explain that.

DR. CHUI: I do want to respond are we ready to move forward. I think we are. I actually I think move forward with clinical trials and approvals for vascular dementia. I think we are ready to move forward based on

what the data show and looking at how the groups were defined and just use what the data show how the groups were defined to move ahead with the labeling.

The diagnosis of Alzheimer's disease has its problems because we don't have a biomarker for Alzheimer's disease, and yet we have gone forward with that. If we could see the neurofibrillary tangles and neuritic plaques--of course, they are not the beginning of the problem either, but if we could see them and we saw them throughout the cortex, we would say this person has Alzheimer's.

We don't have that. We are labeling, we are allowing treatment for Alzheimer's disease. We have no notion of the pathology in Alzheimer's disease, but we assume that the pathology is there. It is causing the dementia.

For vascular dementia, we have the opposite. We can see the pathology. We can see it in the imaging. We just don't know if it is causing the dementia. So there are two sources of uncertainty for both diagnoses. It is just that the uncertainty is in a different camp.

In the Alzheimer's, we don't know if the pathology is there but we assume, if it is there, it is causing the dementia. In the vascular camp, we can see the pathology. We just don't know if it is causing the dementia.

So I think that it is really a tossup. There is a certain amount of uncertainty around both of them. I think we are ready to move forward with treatment for Alzheimer's because people diagnosed by these criteria have such-and-such a predictive value in the sense that it is not perfect, but the data show that it helps.

I think the same, the NINDS/AIREN criteria are very conservative so we are erring on the conservative side. We are picking people that we really think, by all of our best knowledge at this time, probably have a causal relationship between the vascular disease we see and the clinical syndrome.

So if the data show that these patients diagnosed with these criteria are improving, then I think that that should speak for itself.

DR. KAWAS: Can I ask if you think we are ready to move forward with studies of people with pure dementia, mixed vascular dementia, put them both together and call them one group, like dementia with a vascular component of unclear significance?

DR. CHUI: Both. I think what we saw today, what was presented, seemed reasonable to me, that I think the data from Europe with galantamine showing that these groups have different courses, they have predictive validity. Then we would look at the interesting results as they come out.

DR. KAWAS: Since we haven't been able to see the galantamine results yet, I can fantasize in any direction I want. What if the results, for example, showed a substantially larger treatment effect in the mixed group than it did in the pure group? What would you think, or interpret or feel about indication and labeling then?

DR. CHUI: I think you would say that it is effective for people with mixed. I would extrapolate--

DR. KAWAS: Why wouldn't you just say it is effective for people who have Alzheimer's disease, whether or not they have a stroke, also?

DR. CHUI: That's fine, too. It just semantics. I could do that, too. Either way. I think if the drug effect is greater in the mixed group than it is in the vascular group, then I would interpret that as saying that it is an Alzheimer effect. There is kind of an Alzheimer dose-effect there. If there is more Alzheimer's disease, then you see a greater effect.

But, as you said before, or you said, Ranjan, right now the indications, the labeling for cholinesterase, are limited to people with pure Alzheimer's disease. If it works also in people that have Alzheimer's disease plus a vascular lesion, why should we prevent them from getting treatment?

DR. KAWAS: But that is different from saying it

works in vascular dementia. We already know it works in Alzheimer's disease. Then you can just say it works in Alzheimer's disease even if you have a stroke.

DR. CHUI: Fine. Then the next is what does it show in the other group, the one that is defined by NINDS/AIREN. That is the interesting one.

DR. KAWAS: Would something only get the indication for vascular dementia if it worked in the pure group, then, presumably, at least as well, if not better? But if it worked in the mixed group, then maybe it really isn't--

DR. CHUI: Right. To me, that is a reasonable recommendation.

DR. KAWAS: Does that help? Who else wants to help Dr. Katz?

DR. DUARA: I think the cleanest way to do this, actually, would be--and I don't know if anyone will do it, or maybe they are already doing it, is to look at people who have had a stroke and treat them with whatever is being proposed. Let's say it is a cholinesterase inhibitor and see what happens to these people versus those who don't get cholinesterase inhibitors and see whether the cognitive impairment that you could detect presumably--I mean, we are talking about people who have had a stroke in whom you can see a cognitive deficit, which you presume is a result of

the stroke, and seeing what happens to these people in a double-blind controlled study.

But if we don't have that data, in the absence of that kind of data, I think that we should certainly consider what Helena just said which is look at people who are diagnosed to have vascular dementia.

DR. KAWAS: So it sounds like people are interested in moving ahead at least with studies so that they will have more information.

I think it has been a very interesting discussion. We will take a few more comments, but if anyone has any specific questions or things they want to bring up, now is the time.

DR. IDDEN: Hi. My name is Dr. Joanna Idden from Cambridge in England. I just wanted to go back to a point that you skimmed over a little earlier and then someone else jumped to something else which is what outcome measures should be used in clinical trials.

I was very interested to find that the two speakers here actually said ADAS-Cog. Dr. Chui said executive function tests. I am a neuropsychologist. I am an independent neuropsychologist and I very much feel that this is a very interesting question. It is something I am always asked and it is something that is a big problem for a lot of people, deciding on the outcome measures in their

studies.

I believe that there are many, many valid tests that have been well developed, very sensitive, very specific, that may look at both executive function and other areas of function, verbal measures, et cetera. They are graded in difficulty, some of these tests. Some of them are specific to types of function in neural areas.

So why is it that ADAS-Cog seems to be so stolidly stuck there for all dementia trials when, actually, it may not be the test of choice, or the test battery of choice. I would like to know how the FDA stands on this test.

DR. KAWAS: In that case, we will let Dr. Katz answer and the rest of us are going to be very quiet.

DR. KATZ: I think we have no stance on its use in so-called vascular dementia. We have taken a position sort of by tradition about its use in Alzheimer's disease because, presumably, it is validated in Alzheimer's disease.

But what it does in patients with this entity, I don't know. The point is, when it comes to picking a test and requiring it--and, by the way, we don't require the ADAS-Cog for Alzheimer's drugs; it is just that everybody is using it, presumably because experts in the field think that it has some relevance to the condition.

We are asking the few experts who are left here today what they think. We are just listening. We haven't

taken a position.

DR. GORELICK: Just very quickly, I think by virtue of the many, many times these instruments have been used in the Alzheimer's trials that they are going to spill into the vascular-dementia trials and we are going to have a little more confidence in them, and that is why we are using them. If we had to start from scratch to start developing instruments, it would take a long time and we want something that is easy to apply, or relatively easy to apply, and that we know a lot about its usage.

DR. KAWAS: Well said.

Any final comments from the panel before we adjourn?

DR. CHUI: Just a small point. The ADAS-Cog reminds me of the Fulstein MSSE. Why is the Fulstein MSSE shown all over the world? It is not the best test as it was written on a napkin, I understand, at the very beginning. But it has become a familiar dinner paraphernalia.

DR. GORELICK: Just a final comment. I am creeping further and further upstream as I hear more and more.

DR. KAWAS: Primary prevention; definitely.

It has been a very interesting discussion for me and I want to thank all of the panelists and the invited speakers and the committee members and the FDA and,

particularly, Dr. Titus and Dr. Mani and the audience.

This meeting is adjourned.

[Whereupon, at 2:45 p.m., the meeting was adjourned.]

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