

Does *Ginkgo biloba* Reduce the Risk of Cardiovascular Events?

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Background—Cardiovascular disease (CVD) was a preplanned secondary outcome of the Ginkgo Evaluation of Memory Study. The trial previously reported that *Ginkgo biloba* had no effect on the primary outcome, incident dementia.

Methods and Results—The double-blind trial randomly assigned 3069 participants over 75 years of age to 120 mg of *G biloba* EGb 761 twice daily or placebo. Mean follow-up was 6.1 years. The identification and classification of CVD was based on methods used in the Cardiovascular Health Study. Differences in time to event between *G biloba* and placebo were evaluated using Cox proportional hazards regression adjusted for age and sex. There were 355 deaths in the study, 87 due to coronary heart disease with no differences between *G biloba* and placebo. There were no differences in incident myocardial infarction (n=164), angina pectoris (n=207), or stroke (151) between *G biloba* and placebo. There were 24 hemorrhagic strokes, 16 on *G biloba* and 8 on placebo (not significant). There were only 35 peripheral vascular disease events, 12 (0.8%) on *G biloba* and 23 (1.5%) on placebo ($P=0.04$, exact test). Most of the peripheral vascular disease cases had either vascular surgery or amputation.

Conclusions—There was no evidence that *G biloba* reduced total or CVD mortality or CVD events. There were more peripheral vascular disease events in the placebo arm. *G biloba* cannot be recommended for preventing CVD. Further clinical trials of peripheral vascular disease outcomes might be indicated.

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Key Words: anticoagulation ■ peripheral vascular disease ■ cardiovascular disease ■ stroke ■ trials

We report the vascular disease secondary end points from the Ginkgo Evaluation of Memory Study (GEMS) of *Ginkgo biloba*, a randomized, double-blind, placebo-controlled clinical trial conducted between 2000 and 2008.^{1,2} Vascular end points included cardiovascular disease (CVD), defined as angina pectoris, myocardial infarction (MI), congestive heart failure (CHF), stroke/cerebrovascular accident (CVA), transient ischemic attack (TIA), peripheral vascular disease (PVD), and CV-related deaths. There have been no previous clinical trials to evaluate whether *G biloba* in the form of EGb 761, a highly purified extract of *G biloba*, prevents CVD.³⁻⁵ We reported previously that *G biloba* had no effect on the primary outcome, incidence of dementia, and Alzheimer disease.²

G biloba has been widely used in Europe for the treatment of PVD. Randomized clinical trials have suggested that *G biloba* is associated with increasing walking distance before

the development of symptoms of lower extremity pain, that is, intermittent claudication.⁶

The physiological effects of *G biloba* on the cardiovascular system are uncertain. Several studies have suggested antioxidant and free-radical scavenger effects. There is also suggestion of inhibition of platelet aggregation. There have been reports of association *G biloba* with bleeding, which has been attributed to antiplatelet aggregation effects. It was also suggested that *G biloba* improved blood flow by increased release of nitric oxide and the inhibition of nitric oxide degradation in the endothelium.⁷⁻¹⁰

Flavonoids are a component of *G biloba*. There is considerable interest in the potential antioxidant, anti-inflammatory, vasodilation, and platelet inhibition activity by various flavonoids. Several but not necessarily all large longitudinal studies have suggested some benefit of overall consumption of flavonoids on the risk of coronary heart disease (CHD).¹¹⁻¹⁸

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WHAT IS KNOWN

- *Ginkgo biloba* is a flavonoid that has previously been shown to improve walking in patients with peripheral vascular disease.

WHAT THE STUDY ADDS

- In a secondary end point analysis of *G biloba* in the Ginkgo Evaluation of Memory Study, *G biloba* did not reduce incidence or mortality from coronary heart disease or stroke.
- There were fewer peripheral vascular disease events in participants taking *G biloba* (n=12, 8%) than placebo (n=23, 1.5%) ($P=0.04$).
- *G biloba* may reduce risk of peripheral vascular disease, especially among high-risk individuals with low ankle-brachial index.
- This positive effect on peripheral vascular disease is consistent with previous studies and requires further evaluation in larger trials before implementation in clinical practice.

Methods

A detailed description of the study methods and recruitment has been published.¹ The study was conducted under an investigational new drug application with the Food and Drug Administration under the auspices of the National Center of Complementary and Alternative Medicine (NCCAM). The study was built on the infrastructure of the Cardiovascular Health Study (CHS) clinical study at the University of Pittsburgh, University of California Davis, Johns Hopkins University, and Wake Forest University.¹⁹ A Clinical Coordinating Center located at the Wake Forest University was charged with the oversight of clinical operations. The Cognitive Diagnostic Center was located at the University of Pittsburgh. The Data Coordinating Center was at the University of Washington in Seattle and the Laboratory Center at the University of Vermont.

The secondary end points were defined at the beginning of the trial and the analysis planned before the availability of the results of the trial (ie, prespecified).

Recruitment and Eligibility

Participants were recruited both from the CHS and volunteers in the communities. Recruitment was done in 3 phases; cognitive and medical or other exclusions were identified at each phase. The Telephone Interview for Cognitive Status was used to screen potential participants before inviting them into the clinic for further screening.^{1,2} During the initial screening visit, participants completed several cognitive screening tests and additional neuropsychological testing, phlebotomy, and functional assessment. Eligibility for the trial included no current dementia, willingness to participate for 5 years in the trial, age at least 75 years, English speaking, identification of a person to serve as a proxy, and normal levels of specific blood tests (Table 1). Participants with neurological or neurodegenerative diseases were excluded from the study. Anyone receiving cognitive enhancers or other treatment of Alzheimer disease were excluded, as were individuals taking high doses of vitamin E or taking over-the-counter *G biloba*. Subjects taking anticoagulants were excluded. Eligible participants were invited back for a baseline visit for further eligibility review and random assignment.¹

The baseline examination included a physical examination and a neurological examination, ECG, and ankle-brachial index (ABI) measurement. Individuals with prior CVD were allowed into the study. However, individuals having prevalent CHF with disability were excluded. Persons found to have abnormal levels of thyroid-

stimulating hormones, serum B₁₂, hematocrit, white blood cell count, or platelets at the screening visit were also excluded.¹

Randomization

Enrolled participants were randomly assigned to 120 mg *G biloba* as EGb 761 or placebo to be taken twice per day. Randomization was done separately for each clinic site.^{1,2} Assignment to *G biloba* or placebo was determined by permuted block design by site to ensure that allocation between treatment groups was well balanced. Participants assigned to active treatment and placebo were kept in their randomly assigned group regardless of their drug compliance, in accordance with an intention-to-treat analysis. All clinic center personnel and participants were blinded to treatment assignment for the duration of the study. Semiannual visits included pulse, blood pressure, current medications, interval medical history and adverse events, functional assessment, drug adherence, and cognitive evaluations.²

Ascertainment of CHD Events

At each 6-month visit and interim 3-month drug adherence monitoring phone call, subjects or their proxies were asked to report serious adverse events in compliance with Food and Drug Administration regulations. All subjects provided authorization to release medical records. All serious adverse events reported as overnight hospitalizations or deaths were investigated through the collection of medical records and reviewed by a blinded field center physician investigator. Records used for review included hospital face sheets with *International Classification of Diseases* (ICD), Ninth Revision, diagnostic codes, discharge summaries, history and physical examinations, and other documents, depending on the diagnosis. Noncertified death certificates with cause of death were obtained for fatal events.

Identification and classification of vascular outcomes were based on methods from the CHS.²⁰ Each field center abstracted the ICD codes for diagnoses from the hospitalization face sheet, and codes were searched to flag any possible vascular outcomes. Local physicians were also required to determine whether the hospitalization was due to a cardiovascular or cerebrovascular cause or if the serious adverse event resulted in death. Case records with vascular ICD codes or marked by the local physician as being in any of the vascular disease categories were forwarded to the University of Pittsburgh for abstraction and adjudication. In addition to the face sheet, discharge summary, and history and physical examination, review of coronary events included cardiac consults and diagnostic laboratory tests and procedures. Cerebrovascular event reviews also included neurological consults. Vascular outcomes were defined as MI, angina pectoris, CHF, CVA/stroke, TIA, PVD, and coronary revascularization. Cases from all 4 clinical centers were classified by 2 reviewers of the University of Pittsburgh blinded to treatment assignment. All deaths were classified by underlying cause of death using death certificates and, if applicable, hospital records and autopsy reports. The classification included atherosclerotic CHD (subclassified as definite fatal MI, definite fatal CHD, or possible fatal CHD), cerebrovascular disease (including stroke/CVA or late effect of stroke), atherosclerotic cardiovascular disease noncoronary (including ruptured aortic aneurysm), other cardiovascular disease not CHD or CVA (including valvular heart disease and pulmonary embolism), and all other causes. Morbid CVD events were classified as definite, probable, or not present.

Drug Treatment

Participants were randomly assigned to twice-daily doses of either 120 mg *G biloba* extract or an identically appearing placebo. *G biloba* EGb 761 was supplied for the study by the Schwabe Pharmaceuticals (Karlsruhe, Germany).^{1,2} A 120-mg dose in pill form containing 28.8 mg of *G biloba* flavone glycosides and 7.2 mg of terpene lactones was prepared for use in this study. These values were confirmed by an independent laboratory for each batch of product used in the GEMS.²

Table 1. Demographic and Risk Factors at Randomization: *G biloba* Versus Placebo Versus CHS, Baseline Age 75 to 84 Years

| | <i>G biloba</i> | | Placebo | | Total | | CHS, Ages 75–84 y (n=1765) |
|---------------------------------------|-----------------|------|---------|------|--------------|------|-------------------------------|
| | n | % | n | % | n | % | |
| Age, y | | | | | | | |
| <80 | 1027 | 66.5 | 1004 | 65.9 | 2031 | 66.2 | |
| 80–84 | 418 | 27.1 | 430 | 28.2 | 848 | 27.6 | |
| ≥85 | 100 | 6.5 | 90 | 5.9 | 190 | 6.2 | |
| White | 1482 | 95.9 | 1448 | 95.0 | 2930 | 95.4 | 84.2 |
| Male | 843 | 54.6 | 808 | 53.0 | 1651 | 53.7 | 44.4 |
| Education | | | | | | | |
| High school or less | 570 | 36.9 | 534 | 35.0 | 1104 | 35.9 | 58.5 |
| Some college | 381 | 24.7 | 395 | 25.9 | 776 | 25.2 | 8.5 |
| College graduate | 251 | 16.3 | 229 | 15.0 | 480 | 15.6 | 32.9 |
| Postgraduate | 343 | 22.2 | 366 | 24.0 | 709 | 23.1 | 32.9 |
| Self-reported history | | | | | | | |
| Heart attack | 148 | 9.6 | 162 | 10.0 | 300 | 9.8 | 12.1 |
| Angina | 157 | 10.2 | 147 | 9.7 | 304 | 10.0 | 20.7 |
| Stroke | 43 | 2.8 | 45 | 3.0 | 88 | 2.9 | 5.7 |
| Heart failure | 28 | 1.8 | 33 | 2.2 | 61 | 2.0 | 6.7 |
| Hypertension | 833 | 53.9 | 832 | 54.6 | 1665 | 54.4 | 48.8 |
| Diabetes | 139 | 9.1 | 138 | 9.1 | 277 | 9.1 | 12.1 |
| Smoking history | | | | | | | |
| Never | 602 | 39.2 | 622 | 41.3 | 1224 | 39.9 | 53.2 |
| Former | 846 | 55.1 | 805 | 53.4 | 1651 | 53.8 | 39.6 |
| Current | 71 | 4.6 | 65 | 4.3 | 136 | 4.3 | 7.1 |
| Systolic blood pressure | 132.6 | 18.1 | 133.2 | 18.4 | 132.9 (18.3) | | 141 (23) |
| Diastolic blood pressure | 68.8 | 9.9 | 68.9 | 9.9 | 68.9 (9.9) | | 70 (12) |
| Body mass index | | | | | | | |
| Underweight (<20 kg/m ²) | 33 | 2.1 | 46 | 3.0 | 79 | 2.6 | 5.4 |
| Normal (20–25 kg/m ²) | 463 | 30.1 | 447 | 29.4 | 910 | 29.7 | 39.3 |
| Overweight (25–30 kg/m ²) | 722 | 47.0 | 688 | 45.2 | 1410 | 45.9 | 39.9 |
| Obese (≥30 kg/m ²) | 319 | 20.8 | 340 | 22.4 | 659 | 21.5 | 15.0 |

All differences between GEMS and CHS are statistically significant ($P<0.05$), except for diastolic blood pressure.

Statistical Methods

Descriptives of demographic characteristics within each treatment group were calculated as count and percent for discrete variables and mean with standard deviations for continuous variables. The following end points were combined for additional analysis: MI and angina pectoris for CHD; stroke and TIA for CVA; and the combination of CHD and CVA. Time-to-event analyses comparing *G biloba* with placebo were completed on (a) total and CVD deaths, (b) incident CVD events (time to first event) for persons reported to be free of the specific outcome at baseline, and (c) total CVD events (time to first event), allowing both incident and recurrent outcomes to be included. Calculation of rates for incident cardiovascular events excluded those participants who reported the specific condition at baseline. For the combination of incident and prevalent events, all participants were included in the analysis. Person-time in years was calculated as days between date of the baseline clinic visit to the day of the first occurrence of either the cardiovascular event of interest, death, dementia, or last follow-up visit.²

Differences in time to events between *G biloba* and placebo were evaluated using Cox proportional hazards regression adjusted for sex

and age, using a categorical variable for adjustment in the models (<80 years, 80 to 84 years, and ≥85 years). Differences in incidence rates of MI and stroke were also calculated and presented per year in the study using the binomial exact test. All analysis was performed using Stata version 10 (StataCorp, College Station, Tex).

Power estimates were originally based on rates from the CHS, age ≥75, stroke 2%, CHD end point 5%. Based on those estimates, we had 89% power for a 35% reduction for stroke, 75% power for a 30% decrease, and for CHD 99% power for a 35% reduction and 92% power for a 25% reduction.¹ The overall incidence of composite CVD events in the GEMS was approximately 4% per year and for stroke and TIA ≈1.5% per year.

Results

There were 3069 community volunteers age ≥75 (mean age, 79 years) randomly assigned to placebo (n=1524) or *G biloba* (n=1545) 120 mg twice daily (Table 1). Approximately 95% of the participants were white; 23% had some postgraduate education. One quarter of the participants had a

Table 2. Total and Cardiovascular Deaths: *G biloba* Versus Placebo

| | <i>G biloba</i> | | | | Placebo | | | | Total Rate per 1000 Person-Years | Age- and Sex-Adjusted HR (95% CI) | Statistically Different <i>P</i> Value* |
|---|-----------------|-------|-------|----------------------------|---------|-------|-------|----------------------------|----------------------------------|-----------------------------------|---|
| | Men | Women | Total | Rate per 1000 Person-Years | Men | Women | Total | Rate per 1000 Person-Years | | | |
| 1. Atherosclerotic CHD | 24 | 21 | 45 | 5.3 | 24 | 18 | 42 | 5.0 | 5.1 | 1.06 (0.70 to 1.62) | 0.78 |
| 2. CVD | 4 | 8 | 12 | 1.4 | 12 | 8 | 20 | 2.4 | 1.9 | 0.59 (0.29 to 1.21) | 0.15 |
| 3. Other atherosclerotic, not coronary or cerebrovascular | 3 | 2 | 5 | 0.6 | 3 | 3 | 6 | 0.7 | 0.7 | 0.83 (0.25 to 2.72) | 0.76 |
| 4. Other cardiovascular disease, not atherosclerotic | 5 | 6 | 11 | 1.3 | 5 | 4 | 9 | 1.1 | 1.2 | 1.23 (0.351 to 2.97) | 0.65 |
| 5. All CHD and CVD combined (1 through 4) | 36 | 37 | 73 | 8.5 | 44 | 33 | 77 | 9.1 | 8.8 | 0.94 (0.68 to 1.30) | 0.71 |
| 6. Noncardiovascular | 68 | 56 | 124 | 14.5 | 62 | 49 | 111 | 13.1 | 13.8 | 1.11 (0.86 to 1.43) | 0.44 |
| 7. Total deaths | 104 | 93 | 197 | 23.0 | 106 | 82 | 188 | 22.2 | 22.6 | 1.04 (0.85 to 1.27) | 0.70 |

HR indicates hazard ratio, calculated by Cox proportional hazard model.

**P* value calculated by Cox proportional hazard model adjusted for age and sex.

history of CVD, approximately 55% reported history of hypertension, and 9% had diabetes. Only 4.5% currently smoked cigarettes.

Recruitment began in September 2000 to June 2002. Participant close-out began in October 2007 and was completed in April 2008. Median follow-up was 6.1 years, with a maximum of 7.3 years. Adherence varied from 90% at 6 months, 79% at 2 years, 73% at 4 years, and at the end of the trial, 60.3% of those receiving active therapy were taking their assigned study medication. Adherence did not differ between those taking *G biloba* and those taking placebo.²

Deaths

There were 385 deaths during the trial: 188 (22.2/1000 person-years) in the placebo group and 197 (23.0/1000 person-years) in the *G biloba* active arm (Table 2). Eighty-seven of the deaths were due to CHD: 42 in the placebo group and 45 in *G biloba* arm. There were no differences in the distribution of other CV or non-CV deaths by treatment arm. There were also no differences in distribution of deaths by *G biloba* versus placebo for men (210, 12.8%) or women (175, 12.3%).

Hospitalized CV Events

There were 164 hospitalized clinical MIs, 207 cases of reported angina pectoris, 151 strokes, 73 TIAs, and 35 PVD events. The measurement of incident CVD was limited, as noted, to those individuals who had no self-reported baseline history of CVD and had their first event during the trial. There were no significant differences in incidence of any of the CV outcomes by *G biloba* versus placebo arm (Table 3). Event rates were slightly higher in men than in women, except for stroke. There was, however, no difference in event rates by sex by arm in the trial.

There was no evidence of any reduction in risk of total CVD or CHD events, including recurrent events, for *G biloba* versus placebo for men or women. No differences were found between the *G biloba* and placebo arms of the study for incident plus recurrent CV events (Table 4).

Stroke

Incidence of stroke was slightly higher in the *G biloba* than in the placebo arm of the trial, but the difference was not statistically significant (Table 3). Mortality rate for stroke

Table 3. Hospitalizations for Incident Cardiovascular Events Based on No Self-Reported Baseline History, Fatal and Nonfatal by Subject, *G biloba* Versus Placebo by Sex

| | <i>G biloba</i> | | | | Placebo | | | | Total Rate per 1000 Person-Years | Age- and Sex-Adjusted HR (95% CI) | Statistically Different <i>P</i> Value* |
|---|-----------------|-------|-------|----------------------------|---------|-------|-------|----------------------------|----------------------------------|-----------------------------------|---|
| | Men | Women | Total | Rate per 1000 Person-Years | Men | Women | Total | Rate per 1000 Person-Years | | | |
| 1. MI | 41 | 27 | 68 | 9.0 | 25 | 35 | 60 | 8.1 | 8.5 | 1.12 (0.79 to 1.58) | 0.54 |
| 2. Angina | 43 | 23 | 66 | 8.9 | 53 | 23 | 76 | 10.4 | 9.6 | 0.84 (0.61 to 1.18) | 0.32 |
| 3. CHD (MI and/or angina) | 66 | 41 | 107 | 15.5 | 60 | 50 | 110 | 16.3 | 15.9 | 0.94 (0.72 to 1.23) | 0.66 |
| 4. CHF | 65 | 47 | 112 | 13.9 | 58 | 64 | 122 | 15.4 | 14.6 | 0.91 (0.71 to 1.18) | 0.48 |
| 5. Stroke | 39 | 34 | 73 | 9.0 | 22 | 37 | 59 | 7.4 | 8.2 | 1.22 (0.87 to 1.72) | 0.25 |
| 6. TIA | 17 | 10 | 27 | 3.5 | 16 | 15 | 31 | 4.1 | 3.8 | 0.87 (0.52 to 1.45) | 0.59 |
| 7. CVD (stroke and/or TIA) | 57 | 42 | 99 | 13.0 | 38 | 50 | 88 | 11.5 | 12.2 | 1.12 (0.84 to 1.50) | 0.42 |
| 8. Total CHD and CVD combined (3 and 8) | 93 | 64 | 157 | 24.9 | 75 | 79 | 154 | 24.78 | 24.8 | 1.00 (0.80 to 1.25) | 0.98 |

HR indicates hazard ratio, calculated by Cox proportional hazard model.

**P* value calculated by Cox proportional hazard model adjusted for age and sex.

Table 4. Incident and Recurrent Cardiovascular Hospitalized Events in GEMS: Fatal and Nonfatal, *G biloba* Versus Placebo, by Sex With and Without History of CVD at Baseline

| | <i>G biloba</i> | | | | Placebo | | | | Total Rate per 1000 Person-Years | Age- and Sex-Adjusted HR (95% CI) | Statistically Different <i>P</i> Value* |
|---|-----------------|-------|-------|----------------------------|---------|-------|-------|----------------------------|----------------------------------|-----------------------------------|---|
| | Men | Women | Total | Rate per 1000 Person-Years | Men | Women | Total | Rate per 1000 Person-Years | | | |
| 1. MI | 68 | 35 | 103 | 12.1 | 40 | 49 | 89 | 10.5 | 11.3 | 1.16 (0.82 to 1.64) | 0.30 |
| 2. Angina | 88 | 56 | 144 | 16.9 | 83 | 42 | 125 | 14.8 | 15.8 | 1.16 (0.85 to 1.57) | 0.74 |
| 3. CHD (MI and/or Angina) | 148 | 88 | 236 | 37.6 | 121 | 88 | 209 | 24.7 | 26.2 | 1.13 (0.89 to 1.44) | 0.75 |
| 4. CHF | 107 | 94 | 201 | 23.5 | 108 | 112 | 220 | 26.0 | 24.8 | 0.92 (0.67 to 1.25) | 0.51 |
| 5. Stroke | 45 | 43 | 88 | 10.3 | 34 | 48 | 82 | 9.7 | 10.0 | 1.08 (0.77 to 1.51) | 0.48 |
| 6. TIA | 22 | 14 | 36 | 4.2 | 23 | 21 | 44 | 5.2 | 4.7 | 0.82 (0.51 to 1.32) | 0.38 |
| 7. CVD (stroke and/or TIA) | 67 | 57 | 124 | 14.5 | 57 | 69 | 126 | 14.9 | 14.7 | 0.99 (0.75 to 1.30) | 0.77 |
| 8. Total CHD and CVD combined (3 and 8) | 215 | 145 | 360 | 42.1 | 178 | 157 | 335 | 39.6 | 40.9 | 1.08 (0.89 to 1.31) | 0.56 |

HR indicates hazard ratio, calculated by Cox proportional hazard model.

**P* value calculated by Cox proportional hazard model adjusted for age and sex.

was higher in the placebo arm, although this difference was not statistically significant (Table 2). The incidence of pure vascular dementia was previously reported to be higher in the placebo arm. We also previously reported that there were 24 hemorrhagic stroke cases (16 on *G biloba* and 8 on placebo; hazard ratio, 1.97 [0.84 to 4.16]; *P*=0.12).² Of the 24 hemorrhagic strokes, 2 were subarachnoid hemorrhage and 22 were intracranial hemorrhage. Five of 16 participants in the *G biloba* arm and 2 of 8 in the placebo arm were off therapy at the time of the intracranial hemorrhage. Only 2 participants were taking anticoagulants at the visit before hemorrhagic stroke (medical need required cessation of drug, although subjects were still followed). Thus, 11 hemorrhagic strokes occurred on treatment with *G biloba*, and 6 such strokes occurred in the placebo arm (not statistically significant).

Rates of major bleeding did not differ between treatment groups (hazard ratio, 0.97 [0.77 to 1.23]; *P*=0.81). The incidence of bleeding did not differ by use of aspirin therapy assigned to either *G biloba* or placebo (1.98 versus 1.76/100 person-years, *P*=0.44).¹

Peripheral Vascular Disease

There were only 35 PVD events in the trial: 12 (0.8%) in *G biloba* arm and 23 (1.5%) on placebo (*P*=0.04 exact test). Most (27 of 35 [77%]) PVD cases had a surgical, revascularization, or amputation procedure for symptomatic PVD: 18 of 23 (78.3%) on placebo and 9 of 12 (75.0%) on *G biloba*. There was 1 case of popliteal aneurysm secondary to a diagnostic procedure in the placebo arm. The risk of PVD, incident CHD, or total mortality was related directly to ABI at baseline, with most cases occurring in participants with ABI \leq 1.1 (Table 5). The incidence of PVD was 10.2/1000 person-years for ABI <0.9 in the *G biloba* arm (n=7) versus 17.5/1000 person-years for placebo (n=12) (*P*=0.26). For participants who entered with ABI in the 3rd or 4th quartile \geq 1.1, there were only 2 events in the *G biloba* arm and 4 in the placebo group. Two participants did not have measurement of ABI at baseline. We further reviewed records that had some PVD codes on hospital discharge records but did not reach criteria for clinical PVD in the study. There were

54 records; 16 had a history of lower extremity PVD in the hospital record, usually a history of claudication but no concurrent therapy (7 in the *G biloba* arm and 9 in the placebo arm).

Age Effects

We further evaluated the incidence of CV events by age at entry to the trial, <80 years, 80 to 84 years, and \geq 85 years (not shown). There were no differences in the incidence of any of the CV outcomes in any age group as defined by age at entry to the trial. The incidence of CHD, MI, and angina pectoris increased little by age (from 14.3/1000 person-years for age <80 years to 16.3/1000 person-years for age \geq 85 years). The incidence of CHF, however, increased dramatically from 14.35 in those <80 years to 30.1/1000 person-years in those age \geq 85 years. There was also no difference in the incidence of MI or stroke by time in the trial for *G biloba* versus placebo (not shown).

Discussion

GEMS did not demonstrate that *G biloba* 120 mg twice daily in older individuals age \geq 75 years reduced the risk of either CHD or CVD mortality, total hospitalizations, or incident CVD/CHD events. *G biloba* 120 mg twice daily cannot be recommended for prevention of CV mortality or incident or recurrent CVD/CHD events in this age group. Results were similar for men or women or by age groups for incidence or mortality by *G biloba* versus placebo. There is no evidence of any benefit by longer duration in the trial. It remains possible, however, that the benefits of *G biloba*, should there be any, require many years of therapy, perhaps beginning at an earlier age. GEMS participants probably had extensive atherosclerotic disease even without a history of clinical disease. The potential physiological effects of *G biloba* on thrombosis, for example, platelet function and endothelial function,^{1,2,4} would have been expected to decrease the incidence of CVD/CHD if there was a true benefit. It is also possible that *G biloba* reduces the risk of CHD if taken at younger ages.

There were only 35 peripheral vascular events in the trial. The difference between *G biloba*¹² and placebo²² was significant but based on very small numbers. These results are

Table 5. Baseline ABI Quartiles in Treatment Groups for Incident CHD, PVD, and All-Cause Mortality

| | <i>G biloba</i> | | Rate per 1000 | Placebo | | Rate per 1000 | Total | Statistically Different P Value† | Statistically Different P Value* |
|---------------------|-----------------|----|---------------|---------|----|---------------|-------|----------------------------------|----------------------------------|
| | n | % | | n | % | | | | |
| Incident PVD | | | | | | | | | |
| ≤0.9 | 7 | 64 | 10.24 | 12 | 55 | 17.54 | 19 | 0.255 | |
| 1st quartile | 7 | 64 | 3.44 | 15 | 68 | 7.62 | 22 | 0.082 | 0.051 |
| 2nd quartile | 2 | 18 | 1.18 | 3 | 14 | 1.69 | 5 | 0.679 | |
| 3rd quartile | 0 | 0 | 0 | 1 | 4 | 0.41 | 1 | 1.000 | |
| 4th quartile | 2 | 18 | 0.90 | 3 | 14 | 1.46 | 5 | 0.634 | |
| Incident CHD | | | | | | | | | |
| ≤0.9 | 34 | 20 | 53.24 | 25 | 16 | 37.10 | 59 | 0.151 | |
| 1st quartile | 63 | 37 | 32.89 | 51 | 32 | 26.79 | 114 | 0.230 | 0.516 |
| 2nd quartile | 35 | 20 | 21.55 | 36 | 23 | 21.37 | 71 | 0.989 | |
| 3rd quartile | 42 | 24 | 18.78 | 34 | 21 | 14.58 | 76 | 0.296 | |
| 4th quartile | 32 | 19 | 14.88 | 38 | 24 | 19.50 | 70 | 0.237 | |
| All-cause mortality | | | | | | | | | |
| ≤0.9 | 28 | 15 | 39.92 | 33 | 18 | 46.14 | 61 | 0.558 | |
| 1st quartile | 59 | 31 | 28.77 | 64 | 35 | 31.85 | 123 | 0.645 | 0.663 |
| 2nd quartile | 48 | 25 | 28.28 | 42 | 23 | 23.54 | 90 | 0.385 | |
| 3rd quartile | 50 | 27 | 21.26 | 37 | 21 | 15.31 | 87 | 0.140 | |
| 4th quartile | 32 | 17 | 14.37 | 38 | 21 | 18.53 | 70 | 0.298 | |

First quartile, <1.02; 2nd quartile, 1.02 to 1.1; 3rd quartile, 1.1 to 1.185; 4th quartile, >1.185.

*P value calculated by Cox proportional hazard model adjusted for age and sex.

†P value calculated by Cox proportional hazard model adjusted for age and sex in each ABI.

consistent with studies in Europe that reported increased walking time or distance without pain in trials of *G biloba* versus placebo among clinical PVD patients.^{6,21} A recent report from the Stanford Prevention Research Center evaluated pain-free walking distance among 62 adults with claudication symptoms. Maximal treadmill walking time increased 20±80 seconds (10%) in the placebo group and 91±242 seconds (40%) in the participants given 300 mg of EGb 761 *G biloba* over a 4-month period ($P=0.12$). Lack of statistical significance may have been due to the small sample size. There was also substantial heterogeneity of the results.²² A randomized trial from Australia, using 22 subjects, noted that exercise but not *G biloba* improved walking times in patients with PVD.²³ The PVD cases in GEMS had severe PVD, usually requiring surgery or amputation. We do not have data on symptomatic PVD that did not require hospitalization or surgical procedure, such as outpatient diagnoses. The number of events is too small to determine definitively whether *G biloba* might have a unique effect on PVD.⁴ We measured ankle-brachial blood pressure at entry to the trial but did not have repeat measures of ankle-brachial blood pressure or other measures of PVD during the trial. We also did not measure out-of-hospital PVD diagnoses or hospitalizations that included PVD but in which there was not a specific diagnostic or surgical procedure for PVD. It is possible that *G biloba* has a unique effect on PVD by increasing blood flow secondary to effects on endothelial function, for example, nitric oxide.^{4,6} A larger study would be needed to evaluate the PVD end point.

The higher number of cerebral hemorrhages (16 in *G biloba* arm versus 8 in placebo and 11 versus 6 in the groups

on treatment) would also be consistent with the reported increased risk of bleeding among patients taking *G biloba*.²¹

A limitation of this trial is the absence of measures of blood levels or urinary excretion of the flavonoids or terpenoids in participants on EGb 761 *G biloba*. We were limited to data on drug adherence in 2 arms and analysis of the chemical composition of the pills.¹ It is very difficult to measure the amount of *G biloba* that was absorbed and their metabolic products.²⁴ One study has successfully reported isolation of both quercetin and kaempferol in blood. One small sample of older individuals reported similar absorption in elderly versus younger individuals.²⁵ The other major limitation of the study is the absence of measures of PVD at the end of the trial. There is no evidence at the present time from clinical trials that *G biloba* reduces the risk of CVD, either primary or secondary prevention.

An important issue is whether the reduced risk of clinical PVD is strong enough for either a new larger trial of *G biloba* or for clinical use for older individuals with low ABI. A new clinical trial probably would have to be restricted to individuals with low ABI, that is, first quartile, <1. The trial would be limited by high risk of CHD, stroke, and other medication use, especially statins, aspirin, antihypertensive therapy, and diabetes mellitus. A large sample size and need for careful measurement of PVD outcomes would be required.

We do not believe that the results of the GEMS trial are a definitive indication for use of *G biloba* for individuals with low ABI but do add to the data on potential benefit of *G biloba* in PVD.

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Disclosures

None.

References

- DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, Burke G, Fried L, Kuller LH, Robbins J, Tracy R, Wollard N, Dunn L, Kronmal R, Nahin R, Furberg C, for the GEMS Investigators. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of *Ginkgo biloba* extract in prevention of dementia. *Contemp Clin Trials*. 2006;27:238–253.
- DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, Lopez OL, Burke G, Carlson MC, Fried LP, Kuller LH, Robbins JA, Tracy RP, Wollard NF, Dunn L, Snitz BE, Nahin RL, Furberg CD, for the Ginkgo Evaluation of Memory Study Investigators. *Ginkgo biloba* for prevention of dementia: a randomized controlled trial. *JAMA*. 2008;300:2253–2262.
- Gardner CD, Messina M, Lawson LD, Farquhar JW. Soy, garlic, and ginkgo biloba: their potential role in cardiovascular disease prevention and treatment. *Curr Atheroscler Rep*. 2003;5:468–475.
- Mahady GB. Ginkgo biloba for the prevention and treatment of cardiovascular disease: a review of the literature. *J Cardiovasc Nurs*. 2002;16:21–32.
- Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Clinical use and molecular mechanisms of action of extract of *Ginkgo biloba* leaves in cardiovascular disease. *Cardiovasc Drug Rev*. 2004;22:309–319.
- Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med*. 2000;108:276–281.
- Kudolo GB, Dorsey S, Blodgett J. Effect of the ingestion of *Ginkgo biloba* extract on platelet aggregation and urinary prostanoid excretion in healthy and type 2 diabetic subjects. *Thromb Res*. 2003;108:151–160.
- Gardner CD, Zehnder JL, Rigby AJ, Nicholus JR, Farquhar JW. Effect of Ginkgo biloba (EGb 761) and aspirin on platelet aggregation and platelet function analysis among older adults at risk of cardiovascular disease: a randomized clinical trial. *Blood Coagul Fibrinolysis*. 2007;18:787–793.
- Tribble DL. Antioxidants and atherosclerotic cardiovascular disease: unresolved issues. *Coron Artery Dis*. 2001;12:541–546.
- Mehlsen J, Rabaek H, Wiinberg N, Winther K. Effects of a Ginkgo biloba extract on forearm haemodynamics in healthy volunteers. *Clin Physiol Funct Imag*. 2003;22:375–378.
- Hamer M, Steptoe A. Influence of specific nutrients on progression of atherosclerosis, vascular function, haemostasis and inflammation in coronary heart disease patients: a systematic review. *Br J Nutr*. 2006;95:849–859.
- Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ*. 1996;312:478–481.
- Lagiou P, Samoli E, Lagiou A, Tzonou A, Kalandidi A, Peterson J, Dwyer J, Trichopoulos D. Intake of specific flavonoid classes and coronary heart disease: a case-control study in Greece. *J Clin Nutr*. 2004;58:1643–1648.
- Mink PJ, Scrafford CG, Barraj LM, Harnack L, Hong C-P, Nettleton JA, Jacobs DR Jr. Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. *Am J Clin Nutr*. 2007;85:895–909.
- Lin J, Rexrode KM, Hu F, Albert CM, Chae CU, Rimm EB, Stampfer MJ, Manson JE. Dietary intakes of flavonols and flavones and coronary heart disease in US women. *Am J Epidemiol*. 2007;165:1305–1313.
- Selmi C, Mao TK, Keen CL, Schmitz HH, Gershwin ME. The anti-inflammatory properties of cocoa flavonols. *J Cardiovasc Pharmacol*. 2006;47:S163–S171.
- Keen CL, Holt RR, Oteiza PI, Fraga CG, Schmitz HH. Cocoa antioxidants and cardiovascular health. *Am J Clin Nutr*. 2008;81:298S–303S.
- Hirvonen T, Tornwall ME, Pietinen P, Korhonen P, Albanes D, Virtamo J. Flavonol and flavone intake and the risk of intermittent claudication in male smokers. *Eur J Epidemiol*. 2004;19:305–311.
- Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, O'Leary DH, Psaty B, Rautaharju P, Tracy RP, Weiler PG, for the Cardiovascular Health Study Research Group (CHS). The Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991;1:263–276.
- Ives DG, Fitzpatrick AL, Bild DE, Psaty BM, Kuller LH, Crowley PM, Cruise RG, Theroux S. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol*. 1995;5:278–285.
- Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. *Am J Cardiol*. 2006;98:673–680.
- Peters H, Kieser M, Holscher U. Demonstration of the efficacy of ginkgo biloba special extract EGb 761 on intermittent claudication—a placebo-controlled, double-blind multicenter trial. *Vasa*. 1998;27:106–110.
- Gardner CD, Taylor-Piliae RE, Kiazand A, Nicholus J, Rigby AJ, Farquhar JW. Effect of *Ginkgo biloba* (EGb 761) on treadmill walking time among adults with peripheral artery disease: a randomized controlled clinical trial. *J Cardiopulm Rehabil Prev*. 2008;28:258–265.
- Pietta PG, Mauri PL. Identification of *Ginkgo biloba* flavonol metabolites after oral administration to humans. *J Chromatogr B*. 1997;693:249–255.
- Wojcicki J, Gawronska-Szklarz B, Bieganski W, Patalan M, Smulski H, Samochowicz L, Zakrzewski J. Comparative pharmacokinetics and bioavailability of flavonoid glycosides of Ginkgo biloba after a single oral administration of three formulations to healthy volunteers. *Mater Med Pol*. 1995;27:141–146.

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