The Efficacy of Ginkgo for Elderly People with Dementia and Age-Associated Memory Impairment: New Results of a Randomized Clinical Trial

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OBJECTIVES: To evaluate the efficacy, the dose-dependence, and the durability of the effect of the ginkgo biloba special extract EGb 761 (ginkgo) in older people with dementia or age-associated memory impairment.

DESIGN: A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial.

SETTING: Homes for the elderly in the southern part of the Netherlands.

PARTICIPANTS: Older persons with dementia (either Alzheimer's dementia or vascular dementia; mild to moderate degree) or age-associated memory impairment (AAMI). 214 Participants were recruited from 39 homes for the elderly.

INTERVENTION: The participants were allocated randomly to treatment with EGb 761 (2 tablets per day, total dosage either 240 (high dose) or 160 (usual dose) mg/day) or placebo (0 mg/d). The total intervention period was 24 weeks. After 12 weeks of treatment, the initial ginkgo users were randomized once again to either continued ginkgo treatment or placebo treatment. Initial placebo use was prolonged after 12 weeks.

MEASUREMENTS: Outcomes were assessed after 12 and 24 weeks of intervention. Outcome measures included neuropsychological testing (trail-making speed (NAI-ZVT-G), digit memory span (NAI-ZN-G), and verbal learning (NAI-WL)), clinical assessment (presence and severity of geriatric symptoms (SCAG), depressive mood (GDS), self-perceived health and memory status (report marks)), and behavioral assessment (self-reported level of instrumental daily life activities).

RESULTS: An intention-to-treat analysis showed no effect on each of the outcome measures for participants who were assigned to ginkgo (n = 79) compared with placebo (n = 44) for the entire 24-week period. After 12 weeks of treatment, the combined high dose and usual dose ginkgo groups (n = 166) performed slightly better with regard to self-reported activities of daily life but slightly worse with regard to self-perceived health status compared with the placebo group (n = 48). No beneficial effects of a higher dose or a prolonged duration of ginkgo treatment were found. We could not detect any subgroup that benefited from ginkgo. Ginkgo use was also not associated with the occurrence of (serious) adverse events.

CONCLUSIONS: The results of our trial suggest that ginkgo is not effective as a treatment for older people with mild to moderate dementia or age-associated memory impairment. Our results contrast sharply with those of previous ginkgo trials. J Am Geriatr Soc 48:1183–1194, 2000.

Key words: ginkgo biloba; dementia; memory impairment; cognitive decline; randomized clinical trial

Ginkgo biloba special extracts, such as EGb 761 and LI 1370, are obtained through a standardized process of enrichment and purification of the original, full extract from dried leaves of the ginkgo biloba tree. They contain fixed concentrations of two active substance classes: ginkgo flavonol glycosides (16–25%) and terpene trilactones (usually 6%). Preparations based on these special extracts have entered the European drug market since 1965. Today the use of ginkgo is widespread, both as an officially licensed drug that requires prescription by a physician, and as an over-the-counter medicine. Brand names such as Tebonin®, Kaveri®, rökan®, and Tanakan® have become commercial bestsellers in Germany and France. In recent years the use of ginkgo mono- and multipreparations seems to have expanded beyond its traditional boundaries, and ginkgo products seem to be on the verge of conquering new markets in North America.[1,2]

Ginkgo drugs are prescribed and consumed for various indications. A recent review of the available scientific information concerning the ginkgo biloba special extract EGb 761, which covers both the (bio)chemical and the clinical aspects, mentions four major types of action.[3] First, ginkgo is believed to exert a vasoregulatory action, which protects blood vessels and various tissues and might explain its use in managing cerebral insufficiency states, neurosensory disturbances, and peripheral occlusive arterial disease. Second, it is supposed to have a cognition-enhancing action, which relates

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to its use in treating Alzheimer's disease and various other dementias. Third, a stress-alleviating action is attributed to the use of ginkgo, which might explain its claimed anxiolytic and antidepressive effects. Finally, a gene-regulatory action is sometimes suggested, which might explain why most clinically beneficial effects of the extract seem to require repeated administration. A wealth of documented data from fundamental research seems to refer to plausible mechanisms that underlie the proposed clinical actions attributed to ginkgo constituents.[3]

Recent reviews of the clinical literature have suggested strongly a positive effect of ginkgo in patients with cerebral insufficiency, peripheral arterial occlusive disease, and several other disorders.[4–12] The claimed beneficial influence of ginkgo on cerebral insufficiency – including more focused conditions, such as Alzheimer's disease, vascular dementia, and cognitive impairment no dementia – especially seems to attract the attention of the medical world. This interest is fed, in part, by general endeavors to develop either pharmacological or nonpharmacological treatments for dementia that combine efficacy and safety but that have not yet been very successful. Probably the most talked-about study, especially in the United States, is the ginkgo trial that was published in 1997 by Le Bars et al. in *JAMA*. [13] Three hundred twenty-seven outpatients with mild to moderate dementia, either Alzheimer's disease (AD) or vascular dementia (VD), were included in this trial. Only 137 participants completed the 24-week intervention period. The authors reported less impairment for the ginkgo group compared with the placebo group on the ADAS-cog (−0.1 vs −1.5; $P = .04$), a small, beneficial effect on the Geriatric Evaluation by Relative's Rating Instrument (GERRI: +0.06 vs −0.08; $P = .004$), but no difference for the Clinical Global Impression of change (CGI: 4.2 vs 4.2).

In 1993 we initiated a trial to confirm the results of previous studies of ginkgo biloba in patients with cognitive decline. Moreover, our trial – the Maastricht Ginkgo Trial – aimed at investigating two additional research questions regarding dose-dependence and the persistence of the ginkgo effect. We designed the trial in agreement with the latest guidelines for the evaluation of antidementia drugs and cognition enhancers.[14,15] For a detailed description of the design, the conduct, and the results of the Maastricht Ginkgo Trial, we refer the reader to the final trial report and a thesis based on this trial.[16,17]

In our trial we used various outcome measures to assess the effect of ginkgo. Part of the results, viz. regarding SKT (Syndrom Kurz Test, a brief test battery of memory and attention), CGI-2 (Clinical Global Impression of change in cognitive functioning), and NAI-NAA (Nürnberger Alters Inventar Alltagsaktivitäten Skala, an activities of daily living scale, rated by senior caregivers), will be communicated through a separate publication. The current paper describes the results for three neuropsychological function tests, four measures of clinical assessment, and one measure at the behavioral level.

METHODS

Patient Selection

The target population encompassed subjects from two diagnostic categories: patients with dementia according to DSM-III-R[18] and ICD-10[19] criteria, and nondemented patients with age-associated memory impairment (AAMI).[20–22] Patients with AD, VD, or a mixed type of dementia were included in the dementia group.

The sources of recruitment were 39 old peoples' homes in the southern part of the Netherlands. The patient selection was based on a multistage screening procedure. For the differential diagnosis of dementia, we applied the SIDAM,[23,24] a Germany-based semistructured interview that includes the Mini-Mental State Examination (MMSE)[25] and the Hachinski Ischemic Score (HIS).[26] The SIDAM keeps close track of the DSM-III-R criteria for dementia. We admitted only subjects with a mild or moderate stage of dementia, as assessed by the results of the SIDAM interview and by a score between 8 and 23 on the Syndrom Kurz Test (SKT; Syndrome Short Test; full range: 0–27). The SKT is a brief psychometric test battery for the assessment of memory and attention.[27,28]

For the AAMI diagnosis subjects had to satisfy the following inclusion criteria: impaired cognitive functioning indicated by a score between 8 and 23 on the SKT; impaired cognitive functioning shown by the presence of self-reported memory complaints on a modified version of the Memory Assessment Clinics Questionnaire (MAC-Q), a brief, 5-item memory questionnaire referring to memory problems in daily life[29] (total score ≥ 12 (full range: 5–25)) assigned by either the study subject or the nursing staff; and absence of dementia (SIDAM).

In addition to these inclusion criteria, subjects of both subgroups had to meet the following enrollment criteria: age ≥ 50 years; written informed consent by patient and/or legal representative; absence of severe depression (Geriatric Depression Scale (GDS) 15-item version, total score <11 (full range: 0–15))[30,31]; presence of an adequate level of premorbid intelligence (IQ > 80, global assessment); sufficient compliance and absence of placebo-response during the 3-week run-in period; no expectation of premature withdrawal; absence of serious comorbidity, in particular pathological conditions considered either nontreatable underlying causes of dementia and cognitive disorders or sources of interference with the trial conduct (e.g., various neurological disorders, brain traumata, tumors, severe infectious diseases, absorption disorders); and absence of impermissible co-interventions, in particular drugs with a debilitating influence on psychical or cognitive functioning and drugs with a claimed nootropic action (e.g., antipsychotic drugs, antiparkinson medication, neuroleptics, cholinergic therapy, antidepressants, vasoactive drugs).

The trial protocol complied with the ethical rules for human experimentation as stated in the Declaration of Helsinki and was approved by the Maastricht Academic Hospital/Maastricht University Medical-Ethical Committee.

Intervention

The experimental intervention consisted of the daily intake of either 160 mg or 240 mg of a ginkgo biloba special extract. Two film-coated tablets were administered per day, each containing either 80 mg or 120 mg of ginkgo, (EGb 761, standardized on 24% ginkgo flavonol glycosides and 6% terpene trilactones (ginkgolides, bilobalid)). The placebo intervention consisted of two tablets per day that contained no ginkgo extract. Special efforts were made to improve the comparability of verum and placebo with respect to appearance, color, smell, taste, granularity, and solubility. In order

to mimic the typical taste of ginkgo extract, 2 mg of quinine hydrochloride was added to the placebo tablets. The study participants took their daily dose at fixed times (morning and evening, during meals). Most of them did this under direct supervision of a nursing staff member. The study medication was packaged and labeled in accordance with the requirements of the Dutch Act of Medicine Supply and the guidelines for Good Clinical Practice.

Random Allocation

The trial was designed as a randomized, placebo-controlled, double-blind trial. In order to be able to answer all three research questions — addressing the efficacy, the dose-effect relationship, and the persistence of any effect of ginkgo biloba treatment, respectively — we used a two-stage randomization strategy (see Figure 1: study design). After a 3-week run-in period on placebo, the eligible subjects were randomly allocated to one of three regimens: ginkgo 160 mg/day (usual dose), ginkgo 240 mg/day (high dose), or placebo. This tripartition aimed at the elucidation of the dose-dependence of any treatment effect. After having completed the first 12-week treatment period, subjects exposed to ginkgo initially were randomized once again to enter a second 12-week treatment period, either to continued ginkgo or to placebo therapy; placebo use during the first 12 weeks was sustained for another 12 weeks. The purpose of the second randomization procedure was to enable an analysis of the durability of any intervention effect after discontinuation of initial ginkgo therapy.

A computer-generated random sampling set was used for concealed random allocation of the study subjects. Random number assignment and labeling and distribution of the study medication were performed independently. Before randomization, we prestratified the eligible study subjects according to their diagnostic subcategory (dementia vs AAMI), and perceived change in memory complaints during the 6-month pretreatment phase (improvement or no change vs impairment). The first randomization step (Week 0) was conducted in blocks of five patients and according to a 2 : 2 : 1 allocation ratio (ginkgo 240 mg : ginkgo 160 mg : placebo). To enhance the power of the study, the original ratio was later changed to 1 : 1 : 1. The second randomization step (Week 12) involved blocks of two patients and a 1 : 1 (ginkgo : placebo) allocation ratio.

This two-phasic random allocation strategy eventually yielded an exposure contrast between five treatment groups of approximately equal size: (1) ginkgo 240 mg (24 weeks); (2) ginkgo 160 mg (24 weeks); (3) placebo (24 weeks); (4) ginkgo 240 mg (12 weeks) + placebo (12 weeks); (5) ginkgo 160 mg (12 weeks) + placebo (12 weeks).

Outcome Measures

The current guidelines for the evaluation of the efficacy of antidementia and cognition-enhancing drugs recommend measurement of outcomes at three different function levels: psychometric, psychopathological, and behavioral functioning.[32] As stated in the introduction, this article describes the results for three psychometric tests, four measures of clinical assessment, and one measure related to activities of daily living:

- The *Zahlennachsprechen Test G* (ZN-G; Digit Memory Span G). This test, an adapted version of the classic digit span test, is a short-term memory test aimed at the immediate reproduction of digit combinations of increasing length. The test entails two complementary formats, forward and backward reproduction. The total score (range: 0–17) is obtained by summation of the scaled scores for both formats.
- The *Wortliste* (WL; Word List). This is a verbal learning type of test, in which eight carefully selected words have to be recalled and recognized. The scores obtained for the free, immediate recall procedure and the delayed recognition procedure (after about 20 minutes, mixed up with 8 distracter items) are combined to give a total score ranging from 0 to 16.
- The *Zahlen-Verbindungs-Test G* (ZVT-G). This is an adapted version of part A of the classic trail-making test, in which 30 numbers have to be connected in the right sequence and as quickly as possible. The test is supposed

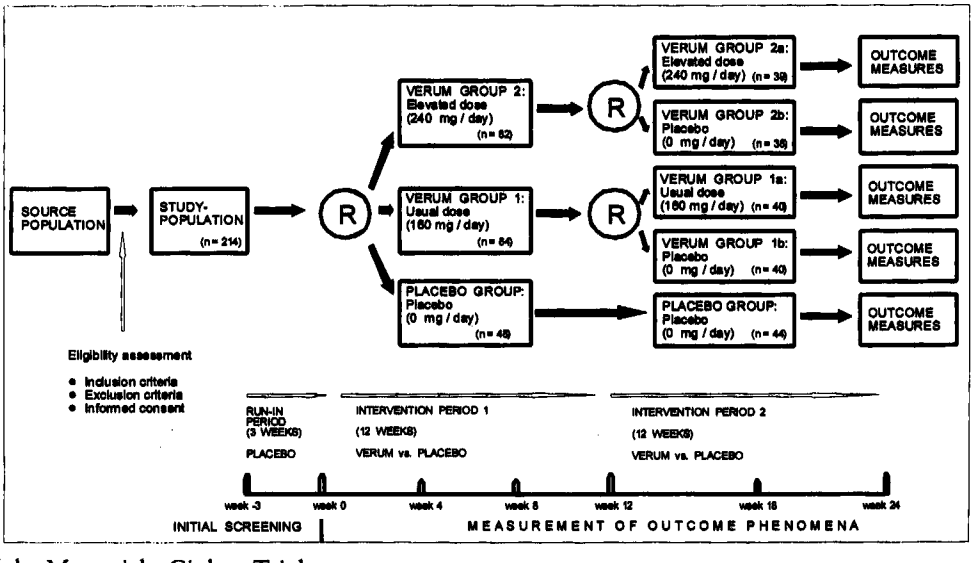

Figure 1. Design of the Maastricht Ginkgo Trial.

to measure cognitive speed, and also planning and organization.

The *Sandoz Clinical Assessment-Geriatric Scale* (SCAG). The SCAG is an 18-item geriatric symptom rating scale.[33–36] The target symptoms are supposed to represent several domains of impaired functioning: cognitive dysfunction, disturbed interpersonal relationship, affective disorders, inability to cope with the ordinary activities of daily life, and somatic dysfunction (e.g., fatigue, dizziness, poor appetite). The total score ranges from 18 to 126, but is sometimes expressed as the mean item score.

Depressive mood, expressed by the 15-item version of the *Geriatric Depression Scale* (GDS).[30,31,37,38] The GDS total score ranges from 0 to 15. Since higher GDS-scores indicate the presence of severe depressive symptomatology and, therefore, pseudodementia, patients with baseline scores ≥ 11 were excluded from the trial.

Self-perceived health status. This was measured on a 0 to 10 scale (report mark).

Self-perceived memory status. This was measured on a 0 to 10 scale as well (report mark).

The *Nürnberger Alters Alltagsaktivitäten Skala* (NAA; Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living). The NAI-NAA has been designed to measure cognition-related behaviour. It consists of 20 items, covering instrumental daily life activities (e.g., getting dressed, performing light household tasks), social activities (e.g., visiting other people), and general cognitive performance (e.g., writing postcards, financial management). Summation of the individual item scores yields a total score from 20 (very good) to 60 (very poor). Here we discuss the results of the self-assessment version of the NAA.

The ZVT-G, ZN-G, WL and NAA are all components of the Nürnberger Alters Inventar (NAI; Nuremberg Gerontopsychological Inventory), a German battery of psychometric tests, questionnaires and observational rating scales, that aims to measure cognitive functioning, performance of daily life activities, well-being and care needs. Although classic psychometric concepts underlie many of these tests and rating scales, most of them have been adapted to the specific needs of the older population.[39] In order to prevent any testing effect, we applied three parallel versions of the NAI-subtests ZVT-G, ZN-G and WL.

Two sources of information were used to collect data regarding these outcome measures: observation-based assessments by the nursing staff in the homes for the elderly (SCAG) and structured interviews (including psychometric testing) by trained interviewers (the other outcome measures). Outcomes were measured at baseline and after 4, 8, 12, 18, and 24 weeks of treatment. Table 1 contains an overview of the measurement time schedule and the score ranges for each of the outcome measures presented here.

The occurrence of (serious) adverse events was monitored continuously. One of the tools used for this purpose was a checklist of health complaints, which was completed by the nursing staff at each measuring time point. Use of co-interventions and level of compliance with the study medication (pill counting) were registered as well.

Data Management and Statistical Analysis

To assess the required sample size we performed several calculations for the various outcome measures before the start of the trial. Most of them were continuous and therefore able to resist relatively small sample sizes. We concluded that 50 evaluable subjects in each of the five trial arms would be sufficient, and anticipating a 20% dropout rate, we aimed at the random allocation of 300 participants. For instance, for the NAI-NAA we calculated that 54 participants would be sufficient to detect a clinically meaningful effect of 4 scale-points after 24 weeks (assumptions: normal distribution,

Table 1. Timing and Scale Ranges of Outcome Measures

Measure	Time Schedule (weeks)							Range of Scores	
	−3	0	4	8	12	18	24	Status Score	Change Score
Neuropsychological assessment									
NAI-ZVT (Zahlen-Verbindungs-Test: trail making test; seconds)		X			X		X	0 to 300	−300 to +300
NAI-ZN (Zahlen-Nachsprechen-Test: digit span test)		X			X		X	0 to 17	−17 to +17
NAI-WL (Wordliste: verbal learning test):									
Forward		X			X		X	0 to 8	−8 to +8
Backward		X			X		X	0 to 8	−8 to +8
Total		X			X		X	0 to 16	−16 to +16
Clinical assessment									
Sandoz Clinical Assessment-Geriatric Scale (SCAG) (18 items, mean item score; hetero-assessment)		X	X	X	X	X	X	1.0 to 7.0	−6.0 to +6.0
SCAG-19 (overall impression; hetero-assessment)		X	X	X	X	X	X	1 to 7	−6 to +6
Geriatric Depression Scale (GDS-15 items; self-assessment)	X				X		X	0 to 15	−15 to +15
Health status (report mark; self-assessment)		X	X	X	X	X	X	0 to 10	−10 to +10
Memory status (report mark; self-assessment)		X	X	X	X	X	X	0 to 10	−10 to +10
Behavioural assessment									
NAI-NAA (Nürnberger Alters Inventar—instrumental activities of daily living of elderly people; self-assessment)		X			X		X	20 to 60	−40 to +40

Underlined printing is used to represent the most favorable extreme status score or change score.

population SD = 5.0, treatment allocation ratio = 2:1, α = 0.05, 1-β = 0.80).

The protocol for statistical analysis was established before the start of the data collection. First we performed an intention-to-treat analysis by comparing the 0- to 24-week changes in scores between the subgroups who received ginkgo (160 mg and 240 mg combined) and placebo during the entire 24-week treatment period. All study subjects for whom both baseline and 24-week follow-up scores could be made available qualified for this analysis. Missing values were substituted according to a predefined replacement algorithm, with the last-observation-carried-forward principle as the main feature.

We also analyzed the effects of 12 weeks of ginkgo treatment, by comparing the 0- to 12-week changes in scores between the combined ginkgo groups and the placebo group. To identify a possible dose-effect relationship, we contrasted the changes in scores for each of the dosage categories (ginkgo 240 mg/day, ginkgo 160 mg/day, placebo) after both 24 and 12 weeks of intervention. To assess the persistence of any intervention effect, we compared the changes in scores after 24 weeks between the study subjects who were assigned to continue on ginkgo, either 240 or 160 mg/day, and those who were assigned to stop taking ginkgo after 12 weeks of treatment.

The statistical procedures included the calculation of the means and standard deviations of the changes in score on the outcome parameters for each of the comparison groups as well as the calculation of the point estimates and the 90% confidence intervals of the mean change differences between the comparison groups. We performed multiple linear regression analyses to assess the adjusted effects for each of the outcome measures. Adjustment was made for baseline differences with regard to several potential confounders of the ginkgo effect: age, gender, diagnostic subcategory (AAMI vs dementia), pretreatment level of change in memory complaints, baseline value of the outcome measure concerned, assessed quality of old peoples' home, and level of co-interventions during follow-up.

In addition to the intention-to-treat analysis we performed a per-protocol analysis. To qualify for the per-protocol analysis study subjects had to fulfil minimum requirements regarding predefined levels of compliance with the study medication ($\geq$75% intake), adherence to the outcome measurement time table, and no exposure to unpermitted co-interventions.

RESULTS

The study participants were recruited from the 4459 residents of the 39 homes for the aged that cooperated in our trial. Of this population, 781 were pointed out as potential study candidates by senior caregivers, who believed they were in serious cognitive decline. From January 1994 to June 1996, 513 of these residents were actually screened to verify the presence of a state of mild or moderate dementia or cognitive impairment. Based on the screening results, a check of relevant medical and pharmacotherapeutical data, and their tentative consent, 256 subjects were admitted to a 3-week placebo run-in period preceding the random allocation and actual start of the intervention. By the end of this period, 214 subjects, 63 demented and 151 nondemented patients with substantial cognitive decline, could be randomized to the study. The MMSE baseline-scores of the study population varied between 7 and 29, with 80% in the 12 to 24 range.

During the next 24 weeks of follow-up, 18 subjects withdrew from the study, 13 during the first and five during the second 12-week intervention period. The dropouts were distributed quite homogeneously over the three initial treatment groups: 4/48 (8%), 5/84 (6%), and 9/82 (11%) for placebo, ginkgo 160 mg, and ginkgo 240 mg, respectively. Death (8x), hospital admission/caregiver request (3x), serious concurrent illness (4x), and refusal to undergo further cognitive testing (3x) were registered as reasons for withdrawal.

Table 2 demonstrates the absence of marked differences in baseline characteristics between the three initially formed treatment groups. Probably the most striking difference was found for the trail-making test (ZVT-G). It should be noted, however, that this measure was characterized by some outliers and a rather skewed distribution of individual scores, making the mean and standard deviation less suitable as indicators for central tendency and spread.

Tables 3 and 4 show the changes in the outcome measures for placebo and ginkgo (high dose and usual dose combined) after 24 weeks (Table 3) and 12 weeks (Table 4) of uninterrupted treatment. The tables include effect estimates both before and after adjustment for confounding.

After 24 weeks of treatment, statistically significant effects in favor of ginkgo were found only for the self-perceived level of activities of daily living (NAA) and for trail making speed (ZVT-G); these effects were already present after 12 weeks of treatment. However, both effects were far from impressive and disappeared after adjustment for confounding, except for the 12 week difference in NAA score. Furthermore, we found a statistically significant effect – in favor of placebo – for self-perceived memory status after 12 weeks. Correction for confounding suppressed this effect. At the same time it produced a new statistically significant effect for self-perceived health status. In general, we did not find any remarkable shift in score on most of the outcome parameters during the course of the intervention either in the ginkgo group or in the placebo group.

The absence of a positive effect for both ginkgo dosage groups combined made a dose-related gradient very unlikely in advance. On only two occasions did high-dose ginkgo produce a stronger effect than usual dose ginkgo, once in a positive (self-perceived health status) and once in a negative (WL) sense. After adjustment for confounding, neither effect continued to be statistically significant, as demonstrated by the data in Table 5. Likewise, no significant beneficial effects were found for continued compared with discontinued use of ginkgo (see Table 6).

To evaluate the possibility that a beneficial effect of ginkgo might be the privilege of one or more subgroups of the study population, we performed a series of stratified analyses. These highlight the treatment effects for various subcategories within the study population, based on the following baseline characteristics: age, diagnostic category (dementia vs AAMI), MMSE-score, SKT baseline score, BLE-score (number of experienced biological life events with a possible influence on cognitive functioning). All these baseline characteristics have been dichotomized for the purpose of these analyses. The results of these stratified analyses suggested that none of the evaluated subgroups benefited consistently from ginkgo (compared with placebo).

Table 2. Distribution of Baseline Characteristics by Intervention Subgroup at the Start of the Trial. Absolute Numbers (percentages) are for Categorical Variables, and Mean Values (standard deviations) are for (Semi-)Continuous Variables

		Placebo (n = 48)	Ginkgo 160 mg (n = 84)	Ginkgo 240 mg (n = 82)
Gender	male	9 (19%)	13 (16%)	12 (15%)
	female	39 (81%)	71 (85%)	70 (85%)
Living situation	alone	43 (90%)	73 (87%)	75 (92%)
	together	5 (10%)	11 (13%)	7 (9%)
Cognitive impairment (assessed by staff)	mild	22 (46%)	37 (44%)	35 (43%)
	moderate	26 (54%)	47 (56%)	47 (57%)
Perceived change in memory complaints over last 6 months	increased much	6 (13%)	7 (9%)	9 (11%)
	increased	12 (25%)	25 (31%)	24 (29%)
	the same	27 (56%)	48 (59%)	46 (56%)
	decreased	3 (6%)	1 (1%)	3 (4%)
	decreased much	0 (0%)	0 (0%)	0 (0%)
State of dementia	dementia	14 (29%)	25 (30%)	24 (29%)
	AAMI	34 (71%)	59 (70%)	58 (71%)
Age		82.6 (5.7)	82.8 (4.9)	83.3 (5.3)
Quetelet Index		25.0 (3.7)	24.2 (3.8)	24.9 (3.4)
MMSE (Mini-Mental State)		18.5 (4.5)	18.3 (4.8)	18.4 (4.2)
MAC-Q, modified, assessed by patient (subjective memory complaints)		12.6 (2.7)	12.7 (3.3)	12.0 (2.9)
MAC-Q, modified, assessed by nursing staff (subjective memory complaints)		15.2 (4.4)	16.0 (4.8)	16.1 (3.5)
NAI-ZVT-G (trail making test)		106.8 (57.6)	139.8 (77.4)	122.8 (76.1)
NAI-ZN-G (digit span)		8.1 (1.9)	8.0 (1.5)	8.0 (1.5)
NAI-WL-tot (word list; total score)		5.2 (3.1)	4.8 (3.4)	4.8 (3.0)
SCAG (geriatric symptoms; mean score)		2.5 (0.9)	2.6 (1.0)	2.7 (1.0)
GDS (depression)		3.0 (2.0)	2.5 (2.2)	2.5 (2.4)
Health status (report mark)		7.2 (1.5)	7.4 (1.2)	7.3 (1.4)
Memory status (report mark)		6.7 (1.3)	7.1 (1.1)	6.9 (1.2)
NAI-NAA (activities of daily living; self-assessment)		37.0 (6.4)	37.8 (6.1)	37.1 (5.3)

Scale ranges (underlined printing indicates the most favourable extreme):
MMSE: 0–30; MAC-Q: 5–25; NAI-ZVT-G: 0–300; NAI-ZN-G: 0–17; NAI-WL-tot: 0–16; SCAG: 1.0–7.0; GDS: 0–15; health status: 0–10; memory status: 0–10; NAI-NAA: 20–60.

As part of the evaluation of possible unintended effects, we identified 111 of 214 (52%) study subjects with at least one health complaint during the first intervention period. Treatment-specific rates of these adverse events were 56%, 52%, and 44% for the ginkgo 240 mg, ginkgo 160 mg, and placebo groups, respectively. Dizziness (n = 58), nervousness (n = 49), and headache (n = 32) were the most common symptoms. A total of 113 of 201 (56%) persons with health complaints were registered during the second part of the trial (treatment-specific rates: 46%, 40%, 65%). An obvious association with type of treatment was absent. Thirty-five serious adverse events were notified during the entire trial period: eight deaths, 25 hospital admissions, and two malignancies. These concerned 16% / 19% of the cases initially treated with ginkgo/placebo. A possible association with study treatment was considered for only one case, a placebo user.

DISCUSSION

Our trial did not reveal any systematic and clinically meaningful effect of ginkgo on any of the outcome measures. Statistically significant effects regarding the time needed to complete the trail making test (NAI-ZVT-G) and the self-assessed level of activities of daily living (NAI-NAA) were detected initially, but these effects were eradicated, in part, when the influence of baseline differences was taken into account through multiple linear regression analysis. Therefore, the current results seem to confirm the results reported separately for the SKT (Syndrom Kurz Test), the CGI-2 (Clinical Global Impression), and the NAI-NAA (Nürnberger Alters Inventar Alltagsaktivitäten Skala) applied by the nursing staff, that also failed to demonstrate any beneficial effect of ginkgo.

Our trial disagrees with the vast majority of placebo-controlled randomized trials conducted to assess the clinical efficacy of ginkgo in patients with various types of cerebral insufficiency. A recent review of ginkgo and cerebral insufficiency included 55 trials, 43 of which addressed cognition-related phenomena.[40] Nine trials, most of quite recent date, focused on patients with dementia, either Alzheimer's disease or vascular dementia. They all showed positive, often statistically significant, effects of ginkgo compared with placebo. Eight trials dealt with patients suffering from cognitive im-

Table 3. Comparison of the Mean Baseline Scores, Mean 24-Week Follow-up Scores, Unadjusted Mean 0–24 w. Changes in Score, and Adjusted Mean 0–24 w. Changes in Score (Regression Coefficients) on the Outcome Variables for the Placebo Group (n = 44) and the Combined Ginkgo Groups (n = 79)

Variable	Intervention Subgroup	Mean 0 Week Baseline Score	Mean 24 Week Follow-up Score	Change in Score over 24 Weeks mean (SD)	Unadjusted/ Adjusted* 0–24-Week Change Difference: mean (90% CI)
Trail-making speed	placebo	103.1	115.5	−12.5 (56.2)	+23.5 (+4.7; +42.2)
(NAI-ZVT-G)	Ginkgo	128.3	117.3	11.0 (60.4)	*+18.4 (−0.7; +37.5)*
Digit span	placebo	8.09	7.89	−0.20 (1.68)	−0.08 (−0.60; +0.44)
(NAI-ZN-G)	Ginkgo	8.06	7.79	−0.28 (1.64)	*−0.01 (−0.54; +0.52)*
Word list, total score	placebo	5.19	4.19	−1.00 (2.86)	+0.40 (−0.52; +1.31)
(NAI-WL-tot)	Ginkgo	4.24	3.64	−0.60 (2.88)	*+0.12 (−0.69; +0.93)*
Geriatric symptoms, mean	placebo	2.48	2.45	0.03 (0.74)	+0.04 (−0.20; +0.29)
(SCAG)	Ginkgo	2.75	2.68	0.07 (0.81)	*+0.01 (−0.22; +0.24)*
Depressive mood	placebo	3.00	4.14	−1.14 (3.14)	+0.55 (−0.37; +1.47)
(GDS)	Ginkgo	2.60	3.18	−0.58 (2.82)	*+0.54 (−0.46; +1.54)*
Health status	placebo	7.14	7.30	0.16 (1.29)	−0.32 (−0.77; +0.12)
(report mark)	Ginkgo	7.43	7.27	−0.16 (1.49)	*−0.15 (−0.56; +0.26)*
Memory status	placebo	6.66	6.91	0.25 (1.14)	−0.28 (−0.64; +0.09)
(report mark)	Ginkgo	6.99	6.96	−0.03 (1.19)	*−0.15 (−0.51; +0.21)*
Activities of daily living	placebo	37.00	39.57	−2.57 (4.61)	+1.65 (+0.20; +3.09)
(NAI-NAA)	Ginkgo	37.82	38.74	−0.92 (4.63)	*+1.32 (−0.13; +2.77)*

*Adjusted change difference printed in italics. The number of subjects involved in the regression analysis varied from 118 (NAI-ZVT-G) to 122 (SCAG, report mark health status).

Scale ranges (underlined printing indicates the most favourable extreme):

Status scores: NAI-ZVT-G: 0–300; NAI-ZN-G: 0–17; NAI-WL-tot: 0–16; SCAG: 1.0–7.0; GDS: 0–15; health status: 0–10; memory status: 0–10; NAI-NAA: 20–60.

Change scores: NAI-ZVT-G: −300–+300; NAI-ZN-G: −17–+17; NAI-WL-tot: −16–+16; SCAG: −6.0–+6.0; GDS: −15–+15; health status: −10–+10; memory status: −10–+10; NAI-NAA: −40–+40.

pairment, which was probably not dementia. For these trials, positive effects of ginkgo were reported as well, although not unequivocally and only for some of the outcome measures. Five trials included patients diagnosed by means of a symptom checklist that listed a more or less standardized combination of cognitive and noncognitive signs of cerebral insufficiency. Patients treated with ginkgo were found to be significantly better off in each of these trials. Three trials had as their primary focus affective sequelae of cerebral function impairment, depression in particular. Ginkgo treatment caused alleviation of the state of depressive mood in each trial. Finally, 18 placebo-controlled trials dealt with patients diagnosed with a rather diffuse, unspecified form of cerebral insufficiency. Again, most of the authors reported a beneficial effect according to most of the endpoints measured.[40]

A trail-making (number-connection) test in some form has been applied as one of the endpoints in seven previous placebo-controlled trials with ginkgo. Statistically significant results were found in three of them, after 6 to 12 weeks of intervention.[41–43] A positive trend was found in four trials that made use of the NAI-ZVT test.[44–47] The mean changes in ZVT-score (seconds) in our trial were +6 versus −15 after 12 weeks and +11 versus −13 after 24 weeks (ginkgo vs placebo). The change differences were not statistically significant anymore after adjustment for confounding.

Digit span testing, although not by means of the NAI-ZN subtest, was performed in five earlier trials.[48–52] The changes in our trial were small and statistically not significant: −0.0 versus +0.1 after 12 weeks, and −0.3 versus −0.2 after 24 weeks. An effect of ginkgo was found neither for the forward nor for the backward component of the NAI-ZN.

Five ginkgo trials incorporated the SCAG as one of the outcome measures, either in its original format[49,53–55] or in a slightly modified version.[56] In four trials with daily dosages varying from 80 to 160 mg, ginkgo turned out to be superior to placebo after 3 months,[49,53–55] and in the fifth after 12 months of intervention.[56] The mean changes in SCAG total score in our trial were +3.2 versus +0.7 after 12 weeks and +1.3 versus +0.5 after 24 weeks.

The GDS was used to evaluate the effect of ginkgo on depressive mood in one earlier placebo-controlled trial. However, no results were reported from this trial.[57] In other trials, alternative depression scales were used, e.g., the Hamilton Depression Scale (range: 1–17) in two trials, with positive results,[58,59] Zung's Self-Rating Depression Scale (SDS) also in two trials,[60,61] and the Montgomery Asberg Depression Rating Scale.[62] In our trial we failed to identify any significant changes in depressive mood with the GDS: −0.6 versus −1.2 after 12 weeks and −0.6 versus −1.1 after 24 weeks. However, patients with clinically significant depression were excluded from participation in the study.

Two earlier trials measured the influence of ginkgo on level of daily activities by means of the NAI-NAA rating scale. Whereas Oswald et al. found no effect (35% vs 38% of ginkgo and placebo users with any improvement),[63] Haase et al. reported a substantial difference (+7.5 scale-points) in favor of ginkgo after 4 weeks of intravenous administration.[61] Our trial came up with adjusted effects in favor of

Table 4. Comparison of the Mean Baseline Scores, Mean 12-Week Follow-up Scores, Unadjusted Mean 0–12 w. Changes in Score, and Adjusted Mean 0–12 w. Changes in Score (Regression Coefficients) on the Outcome Variables for the Placebo Group (n = 48) and the Combined Ginkgo Groups (n = 166)

Variable	Intervention Subgroup	Mean 0 Week Baseline Score	Mean 12 Week Follow-up Score	Change in Score over 12 Weeks: mean (SD)	Unadjusted/Adjusted* 0–12-Week Change Difference: mean (90% CI)
Trail-making speed	placebo	102.4	117.0	−14.6 (59.1)	+20.6 (+3.8; +37.3)
(NAI-ZVT-G)	Ginkgo	130.1	124.1	6.0 (58.3)	*+14.5 (−2.1; +31.1)*
Digit span	placebo	8.11	8.16	0.05 (1.18)	−0.05 (−0.47; +0.37)
(NAI-ZN-G)	Ginkgo	8.06	8.05	−0.01 (1.57)	*−0.03 (−0.43; +0.37)*
Word list, total score	placebo	5.36	5.21	−0.14 (2.86)	−0.15 (−1.00; +0.70)
(NAI-WL-tot)	Ginkgo	4.86	4.57	−0.29 (2.97)	*−0.02 (−0.88; +0.84)*
Geriatric symptoms, mean	placebo	2.47	2.44	0.04 (0.61)	+0.15 (−0.06; +0.36)
(SCAG)	Ginkgo	2.68	2.50	0.18 (0.80)	*+0.12 (−0.08; +0.32)*
Depressive mood	placebo	3.05	4.25	−1.20 (3.63)	+0.59 (−0.27; +1.44)
(GDS)	Ginkgo	2.52	3.14	−0.62 (2.84)	*+0.60 (−0.31; +1.51)*
Health status	placebo	7.21	7.26	0.04 (1.63)	−0.28 (−0.70; +0.13)
(report mark)	Ginkgo	7.36	7.12	−0.24 (1.47)	*−0.38 (−0.73; −0.04)*
Memory status	placebo	6.72	7.00	0.28 (1.00)	−0.38 (−0.71; −0.04)
(report mark)	Ginkgo	7.01	6.92	−0.09 (1.27)	*−0.25 (−0.55; +0.05)*
Activities of daily living	placebo	36.64	38.41	−1.77 (5.02)	+1.35 (+0.19; +2.51)
(NAI-NAA)	Ginkgo	37.48	37.90	−0.42 (3.80)	*+1.35 (+0.22; +2.49)*

*Adjusted change difference printed in italics. The number of subjects involved in the regression analysis varied from 189 (NAI-WL-tot) to 206 (SCAG).
Scale ranges (underlined printing indicates the most favourable extreme):
Status scores: NAI-ZVT-G: 0–300; NAI-ZN-G: 0–17; NAI-WL-tot: 0–16; SCAG: 1.0–7.0; GDS: 0–15; health status: 0–10; memory status: 0–10; NAI-NAA: 20–60.
Change scores: NAI-ZVT-G: −300–+300; NAI-ZN-G: −17–+17; NAI-WL-tot: −16–+16; SCAG: −6.0–+6.0; GDS: −15–+15; health status: −10–+10; memory status: −10–+10; NAI-NAA: −40–+40.

ginkgo of +1.4 points after 12 weeks and +1.3 after 24 weeks of therapy. This was much less than the predefined level of clinical relevance (4.0 points).

Outcome measures comparable with the word list test and the report marks for health and memory were not reported for any of the previous ginkgo trials. In our study, neither the immediate reproduction nor the delayed recognition of words were influenced by ginkgo.

In our trial we used a multiphasic screening procedure to recruit residents of old peoples' homes who suffered from either dementia or age-associated memory impairment. This screening procedure entailed a combination of diagnostic tools (questionnaires, psychometric tests, rating scales) that have proven to be valid and reliable. We preferred to include residents of homes for the elderly rather than older people still living at home for several reasons: to create a suitable sampling frame, harboring many eligible study candidates; to be able to promote and supervise the level of compliance with the study medication; to facilitate the conduct of baseline and follow-up measurements as well as other logistic procedures; to gain easy access to additional (medical) information concerning the study subjects; and to avoid an overrepresentation of worriers, people who tend to exhibit an unwarranted amount of fear regarding cognitive deterioration. We realize that, as a consequence of this choice, we have attracted a study population with a special composition as to age structure (older than most of the previous ginkgo study samples) and comorbidity (many concurrent diseases and health complaints). The living environment and care provided to these people may protect them, to some extent, from the mental challenges of daily life in open society. This circumstance may have influenced some of the outcome measurements, especially those relying on self-assessment by the participants. It is possible that the research setting may also have led to underdiagnosis of dementia in our study population. In order to differentiate between dementia and nondementia forms of cognitive decline, the assessment of cognitive functioning on the level of social and daily life functioning is of crucial and decisive importance (DSM-III-R criterion C for dementia). We have noticed a tendency to apply this criterion more leniently in the sheltered environment of a home for the elderly than in the open, noninstitutionalized population.

The power of the trial to detect a clinically meaningful effect as statistically significant was greater than 99% for the NAI-NAA and most other outcome parameters. For the subgroup of demented patients only (23 ginkgo, 13 placebo) the power was about 70% for the NAI-NAA after 24 weeks. To detect effects after 12 weeks, the power was always greater than 99%.

In regard to the study treatment, we applied a high quality ginkgo biloba special extract (EGb 761) with a significant exposure contrast between verum (either 160 or 240 mg of active substance per day) and placebo. We worked diligently to develop a valid placebo. A strict distribution schedule, with intake supervision by the nursing staff and periodical pill counts, was used to enhance the compliance with the intervention regimen. Some potential noncompliers were identified and excluded during the run-in phase, before randomization. Unwanted interference with co-interventions was precluded by means of the enrollment criteria.

In selecting the outcome measures, we have attempted to satisfy the prevailing guidelines for the evaluation of antidementia drugs.[15] The NAI tests and rating scales and the GDS were especially adapted to the specific needs of older people.

Table 5. Comparison of Unadjusted and Adjusted Mean Changes in Score over 24 Weeks on Outcome Measures, Ginkgo High Dosage (240 mg, 0–24 weeks; n = 40) Versus Ginkgo Usual Dosage (160 mg, 0–24 weeks; n = 39) Versus Placebo (0 mg, 0–24 weeks; n = 44)

Variable	Intervention Subgroup	Number	0–24 Week Change in Score: mean (SD)	Unadjusted/Adjusted* 24-Week Change Difference, Ginkgo 240 versus 160: mean (90% CI)
Trail-making speed	placebo	42	−12.48 (56.24)	
(NAI-ZVT-G)	Ginkgo 160	40	14.24 (64.29)	−6.8 (−29.8; +16.2)
	Ginkgo 240	37	7.45 (56.63)	*−2.2 (−27.0; +22.6)*
Digit span	placebo	44	−0.20 (1.68)	
(NAI-ZN-G)	Ginkgo 160	40	−0.18 (1.78)	−0.22 (−0.84; +0.40)
	Ginkgo 240	38	−0.39 (1.50)	*−0.01 (−0.70; +0.68)*
Word list, total score	placebo	42	−1.00 (2.86)	
(NAI-WL-tot)	Ginkgo 160	40	0.03 (2.64)	−1.29 (−2.36; −0.22)
	Ginkgo 240	38	−1.26 (3.02)	*−1.37 (−2.78; +0.04)*
Geriatric symptoms	placebo	44	0.03 (0.74)	
(SCAG; mean score)	Ginkgo 160	40	0.13 (0.91)	−0.11 (−0.41; +0.19)
	Ginkgo 240	39	0.02 (0.69)	*−0.23 (−0.54; +0.08)*
Depressive mood	placebo	44	−1.14 (3.14)	
(GDS)	Ginkgo 160	40	−0.57 (2.93)	−0.02 (−1.10; +1.06)
	Ginkgo 240	37	−0.59 (2.74)	*−0.10 (−1.32; +1.12)*
Health status	placebo	44	+0.16 (1.29)	
(report mark)	Ginkgo 160	40	−0.53 (1.24)	+0.73 (+0.19; +1.27)
	Ginkgo 240	39	+0.21 (1.64)	*+0.41 (−0.15; +0.97)*
Memory status	placebo	44	0.25 (1.14)	
(report mark)	Ginkgo 160	39	−0.18 (1.02)	+0.31 (−0.14; +0.76)
	Ginkgo 240	39	0.13 (1.34)	*+0.23 (−0.26; +0.72)*
Activities of daily living	placebo	44	−2.57 (4.61)	
(NAI-NAA)	Ginkgo 160	40	−0.43 (4.41)	−1.02 (−2.77; +0.73)
	Ginkgo 240	38	−1.45 (4.85)	*−1.43 (−3.21; +0.35)*

*Adjusted change difference printed in italics.
Scale ranges (underlined printing indicates the most favourable extreme):
Status scores: NAI-ZVT-G: 0–300; NAI-ZN-G: 0–17; NAI-WL-tot: 0–16; SCAG: 1.0–7.0; GDS: 0–15; health status: 0–10; memory status: 0–10; NAI-NAA: 20–60.
Change scores: NAI-ZVT-G: −300–+300; NAI-ZN-G: −17–+17; NAI-WL-tot: −16–+16; SCAG: −6.0–6.0; GDS: −15–+15; health status: −10–+10; memory status: −10–+10; NAI-NAA: −40–+40.

On consecutive occasions, we applied parallel versions of NAI neuropsychological tests to avoid repeated testing artefacts. Because of the significant changes that were observed for psychometric, clinical, and behavioral outcomes after 6 and 12 months of intervention in various previous ginkgo trials, and because the purported pharmacological mechanisms of action that underlie the claims for a beneficial effect of ginkgo seem to enable relatively short-term responses, we believed a total follow-up period of 24 weeks would be adequate. However, in this respect one should be aware that neuropsychological, clinical, and behavioral changes probably require an increasing amount of time to become manifest. In particular, the sensitivity to change of the NAI-NAA may be questioned because of the setting in which the activities of daily living were assessed.

We took various measures to improve the comparability of the trial groups, the interventions to be evaluated, and the outcome assessments. To preclude any disturbing influences of prognostic subgroup differences, we allocated the participants randomly and also relied on restriction, prestratification, stratified analysis, and multiple regression analysis. Only minor differences in baseline characteristics between the intervention groups were found. The number of dropouts was limited and was distributed quite homogeneously among the intervention subgroups.

In order to release the active ginkgo compounds as the only source of intervention contrast, people exposed to a broad range of pharmacological and nonpharmacological cognition-affecting principles were filtered out and excluded before the start of the trial. We monitored relevant changes in drug use and medical care, as well as the occurrence of important psychological life events, continuously during the trial. Insufficient compliance with the study medication, often in combination with premature withdrawal, was registered for 10%, 11%, and 17% of the initial placebo, ginkgo 160 mg, and ginkgo 240 mg groups, respectively. A per-protocol analysis, restricted to the valid cases with regard to compliance, exposure to co-interventions, and timing of the outcome measures, did not change the conclusions of the intention-to-treat analysis.

The study outcomes were assessed under blind conditions. To verify blindness, the patients themselves, the nursing staff and the interviewers involved in outcome measurements were all invited to report their perceived study medication (ginkgo 240 mg, ginkgo 160 mg, placebo). These checks did not disclose any association between actual and

Table 6. Comparison of Unadjusted and Adjusted Mean Changes in Score over 24 Weeks on Outcome Measures; Ginkgo 160/240 (24 weeks) (n = 79) Versus Ginkgo 160/240 (12 weeks) + Placebo (12 weeks) (n = 78)

Variable	Intervention Subgroup	Number	0–24 Week Change in Score: mean (SD)	Unadjusted/Adjusted* 24-Week Change Difference: mean (90% CI)
Trail-making speed	Ginkgo + placebo	74	2.6 (54.3)	+8.3 (−7.0; +23.8)
(NAI-ZVT-G)	Ginkgo + Ginkgo	77	11.0 (60.4)	*+10.7 (−4.3; +25.7)*
Digit span	Ginkgo + placebo	76	−0.07 (1.63)	−0.22 (−0.65; +0.22)
(NAI-ZN-G)	Ginkgo + Ginkgo	78	−0.28 (1.64)	*−0.06 (−0.48; +0.36)*
Word list, total score	Ginkgo + placebo	73	−1.25 (2.62)	+0.64 (−0.10; +1.39)
(NAI-WL-tot)	Ginkgo + Ginkgo	78	−0.60 (2.88)	*+0.70 (−0.21; +1.61)*
Geriatric symptoms	Ginkgo + placebo	78	0.12 (0.77)	−0.05 (−0.25; +0.16)
(SCAG, mean score)	Ginkgo + Ginkgo	79	0.07 (0.81)	*−0.02 (−0.22; +0.17)*
Depressive mood	Ginkgo + placebo	77	−0.69 (2.97)	+0.10 (−0.67; +0.88)
(GDS)	Ginkgo + Ginkgo	77	−0.58 (2.82)	*+0.15 (−0.62; +0.92)*
Health status	Ginkgo + placebo	76	−0.17 (1.43)	+0.01 (−0.38; +0.39)
(report mark)	Ginkgo + Ginkgo	79	−0.16 (1.49)	*+0.10 (−0.25; +0.46)*
Memory status	Ginkgo + placebo	75	−0.12 (1.40)	+0.09 (−0.25; +0.44)
(report mark)	Ginkgo + Ginkgo	78	−0.03 (1.19)	*+0.09 (−0.22; +0.40)*
Activities of daily living	Ginkgo + placebo	77	−1.18 (4.35)	+0.26 (−0.94; +1.45)
(NAI-NAA)	Ginkgo + Ginkgo	78	−0.92 (4.63)	*−0.02 (−1.17; +1.13)*

*Adjusted change difference printed in italics.
Scale ranges (underlined printing indicates the most favourable extreme):
Status scores: NAI-ZVT-G: 0–300; NAI-ZN-G: 0–17; NAI-WL-tot: 0–16; SCAG: 1.0–7.0; GDS: 0–15; health status: 0–10; memory status: 0–10; NAI-NAA: 20–60.
Change scores: NAI-ZVT-G: −300–+300; NAI-ZN-G: −17–+17; NAI-WL-tot: −16–+16; SCAG: −6.0–+6.0; GDS: −15–+15; health status: −10–+10; memory status: −10–+10; NAI-NAA: −40–+40.

perceived type of treatment either at 4 or at 18 weeks after the start of the intervention. Given these observations we can hardly imagine that the trial results have seriously been distorted as a result of differential misclassification. However, we cannot rule out totally the possibility of some random outcome measurement error that may have given rise to suppression of actual ginkgo effects.

We conclude that our trial has failed to reproduce the beneficial effects of ginkgo in older patients with dementia and age-associated memory impairment that have been demonstrated by many previous trials. The findings, based on the outcome parameters reported in this article, are in agreement with the results for outcome measures that will be reported elsewhere. We find it difficult to attribute the absence of a consistent treatment effect to flaws and fallacies in the trial design, conduct, and analysis. We believe that our study is one of the most rigorous ever conducted in this field, especially with regard to random allocation, placebo control, blinded outcome measurement, level of compliance, and drop-out rate. Our trial results suggest that treatment with ginkgo is not efficacious, irrespective of dose, in older patients with mild to moderate dementia or age-associated memory impairment. Therefore, we tend to conclude that the Maastricht Ginkgo Trial has scaled down our belief in a beneficial effect of ginkgo for dementia and memory impairment. We realize, however, that the negative results of our trial cannot fully neutralize the positive results of previous studies. Most interesting in this respect are some recent trials that appear to meet quite high methodological standards as well, in particular the trials published by Haase et al.,[61] Kanowski et al.,[62] and Le Bars et al.[13] Judging from the published study results, these trials seem to have several design aspects in common with our study, e.g., random allocation, placebo-controlled intervention, and double-blind outcome assessment. However, dissimilarities can also be noticed. These relate to characteristics of the study population, e.g., sample size, source of recruitment, clinical diagnosis (cases of dementia, both AD and VD, in each of the studies), severity of disease, and age structure. They also relate to intervention characteristics. Finally, the dissimilarities relate to the reported outcome measures. We stated before that Le Bars' trial suffered from a high drop-out rate, especially during the second part of the trial. This was a much smaller problem in both German trials. Although we note differences in study design and conduct between our trial and other trials, the differences do not seem to be enough to explain the discrepancy in the results or to refute the positive results of some recent trials in particular. At this time, we cannot fully rule out the possibility that our negative trial was an 'outlier by chance'.

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