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# Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial

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**Abstract**

Preparations based on special extracts of the *Ginkgo biloba* tree are popular in various European countries. Previous studies have suggested the clinical efficacy of Ginkgo in patients with dementia, cerebral insufficiency, or related cognitive decline. However, most of these studies did not fulfill the current methodologic requirements. We assessed the efficacy of the *G. biloba* special extract EGb 761 in patients with dementia and age-associated memory impairment in relation to dose and duration of treatment. Our study was a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. Study participants were elderly patients with dementia (Alzheimer disease or vascular dementia) or age-associated memory impairment (AAMI). A total of 214 participants, recruited from 39 homes for the elderly in the Netherlands, were randomly allocated to Ginkgo (either 240 mg/d or 160 mg/d) or placebo (0 mg/d). After 12 weeks, the subjects in the two Ginkgo groups were randomized to continued Ginkgo treatment or placebo treatment. Primary outcome measures in this study were the Syndrome Kurz Test (SKT; psychometric functioning), the Clinical Global Impression of change (CGI-2; psychopathology, assessed by nursing staff), and the Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living (NAI-NAA; behavioral functioning). One hundred twenty-three patients received Ginkgo ($n = 79$, 240 and 160 mg/d combined) or placebo ($n = 44$) during the 24-week intervention period. We found no statistically significant differences in mean change of scores between Ginkgo and placebo. The differences were SKT: +0.4 (90% confidence interval [CI] −0.9–1.7); CGI-2: +0.1 (90% CI −0.3–0.4), and NAI-NAA: −0.4 (90% CI −1.9–1.2). A positive difference is in favor of Ginkgo. Neither the dementia subgroup ($n = 36$) nor the AAMI subgroup ($n = 87$) experienced a significant effect of Ginkgo treatment. There was no dose-effect relationship and no effect of prolonged Ginkgo treatment. The trial results do not support the view that Ginkgo is beneficial for patients with dementia or age-associated memory impairment. 

*Keywords:* Ginkgo; EGb 761; Dementia; AAMI; Elderly people; RCT

## 1. Introduction

Efforts to identify substances that stand out for their efficacy and safety in treating dementia and related cognitive disorders have yielded disappointing results until now. Several years ago, the *Lancet* published a criteria-based systematic review that showed a consistent beneficial effect of Ginkgo for patients with cerebral insufficiency [1]. Forty randomized controlled trials were included in that review, 39 of which showed a statistically significant effect or at least a positive trend for Ginkgo. However, the methodologic quality of many trials was considered to be poor. Moreover, the studies entailed a heterogeneous collection of target health problems, ranging from overt dementia to noncognitive manifestations of brain dysfunction, such as vertigo and tinnitus. More recently, the results of several new Ginkgo trials have been published. Most of them focused on dementia, were rather well designed, and showed positive effects of Ginkgo. Probably the most talked about is the trial of the North American EGb Study Group, which was published in the *JAMA* in 1997 and showed a modest improvement of the cognitive performance and the social functioning of the demented patients involved [2].

Medicinal ginkgo preparations are obtained through extraction of dried leaves of the *Ginkgo biloba* tree. *G. biloba* special extracts, such as EGb 761 and LI 1370, have been subjected to a standardized process of enrichment and purification, yielding fixed concentrations of two active

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substance classes (ginkgoflavone glycosides, 16% to 25%; terpene trilactones, usually 6%). These extracts have been registered as drugs for various indications in several European countries. Ginkgo is marketed in these countries under various brand names and has become a commercial best seller. Ginkgo monopreparations and multipreparations with Ginkgo constituents have also attracted a growing popularity as over-the-counter drugs [3,4]. Several mechanisms of action have been described to explain the claimed nootropic properties of Ginkgo: increased tolerance to hypoxia; prevention of membrane damage through free radical scavenger activity; improvement of blood rheology and vasoregulating capacity, resulting in increased blood flow; prevention of post-traumatic or toxin-induced brain edema; platelet activating factor inhibition; and neuroprotective action by direct or by indirect (modulated through blood flow) influences on the nervous system [5].

We initiated a trial to retest the hypothesis that Ginkgo is beneficial to elderly people with dementia or age-associated memory impairment. The promising results of previous trials justified the inclusion of two additional research questions, one dealing with the dose dependency and the other with the durability of any ginkgo effect.

## 2. Methods

### 2.1. Study design

The trial was designed as a multicenter, randomized, placebo-controlled, double-blind trial (Figure 1). The eligible subjects were randomly allocated to one of three treatments: EGb 761 240 mg/d ("high dose"), 160 mg/d ("usual dose"), or 0 mg/d (placebo). This allowed us to study the dose-effect relationship in addition to the efficacy of Ginkgo. Participants who completed the first 12-week treatment period under Ginkgo were randomly allocated for a second 12-week treatment period to continue their Ginkgo treatment or to receive placebo. Initial placebo use was continued during the second intervention period. This allocation scheme for the second intervention period allowed us to study the durability of the intervention effect after the discontinuation of Ginkgo therapy.

For the concealed randomization procedure, we used a computer-generated random sampling set. Random allocation was done within four predefined strata according to diagnostic subcategory (dementia versus age-associated memory impairment [AAMI]) and perceived memory change during the 6-month pretreatment phase (improvement or no change versus impairment). The first random allocation procedure (week 0) was conducted in blocks of five patients and with a 2:2:1 ratio (Ginkgo 240 mg/Ginkgo 160 mg/placebo). By the end of the study, this ratio was changed to 1:1:1 to add statistical power for analyzing the primary research question. The second randomization procedure (week 12) used blocks of two patients and a 1:1 (Ginkgo/placebo) allocation ratio.

The 24-week treatment period was preceded by a 3-week placebo run-in period. Eventually, the repeated random allocation procedure yielded five different treatment groups of approximately equal size: group 1: EGb 240 mg (24 weeks); group 2: EGb 160 mg (24 weeks); group 3: placebo (24 weeks); group 4: EGb 240 mg (12 weeks) + placebo (12 weeks); group 5: EGb 160 mg (12 weeks) + placebo (12 weeks). This article focuses on the first three groups. For a more detailed description of the design, the conduct, and the results of the Maastricht Ginkgo Trial, see the official trial report [6] and a PhD thesis based on this trial [7].

### 2.2. Study population

The target population consisted of patients from two diagnostic categories. First, we included subjects with a diagnosis of uncomplicated dementia according to the DSM-III-R [8] and ICD-10 criteria [9]. Patients with Alzheimer dementia, vascular dementia, or a mixed type of dementia were eligible. Second, we enrolled subjects suffering from AAMI according to the diagnostic criteria proposed by Crook et al [10]. We decided to include AAMI patients and patients with beginning dementia because we assumed that relatively mild stages of cognitive decline provide for the clearest manifestations of any Ginkgo effect and because there are arguments to consider AAMI a precursor lesion of full-blown dementia. From 1 January 1994 to 31 May 1996, we recruited study participants from 39 old peoples' homes in the southern part of the Netherlands, applying a multi-stage screening procedure. For the differential diagnosis of dementia we used the Strukturiertes Interview für die Diagnose einer Demenz vom Alzheimer Typ, der Multiinfarkt-Demenz und Demenzen anderer Ätiologie nach DSM-III-R, DSM-IV und ICD-10 (SIDAM) [11]. This is a Germany-based semi-structured interview that includes the Mini-Mental State Examination (MMSE) [12] and the Hachinski Ischemic Score [13]. It keeps close track of the DSM-III-R criteria for dementia. The degree of severity of dementia had to be mild to moderate as assessed by the SIDAM interview and by a score ranging from 8 to 23 on the Syndrom Kurz Test (SKT), a psychometric test battery for the assessment of memory and attention [14]. For the AAMI diagnosis, subjects had to suffer from impaired cognitive functioning, objectively and subjectively, in the absence of dementia. This was indicated by a score between 8 and 23 on the SKT, combined with the presence of subjective memory complaints (i.e., a total score $\geqslant$12 assigned by the study subject or the nursing staff) using a modified version of the Memory Assessment Clinics Questionnaire, a 5-item questionnaire on specific problems in daily life [15]. Lab tests and CT scans were not performed routinely. In addition, subjects of both diagnostic subgroups had to fulfill the following enrollment criteria: age $\geqslant$50 years; written informed consent by patient or legal representative; absence of severe depression (Geriatric Depression Scale, 15-item version, total score $<$11) [16,17]; presence of an adequate level of premorbid

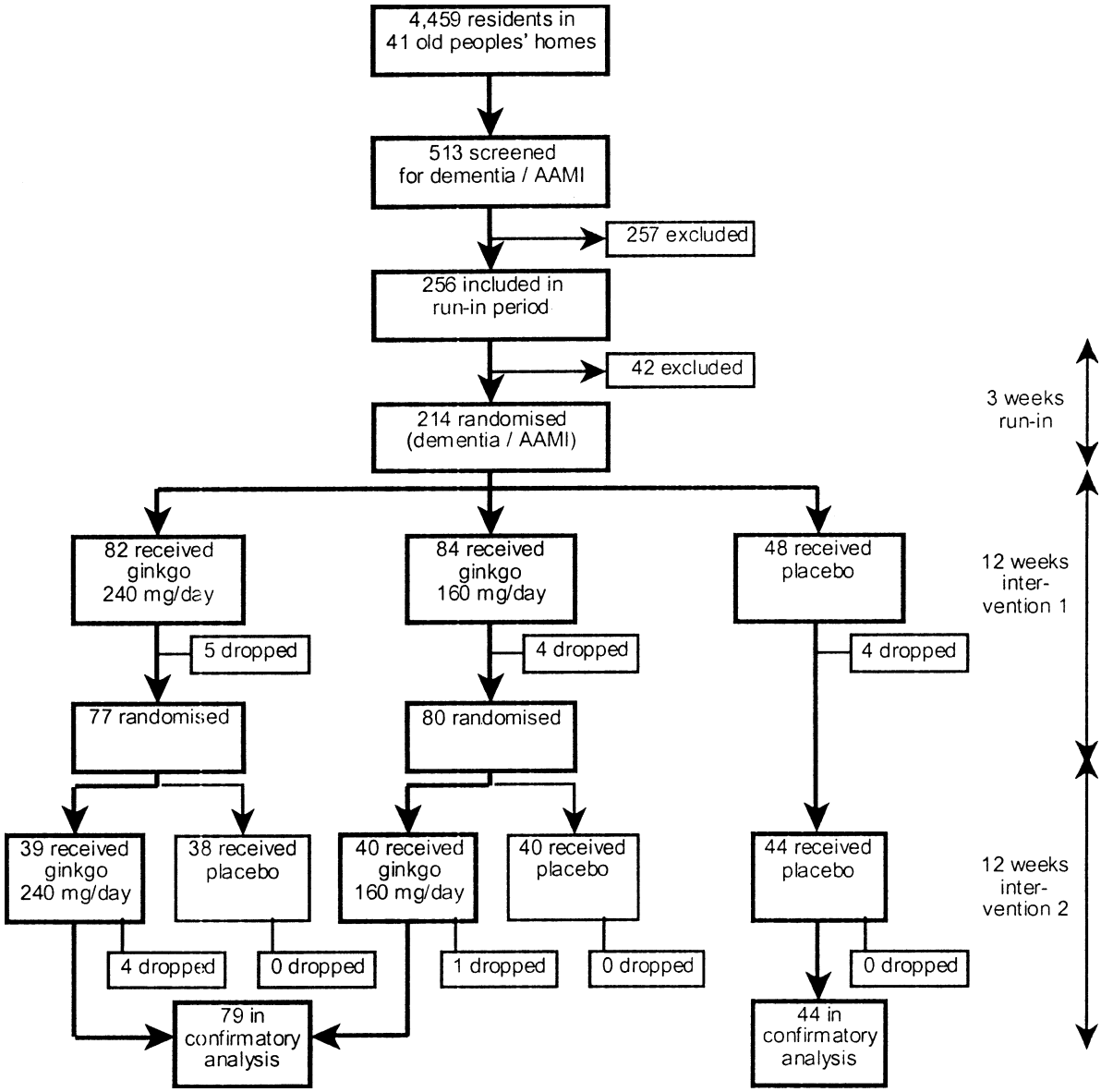


Fig. 1. Trial profile.

intelligence (IQ >80, global assessment); sufficient compliance; absence of placebo response during the run-in period; no expectation of premature withdrawal; absence serious comorbidity, in particular pathologic conditions considered nontreatable underlying causes of dementia; absence of sources of interference with the trial conduct (e.g., various neurologic disorders, brain traumata, tumors, severe infectious diseases, absorption disorders); absence of impermissible cointerventions, in particular drugs with a debilitating influence on cognitive functioning or with a claimed nootropic action (e.g., antipsychotic drugs, antiparkinson medication, neuroleptics, cholinergic therapy, antidepressants, and vasoactive drugs).

Anticipating a 20% dropout rate, we intended to include 300 eligible subjects. This number was based on several sample size calculations. Focusing on the treatment effect for Ginkgo versus placebo after 24 weeks of intervention, we calculated, for instance, that to detect a 3-point difference for the SKT as the outcome measure of interest (scale 0–27), a sample size of at least 66, 22 for each of both the Ginkgo groups and 22 for the placebo group, would be required (population SD = 4 scale-points, allocation ratio = 2:1, $\alpha = .05$, $\beta = .20$). With regard to a responder analysis, based on all three primary outcome measures, a sample size of approximately 210 would be sufficient to identify a twofold increase in response percentage under Ginkgo, assuming 20% responders in the placebo group (allocation ratio = 2:1, $\alpha = .05$, $\beta = .20$).

### 2.3. Intervention methods

Ginkgo was administered orally through two film-coated tablets per day, each containing 80 mg or 120 mg of the

extract, standardized on 24% ginkgoflavone glycosides and 6% terpene trilactones (ginkgolides, bilobalid). The placebo treatment consisted of two film-coated tablets per day, but these contained no Ginkgo extract. We made special efforts to check the comparability of the verum and the placebo tablets with respect to appearance, color, smell, taste, granularity, and solubility. To mimic the typical taste of ginkgo, 2 mg of quinine hydrochloride was added to the placebo tablets. The study participants consumed their daily dose at fixed times (morning and evening, during the meal), mostly under direct supervision of a nursing staff member. The packaging and labeling of the study medication were performed in accordance with the requirements of the Dutch Law of Medicine Supply and the guidelines for Good Clinical Practice.

### 2.4. Study outcomes

To evaluate the intended effects of Ginkgo, we defined primary outcome measures at three different levels, in agreement with recent standards for the evaluation of antidementia drugs and cognition enhancers [18–20].

Cognitive functioning at the psychometric level (neuropsychological testing) was assessed by the SKT. This test battery, which focuses on memory (perceptual motor speed) and attention, was conducted by trained interviewers. The SKT consists of nine 1-minute subtests that are partly speed-oriented and partly span-oriented (e.g., naming objects, arranging blocks, counting symbols, delayed recall of objects, recognition of objects). In our trial, we used three parallel versions. Scaled subtest scores are aggregated to a SKT total status score ranging from 0 (“very good”) to 27 (“very poor”).

Change in clinical signs (psychopathology) over time was assessed by the Clinical Global Impression, item 2 (CGI-2). This rating instrument expresses the global change in observable cognitive functioning directly on a transitional scale ranging from 1 (“very much improved”) to 7 (“very much deteriorated”). The CGI-2 was rated by the nursing staff in each old people’s home.

We measured cognition-related behavior by the Nürnberger Alters Alltagsaktivitäten Skala (NAA; Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living), which is part of the Nürnberger Alters Inventar (NAI; Nuremberg Gerontopsychological Inventory). The NAI is a German battery of psychometric tests, questionnaires, and observational rating scales aimed at the measurement of cognitive functioning, performance of daily life activities, well-being, and care needs [21]. The NAI-NAA, originally developed as a self-assessment scale, consists of 20 items that cover instrumental 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). In our trial, the NAI-NAA was rated by the nursing staff. Summation of the item scores yields a total score from 20 (“very good”) to 60 (“very poor”).

Outcomes were measured after 4, 8, 12, 18, and 24 weeks of treatment (NAA at 12 and 24 weeks only). The study protocol listed also several secondary outcome measures. The results for these measures have been published elsewhere [22]. We registered the occurrence of serious adverse events periodically. For this purpose we used a checklist of health complaints, which was filled out by the nursing staff at each measurement point. We also monitored the exposure to cointerventions and the compliance with the study medication (pill counting).

### 2.5. Statistical analysis

The statistical procedures were designed before the start of the trial as part of the study protocol. The confirmatory analysis of the study results was an intention-to-treat analysis comparing the 0- to 24-week changes in the scores on the three primary outcome measures between the subgroups who received Ginkgo (160 mg and 240 mg combined) and placebo during the entire 24-week treatment period. The hypothesis testing system was headed by a global multivariate Ordinary Least Squares (OLS) test [23] of the null-hypothesis that the subjects treated with EGb 761 and placebo would not differ for any of the three primary outcome measures. This overall test was followed by separate tests for each of the outcome measures in a hierarchical order (first SKT, next CGI-2, and finally NAA).

We also performed various descriptive analyses, multivariate analyses to adjust for baseline differences between the comparison groups, comparisons between the high-dose and the normal-dose Ginkgo groups, comparisons between groups with prolonged versus interrupted Ginkgo use, “per protocol” analyses restricted to the “valid” cases only, and various subgroup analyses.

In addition to the overall OLS test ($\alpha = .05$, one-sided), the statistical procedures included unpaired $t$ tests ($\alpha = .05$, one-sided) of the changes in SKT and NAA (continuous), Mann-Whitney U-tests of the differences in the CGI (categorical), multiple linear regression analyses to estimate the adjusted effect of study treatment on change in SKT and NAA (controlling for baseline differences in scores on several variables: age, gender, diagnostic subcategory [AAMI versus dementia], pre-treatment level of change in memory complaints, baseline value of the outcome measure concerned, assessed quality of old peoples’ homes, level of co-interventions during follow-up), and polychotomous logistic regression analyses to estimate the adjusted effect on CGI (controlling for the same set of independent variables). All participants with baseline and 24-week follow-up scores on the primary outcome variables were included in the intention-to-treat analysis. Missing values were substituted according to a predefined replacement scheme, with the last-observation-carried-forward principle as the main feature. To qualify for the per-protocol analysis, study subjects had to fulfill minimum requirements regarding compliance ($\geqslant$75% intake of prescribed medication), adherence to

the outcome measurement time table, and non-exposure to unpermitted co-interventions. We also performed a responder analysis. Study subjects with a clinically meaningful response to the study treatment for at least two of the three primary outcome variables were regarded as responders. Changes $\geq +3$ for the SKT, $\geq +4$ scale-points for the NAA, and a score $<4$ for the CGI-2 after 24 weeks of follow-up were considered clinically meaningful improvements.

Subgroup analyses and a comparative analysis of the number and type of serious adverse events completed the data analysis.

## 3. Results

A total of 39 old peoples' homes participated in the trial. These homes housed 4459 residents, 781 (18%) of whom were preselected by the nursing staff for presumed cognitive problems. We excluded 268 persons at an early stage of the patient selection procedure mainly because of comorbidity, co-medication, and refusal by the patient; 513 (12%) proceeded to the formal screening interview. Of these, 256 (6%) subjects qualified for the run-in period, and 214 met the remaining enrollment criteria and agreed to sign informed consent. These subjects, 63 with dementia and 151 with AAMI, were randomly allocated to the treatment regimens.

Thirteen of the study participants dropped out during the first 12 weeks, leaving 201 patients to be randomized for the second 12-week intervention period. Another five subjects withdrew during the second intervention phase. The dropouts were distributed as follows: Ginkgo 240 mg: 9/82 (11%); Ginkgo 160 mg: 5/84 (6%); placebo: 4/48 (8%). Reasons for attrition were death ($n = 8$), hospital admission or caregiver request ($n = 3$), serious concurrent illness ($n = 4$), and deliberative avoidance of further cognitive testing ($n = 3$).

Of the 214 randomized study subjects, 123 qualified for the confirmatory analysis, which compared ginkgo (240 or 160 mg/d) with placebo for 24 weeks. Table 1 demonstrates the absence of systematic baseline differences between the combined Ginkgo groups ($n = 79$) and the placebo group ($n = 44$).

The unadjusted effects of Ginkgo treatment are summarized in Table 2. The Ginkgo group and the placebo group showed a minor deterioration over the 24-week follow-up period. The differences between groups were small to non-existent and not statistically significant for any of the outcome measures (SKT: +0.4; CGI-2: +0.0; NAI-NAA: −0.0).

The result of the multivariate global OLS test does not allow us to reject the null hypothesis: $T_{OLS} = .34$ ($P = .37$). In this test, $T_{OLS}$ is the sum of the three $T$ statistics shown in Table 2 divided by the square root of the sum of the Pearson correlation coefficients for each pair of primary outcome measures.

Multiple linear regression analysis to control for potential confounding caused by baseline differences yielded similar estimates of the effects regarding SKT and NAA. For SKT, the adjusted difference in change over 24 weeks was +0.4 scale points (90% confidence interval [CI] −0.9–1.7) in favor of Ginkgo, which is equal to the unadjusted effect. Adjustment for confounding resulted in a shift of the NAA difference to −0.4 (90% CI −1.9–1.2), in favor of placebo. Polychotomous regression analysis on the 24-week CGI-2 score yielded an estimated odds ratio (OR) of 1.4 (95% CI 0.6–3.0), indicating that subjects in the Ginkgo group had 1.4 times more chance to have a favorable shift in their cognitive functioning recorded by the nursing staff. This increase in chance was not statistically significant.

The descriptive analysis of the 12-week intervention results revealed for SKT an effect of +1.0 (90% CI 0.0–2.0), for CGI an effect of −0.0 (90% CI −0.3–0.2), and for NAA an effect of +0.4 (90% CI –0.8–1.7). *t*-Testing produced a borderline significant effect for SKT only ($t = 1.69$, $P = .05$). Multiple linear regression analysis yielded regression coefficients corresponding with adjusted 12-week treatment effects of +1.0 (90% CI −0.1–2.1) and 0.3 (90%

Table 1
Distribution of baseline characteristics by intervention subgroup (placebo 0–24 weeks [$n = 44$] versus Ginkgo 160/240 mg 0–24 weeks [$n = 79$])[a]

| Characteristic | Placebo ($n = 44$) | Ginkgo ($n = 79$) |
|---|---|---|
| Gender | | |
| Male | 8 (18%) | 11 (14%) |
| Female | 36 (82%) | 68 (86%) |
| Communal living situation | | |
| Alone | 39 (89%) | 70 (89%) |
| Together | 5 (11%) | 9 (11%) |
| Level of cognitive impairment | | |
| Mild | 20 (46%) | 33 (42%) |
| Moderate | 24 (55%) | 46 (58%) |
| Perceived memory complaints (6-month pretreatment period) | | |
| Increased | 16 (36%) | 32 (41%) |
| The same/decreased | 28 (64%) | 46 (59%) |
| State of dementia | | |
| Dementia (mild/moderate) | 13 (30%) | 23 (29%) |
| AAMI | 31 (71%) | 56 (71%) |
| Age, y | 82.5(5.8) | 82.6 (5.1) |
| Quetelet index, kg/m$^2$ | 24.9 (3.7) | 24.9 (3.3) |
| MMSE | 18.7 (4.6) | 18.0 (4.9) |
| MAC-Q, modified, assessed by patient (subjective memory complaints) | 12.7 (2.8) | 12.2 (3.0) |
| MAC-Q, modified, assessed by nursing staff (subjective memory complaints) | 15.2 (4.6) | 16.4 (4.3) |
| SKT (memory and attention) | 14.1 (4.6) | 15.6 (4.1) |
| NAI-NAA, assessed by nursing staff (activities of daily life) | 42.0 (8.5) | 44.3 (7.2) |

*Abbreviations*: MMSE, Mini-Mental State Examination; MAC-Q, Memory Assessment Clinics Questionnaire; SKT, Syndrom Kurz Test; NAI, Nürnberger Alters Inventar (Nuremberg Gerontopsychological Inventory); NAA, Nürnberger Alters Alltagsaktivitäten (Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living).

[a] Values are absolute numbers (percentages) for categorical variables and mean values (standard deviations) for (semi) continuous variables. Scale ranges (underlining indicates the most favorable extreme): MMSE: 0–30; MAC-Q: 5–25; SKT: 0–27; NAI-NAA: 20–60.

Table 2
Comparison of the mean baseline scores, mean 24-week follow-up scores, and mean week 0–24 changes in score for SKT, CGI-2, and NAA for the placebo group ($n = 44$), the Ginkgo high-dosage group ($n = 39$), and the Ginkgo usual dosage group ($n = 40$)

| Outcome variable | Intervention subgroup | Mean 0-week baseline score[a] | Mean 24-week follow-up score[a] | 0–24-week change in score[b] | | 0–24-week change[d] difference[b] | | $T$ statistic ($P$ value, one-sided) |
|---|---|---|---|---|---|---|---|---|
| | | | | Mean | (SD)[c] | Mean | (90% CI) | |
| Memory and attention (SKT) | Placebo | 14.1 | 15.3 | −1.2 | (3.8) | | | .53 |
| | Ginkgo 160 + 240 | 15.6 | 16.4 | −0.8 | (4.1) | 0.4 | (−0.9–1.7) | (.30) |
| | Ginkgo 160 | 15.8 | 16.4 | −0.7 | (4.4) | | | .32 |
| | Ginkgo 240 | 15.5 | 16.5 | −1.0 | (3.9) | −0.3 | (−1.9–1.3) | (.37) |
| Clinical global impression (CGI-2) | Placebo | | 4.3 | | (1.1) | | | .23 |
| | Ginkgo 160 + 240 | | 4.3 | | (1.2) | 0.0 | (−0.3–0.4) | (.41) |
| | Ginkgo 160 | | 4.2 | | (1.1) | | | 1.10 |
| | Ginkgo 240 | | 4.4 | | (1.2) | −0.3 | (−0.7–0.2) | (.14) |
| Activities of daily life (NAA) | Placebo | 42.0 | 43.3 | −1.4 | (5.5) | | | −.00 |
| | Ginkgo 160 + 240 | 44.3 | 45.7 | −1.4 | (4.8) | −0.0 | (−1.6–1.6) | (.50) |
| | Ginkgo 160 | 44.0 | 45.2 | −1.2 | (4.9) | | | −.27 |
| | Ginkgo 240 | 44.7 | 46.2 | −1.5 | (4.8) | −0.3 | (−2.1–1.5) | (.40) |

*Abbreviations*: SKT, Syndrom Kurz Test; CGI-2, Clinical Global Impression, item 2; NAA, Nürnberger Alters Alltagsaktivitäten (Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living); SD, standard deviation; CI, confidence interval.

[a] Range of status scores (underlining indicates the most favorable extreme): SKT: 0–27; CGI-2: 1–7; NAA: 20–60.

[b] Range of change scores (underlining indicates the most favorable extreme): SKT: −27–+27; NAA: −40–+40.

[c] For CGI-2: SD 24-week follow-up score.

[d] For CGI-2: 24-week follow-up difference: mean (90% CI).

CI –1.0–1.5) for SKT and NAA, respectively. Polychotomous logistic regression analysis on the 12-week CGI-2 score yielded an estimated OR of 1.3 (95% CI 0.6–2.7).

Table 2 also illustrates that a dose-effect relationship is lacking, which is not surprising, given the absence of a beneficial effect for the combined Ginkgo groups. The results of neither a nonparametric Kruskal-Wallis test nor more powerful tests for trend supported a dose-related effect of Ginkgo. An equivalent analysis of the 12-week follow-up data yielded similar findings, except for a significantly better result regarding the change in NAA scores for the high-dose compared with the low-dose Ginkgo group. Prolongation compared with discontinuation of Ginkgo use after 12 weeks is not accompanied by more beneficial 24-week outcomes (Table 3).

After 24 weeks of treatment, 27 study participants could be classified as "responder" (Table 4). The subgroup that received Ginkgo during the entire period included 14% responders (11/79); the placebo group included 18% (8/44). A statistically significant association between responder status (yes/no) and intervention subcategory was absent ($\chi^2 = .39$, $P = .53$). After 12 weeks of follow-up, we counted 29 responders: 14% (22/160) of the patients on Ginkgo and 16% (7/44) on placebo.

The findings of the per protocol analyses involving 112 study subjects after 24 weeks and 187 after 12 weeks of treatment did not alter the conclusions based on the intention-to-treat analyses.

Stratified analyses were conducted to identify subgroup-specific effects. Compared with demented patients, AAMI patients seemed to have benefitted slightly more from 24 weeks of treatment with Ginkgo 240 mg or 160 mg. A difference in NAA change in favor of placebo was found for the dementia subgroup: –3.4 (90% CI −6.0–−0.9). However, this effect was not statistically significant after adjustment for confounding: −1.9 (90% CI −4.2–0.5). A statistically significant effect on change in SKT score in favor of Ginkgo was found for the AAMI subgroup before (+1.3; 90% CI 0.1–2.6) and after (+1.4; 90% CI 0.0–2.7) adjustment for confounding. Additional subgroup analyses were performed for age (<84 versus ⩾84 years), MMSE baseline score (<19 versus ⩾19 points), SKT baseline score (8–15 versus 16–27 points), and the number of so-called biological life events (BLEs), such as history of general anesthesia, history of brain damage, neurologic disorders, and alcohol abuse, which are believed to have a negative impact on cognitive status (0–2 versus 2–5 BLEs). We failed to identify a consistent effect of Ginkgo for any of these subgroups.

During the first intervention period, 111 (52%) of the 214 study subjects were identified with at least one health complaint. The adverse event rates were 46/82 (56%), 44/84 (52%), and 21/48 (44%) for Ginkgo 240 mg, Ginkgo 160 mg, and placebo, respectively. Dizziness ($n = 58$), nervousness ($n = 49$), and headache ($n = 32$) were the most frequently reported signs. During the second intervention period, symptoms were reported for 113 (56%) of the 201 remaining study subjects, with the treatment-specific rates being 18/39 (46%), 16/40 (40%), and 79/122 (65%), respectively. A clear association with type of treatment did not exist. During the entire trial period, 35 serious adverse events were registered: 8 deaths, 25 hospital admissions, and 2 cases who had developed a malignancy. These events occurred in 26/166 (16%) of the subjects initially treated with Ginkgo and in 9/48 (19%) with placebo. For only one case (a placebo user) was a possible association with study treatment hypothesized.

Table 3
Comparison of the mean baseline scores, mean 24-week follow-up scores, and mean week 0–24 changes in score for SKT, CGI-2, and NAA, Ginkgo 160/240 + Ginkgo 160/240 ($n = 79$) versus Ginkgo 160/240 + placebo ($n = 78$) versus placebo + placebo ($n = 44$)

| Variable | Intervention subgroup | Mean 0-week baseline score[a] | Mean 24-week follow-up score[a] | 0–24-week change in score[b] | | | 0–24-week change[d] difference[b] | | $T$ statistic ($P$ value, one-sided) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean | (SD)[c] | $F$ statistic | Mean | (90% CI) | |
| Memory and attention (SKT) | Placebo + placebo | 14.0 | 15.3 | −1.2 | (3.8) | 0.17 | | | |
| | Ginkgo + placebo | 15.1 | 16.1 | −1.1 | (3.4) | | | | .38 |
| | Ginkgo + ginkgo | 15.6 | 16.4 | −0.8 | (4.1) | | 0.2 | (−0.8–1.2) | (.35) |
| Clinical global impression (CGI-2) | Placebo + placebo | | 4.3 | | (1.1) | 0.10 | | | |
| | Ginkgo + placebo | | 4.4 | | (1.1) | | | | (.33) |
| | Ginkgo + ginkgo | | 4.3 | | (1.2) | | 0.1 | (−0.2–0.4) | −.45 |
| Activities of daily life (NAA) | Placebo + placebo | 42.0 | 43.3 | −1.4 | (5.5) | 0.25 | | | |
| | Ginkgo + placebo | 43.2 | 44.1 | −0.9 | (4.5) | | | | −.67 |
| | Ginkgo + ginkgo | 44.3 | 45.7 | −1.4 | (4.8) | | −0.5 | (−1.7–0.7) | (.25) |

*Abbreviations*: SKT, Syndrom Kurz Test; CGI-2, Clinical Global Impression, item 2; NAA, Nürnberger Alters Alltagsaktivitäten (Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living); SD, standard deviation; CI, confidence interval.

[a] Range of status scores (underlining indicates the most favorable extreme): SKT: 0–27; CGI-2: 1–7; NAA: 20–60.

[b] Range of change scores (underlining indicates the most favorable extreme): SKT: −27–+27; NAA: −40–+40.

[c] For CGI-2: SD 24-week follow-up score.

[d] For CGI-2: 24-week follow-up difference: mean (90% CI).

## 4. Discussion

Our trial did not reveal any benefit of Ginkgo over placebo. With regard to SKT and CGI, we found small differences after 24 weeks of treatment in favor of Ginkgo. These differences were neither statistically significant nor clinically meaningful. The difference was also negligible with respect to NAA. Adjustment for possible confounding by several prognostic variables did not alter these results. After 12 weeks of follow-up, a small but statistically significant effect was registered for SKT in favor of Ginkgo. The effects for NAA and CGI-2 were not statistically significant. Adjustment of the estimated effects by multivariate regression analysis did not change the results. A responder analysis showed almost equal proportions of responders for Ginkgo and placebo after 24 and 12 weeks of intervention. We also did not find a dose-effect relationship or a persistence of any effect after discontinuation of Ginkgo treatment.

To assess to what extent various sources of bias may have produced spurious results, we reflect critically on the adequacy and comparability of the study population, intervention, and outcome measures.

### 4.1. Adequacy

We have deliberately selected residents of old peoples' homes as the source population for our trial to optimize the level of adherence to the study medication and the outcome measurement time schedule. This recruitment strategy has caused an over-representation of the very old (mean age 84 years) and a high level of co-morbidity among the study participants. Moreover, we can imagine that the protective living conditions make residents of old peoples' homes feel less conscious and worried about their cognitive functioning. The provided care and shelter may extinguish some mental challenges that elderly people living in the open community have to cope with. This may also have compromised the correct classification of eligible study subjects because the assessment of the impact of cognitive abilities on the level of social functioning plays a decisive role in the differentiation

Table 4
Number of patients with clinically meaningful improvements for SKT, CGI, and NAA after 24 and 12 weeks of follow-up (intention-to-treat population)

| Number of outcome variables with clinically meaningful improvement after 24 weeks[a] | Placebo + placebo | | Ginkgo 160 + Ginkgo 160 | | Ginkgo 240 + Ginkgo 240 | | Ginkgo 160 + placebo | | Ginkgo 240 + placebo | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $n$ | % |
| 3 variables | 1 | 2.3 | 1 | 2.5 | 1 | 2.6 | | 0.0 | 2 | 5.3 |
| 2 variables | 7 | 15.9 | 6 | 15.0 | 3 | 7.7 | 2 | 5.0 | 4 | 10.5 |
| 1 variable | 7 | 15.9 | 14 | 35.0 | 10 | 25.6 | 15 | 37.5 | 4 | 10.5 |
| 0 variables | 29 | 65.9 | 19 | 47.5 | 25 | 64.1 | 23 | 57.5 | 28 | 73.7 |
| Total | 44 | 100.0 | 40 | 100.0 | 39 | 100.0 | 40 | 100.0 | 38 | 100.0 |

*Abbreviations*: SKT, Syndrom Kurz Test; CGI-2, Clinical Global Impression, item 2; NAA, Nürnberger Alters Alltagsaktivitäten (Nurember Gerontopsychological Rating Scale for Activities of Daily Living).

[a] Clinically meaningful improvement: SKT: ⩾+3 points; CGI-2: <4 points; NAI-NAA: ⩾+4 points.

between dementia and nondementia forms of cognitive decline (see DSM-criterion C for dementia). We believe that part of the study subjects who have been assigned to the AAMI-subgroup in our trial would have deserved the diagnosis of dementia.

We have avoided making a distinction between Alzheimer dementia, vascular dementia, and other types of dementia. Given the nonclinical setting of our trial, we had to face constraints regarding the availability of medical information and the application of sophisticated diagnostic techniques. Moreover, until recently, this kind of information was considered not very relevant for the prescription of Ginkgo—given its multiple mechanisms of action—and for the clinical management of dementia cases in continental Europe [24].

We applied a high-quality, standardized Ginkgo extract (EGb 761), with a significant exposure contrast between verum treatment (either $2 \times 80$ mg or $2 \times 120$ mg of active substance per day) and placebo. Much effort was paid to develop a valid placebo preparation. The distribution schedule, supervision by the nursing staff, and periodic pill counts were safeguards against an irregular or insufficient level of exposure to the active Ginkgo compounds. Potential noncompliers had been filtered out during the run-in phase. Unwanted interference with co-interventions was precluded by means of the enrollment criteria.

In selecting the outcome measures, we have attempted to satisfy the most recent guidelines for the evaluation of anti-dementia drugs [19,20] and to choose measures with documented evidence for validity, reliability, and sensitivity to change. The NAA and SKT are adapted to the specific needs of elderly people. In this trial we used parallel versions. The analysis of repeated measurements revealed a rather unstable pattern of change in the Ginkgo and placebo subgroups for each of the outcome measures (SKT, CGI, and NAA). This may reflect a lack of reliability but may also be considered an indication that the intervention effect apparently was too weak to overrule random measurement error.

### 4.2. Comparability

Selection bias at baseline was largely prevented through random allocation. Additional measures to enhance comparability included restriction of the study population by applying rigorous eligibility criteria and pre-stratification for diagnostic subgroup (dementia versus AAMI) and change in cognitive status during the 6-month pretreatment period (improvement or no change versus deterioration). Several other variables were taken into account in our stratified and multivariate regression analyses. A comparison of various baseline characteristics showed only minor, change-related differences between the intervention groups. The small numbers of dropouts during the entire 24-week intervention period were equally distributed over the initial Ginkgo and placebo groups.

To enhance the comparability of interventions, we pursued standardization of treatment conditions. Subjects with a recent history of potentially influential types of medical and social care were excluded beforehand. Any planned or spontaneously occurring co-interventions were registered and taken into consideration as part of the data analysis. Twenty-eight study subjects violated the predefined criteria for compliance with the study medication, 14 during the first part and another 14 during the second part of the trial. The noncompliance rate was 14% (23/166) for the initial Ginkgo group (doses combined) and 10% (5/48) for the initial placebo group. During the first 12 weeks, relevant changes in co-medication or care setting were notified for 19% (31/166) of the initial Ginkgo users (doses combined) and 17% (8/48) of the initial placebo users. These proportions amounted to 42% (33/79) and 32% (14/44) over the entire 24-week intervention period for the subgroups of Ginkgo and placebo users who qualified for the confirmatory analysis. A per-protocol analysis, excluding all study participants with registered protocol deviations of treatment or measurement, yielded the same results as the intention-to-treat analysis.

We are convinced that the outcomes were assessed under blind conditions. Study participants, caregivers, outcome assessors, and data analysts were all blinded. Checks after 4 and 18 weeks of intervention did not reveal an association between the actual and the perceived type of treatment for any of the outcome reviewers involved (patients, nursing staff, interviewers). The layout of the trial forced us to use many different raters and interviewers, who conducted the screening, baseline, and follow-up measurements. By and large, they were well prepared and dedicated to their job. The study protocol prescribed that, in general, repeated measurements for each study subject had to be conducted by the same rater or interviewer. We noted only a limited number of deviations from the pre-scheduled measurement timetable; these were mainly caused by practical circumstances (holidays, etc.).

The analysis of the study results was hampered by the occurrence of missing values. For instance, after 24 weeks, 27 of the 214 randomized subjects were left without one or more SKT subset scores, 18 without CGI assessment, and 34 without one or more NAA item scores. Based on the "last-observation-carried-forward" principle combined with the "mean value of valid items/subtests" principle, these missing values could be substituted for 24, 14, and 25 cases, respectively. The application of several other accepted methods of missing value replacement yielded comparable results. Moreover, the similarity between the results of the intention-to-treat and per-protocol analyses was striking, suggesting that the occurrence and the "repair" of missing values had not seriously affected the Ginkgo effect estimation. In summary, we do not believe that the trial results are biased by differential misclassification. We realize, however, that nondifferential misclassification may have caused some degree of extinction of a real existing effect.

### 4.3. Other considerations

The multi-purpose character of our study design made it less efficient for answering the main research question dealing with the efficacy of Ginkgo. The confirmatory analysis

dealt with 123 out of the 214 randomized subjects, with quite an imbalance between the contrasted treatments. An excess of study participants was allocated to the initial Ginkgo groups to enable answering the question regarding the persistence of any effect after stopping the Ginkgo treatment. Nevertheless, the trial had enough statistical power to be able to detect a meaningful treatment effect, at least for the total study population.

The results of our trial are dissenting from the results of the vast majority of previously reported Ginkgo trials in the field of cerebral insufficiency and dementia [25,26]. After the systematic review work of Kleijnen et al. [1,27], new evidence for a beneficial effect of Ginkgo was provided in several trials [2,28–35]; most of them had a higher methodologic quality and were more focused on dementia than the earlier trials. In a previous review, we identified nine Ginkgo trials (probably) focusing on patients with clear-cut dementia; eight focusing on patients with an AAMI-like diagnosis of cognitive impairment; 11 focusing on patients with noncognitive symptoms of cerebral insufficiency (e.g., tinnitus, vertigo, headache, etc.); five focusing on patients with cerebral insufficiency diagnosed by means of a more or less standardized checklist of cognitive and noncognitive symptoms; three focusing on patients with affective disorders, especially depressive mood, as the leading symptom of cerebral insufficiency; and 18 focusing on patients with cerebral insufficiency not clearly specified [36]. A beneficial Ginkgo effect was reported from the overwhelming majority of these trials. In the review by Kleijnen et al. [1], only 8 of the 40 studies were assessed to be of "acceptable" methodologic quality. We have noted that most later Ginkgo trials fulfilled considerably higher methodologic requirements regarding internal validity and study size. In addition to an improved methodologic quality, we noted a tendency over the years for smaller effects to be reported. Nevertheless, Letzel et al. concluded that only a few of the trials included in their review [24] met the current standards for the diagnosis of dementia (mild-to-moderate cases, accepted diagnostic criteria) and for the demonstration of a therapeutic effect (three levels of efficacy and clinical global assessment) [29,33]. In a recent systematic review of the clinical evidence of *G. biloba* preparations as a symptomatic treatment for dementia, Ernst and Pittler concluded that nine trials met the inclusion criteria and that these trials, although of varying methodologic quality, suggest that Ginkgo extract is more effective for dementia than placebo [37]. Oken et al. applied even stricter criteria in a meta-analysis of the efficacy of *G. biloba* on cognitive function in Alzheimer disease [38]. For the four studies that met all inclusion criteria, they found a modest but significant overall effect size of 0.40 ($P < .0001$), which can be translated into a 3% difference on the ADAS-Cog subtest. Wettstein compared the results of several antidementia trials, which all used the ADAS-Cog as a primary outcome measure, and found about the same effect for EGb 761 and four cholinesterase inhibitors (tacrine, donepezil, rivastigmine, and metrifonate) [39].

We believe that our study is one of the most rigorous trials conducted in this field, especially with regard to random allocation, placebo control, and blinded outcome measurement. Our trial results suggest that treatment with Ginkgo is not efficacious, irrespective of dose, in elderly patients with mild-to-moderate dementia or age-associated memory impairment. After a Bayesian approach, 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. Although we have noticed differences in study design and conduct between our trial and other trials, which are described into more detail elsewhere [6,7], we have not been able to refute the positive results of some recent trials in particular. These trials seemed to meet quite high methodologic standards and had several design aspects in common with our study. We cannot rule out the possibility that our trial has been an "outlier by chance."

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