Long-term use of standardised ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial

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Summary

Background Prevention strategies are urgently needed to tackle the growing burden of Alzheimer's disease. We aimed to assess efficacy of long-term use of standardised ginkgo biloba extract for the reduction of incidence of Alzheimer's disease in elderly adults with memory complaints.

Methods In the randomised, parallel-group, double-blind, placebo-controlled GuidAge clinical trial, we enrolled adults aged 70 years or older who spontaneously reported memory complaints to their primary-care physician in France. We randomly allocated participants in a 1:1 ratio according to a computer-generated sequence to a twice per day dose of 120 mg standardised ginkgo biloba extract (EGb761) or matched placebo. Participants and study investigators and personnel were masked to study group assignment. Participants were followed-up for 5 years by primary-care physicians and in expert memory centres. The primary outcome was conversion to probable Alzheimer's disease in participants who received at least one dose of study drug or placebo, compared by use of the log-rank test. This study is registered with ClinicalTrials.gov, number NCT00276510.

Findings Between March, 2002, and November, 2004, we enrolled and randomly allocated 2854 participants, of whom 1406 received at least one dose of ginkgo biloba extract and 1414 received at least one dose of placebo. By 5 years, 61 participants in the ginkgo group had been diagnosed with probable Alzheimer's disease (1·2 cases per 100 person-years) compared with 73 participants in the placebo group (1·4 cases per 100 person-years; hazard ratio [HR] 0·84, 95% CI 0·60–1·18; p=0·306), but the risk was not proportional over time. Incidence of adverse events was much the same between groups. 76 participants in the ginkgo group died compared with 82 participants in the placebo group (0·94, 0·69–1·28; p=0·68). 65 participants in the ginkgo group had a stroke compared with 60 participants in the placebo group (risk ratio 1·12, 95% CI 0·77–1·63; p=0·57). Incidence of other haemorrhagic or cardiovascular events also did not differ between groups.

Interpretation Long-term use of standardised ginkgo biloba extract in this trial did not reduce the risk of progression to Alzheimer's disease compared with placebo.

Funding Ipsen.

Lancet Neurol 2012; 11: 851–59

Published Online
September 6, 2012
http://dx.doi.org/10.1016/S1474-4422(12)70206-5

See Comment page 836

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Introduction

Prevalence of Alzheimer's disease is expected to quadruple by 2050.[1,2] A preventive intervention that delays disease onset by a few years could greatly reduce the burden of this disease on society and health-care systems,[3,4] as has been achieved in other chronic conditions.[5]

Few randomised trials have tested the efficacy of an intervention for the reduction of dementia incidence.[6–10] The shortage of such trials might partly be explained by numerous methodological challenges, including the need for an excellent safety profile because large numbers of healthy participants will receive the intervention for a long time, only a few of whom will develop dementia. Drugs investigated so far for either primary or secondary prevention of Alzheimer's disease include hormone replacement therapy, non-steroidal anti-inflammatory drugs, ginkgo biloba extract, vitamin supplements, and cholinesterase inhibitors. All have either failed to show efficacy or have been associated with safety concerns.[11,12]

Standardised ginkgo biloba extract is widely used in some countries by patients with cognitive disorders (eg, memory decline with ageing and Alzheimer's disease),[13] and observational research suggests that it might prevent Alzheimer's disease.[14] Plausible mechanisms of action against Alzheimer's disease include powerful antioxidant effects[15,16] and potential inhibition of caspase-3 activation and amyloid-β aggregation.[17] Standardised ginkgo biloba extract has a good safety profile, although some case reports have suggested an increased risk of bleeding.[18]

Subjective memory complaints in elderly individuals, especially if spontaneously expressed to a doctor,[19] are associated with an increased risk of dementia,[20] and have been linked to brain atrophy and amyloid-β deposition.[21] Therefore, some individuals who present to their doctors with such complaints might be in an early stage of mild cognitive impairment, and could thus be a target population for interventions aimed at prevention of Alzheimer's disease. This population could be identified

by primary health-care systems, thus enabling creation of large-scale public health prevention programmes for Alzheimer's disease.

In the GuidAge study, we aimed to assess the efficacy of standardised ginkgo biloba extract for reduction of the risk of conversion to Alzheimer's disease in elderly individuals spontaneously reporting memory complaints to their primary-care physician (PCP).

Methods

Study design and participants

The protocol for our multicentre, randomised, double-blind, placebo-controlled, parallel-group, 5 year study has been published previously,[22] and was approved by the Independent Ethics Committee of Toulouse University Hospital, Toulouse, France. Participants were recruited throughout France from March, 2002, to November, 2004, by 712 PCPs belonging to clinical research networks (Isoclin, EURAXI Pharma, MG Recherche, and PROCLINICA) or by staff at one of the 25 memory centres participating in the study. These centres were spread out across the country, and were located in 13 of the 22 regions in mainland France. The participating centres were selected on the basis of their proximity to the PCP networks. In the French health-care system, people with memory problems usually consult a PCP first, who might refer the patient to a specialist memory consultant for in-depth cognitive assessments, although patients are permitted to consult a memory centre without referral. All individuals aged 70 years or older who lived in the community and consulted one of the PCPs or memory centre for memory problems were eligible for screening. The initial screening visit was done by the PCP or memory centre investigators, and participants meeting the following selection criteria were retained: an identified proxy and a mini-mental state examination (MMSE)[23] score of more than 25, a Covi anxiety scale[24] score of less than 6, and a geriatric depression scale[25] score of less than 15. The proxy had to be available to accompany participants to memory centre visits, or at least be able to be contacted by telephone to provide information about the participant for the instrumental activities of daily living and clinical dementia rating (CDR) assessments. Before inclusion, all participants attended a validation visit at a memory centre in which participants meeting any of the following criteria were excluded: major objective memory impairment (free and cued selective reminding test [FCSRT][26] score <10th percentile for age, sex, and sociocultural level); CDR[27] of more than 0·5; a diagnosis of dementia (according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM-IV][28] and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA][29] criteria); major depression (DSM-IV criteria); or generalised anxiety (DSM-IV criteria). Participants with mild cognitive impairment were not excluded. Cholinesterase inhibitors were not to be used during trial participation.

Participants' subjective memory complaints were characterised at baseline with visual analogue scales measuring memory function and impairment in everyday life (score range 0–100, highest scores mean poorest function or most impairment) and with the McNair and Kahn Scale,[30] a short self-report questionnaire assessing cognitive difficulties in everyday activities (score range 0–80, highest scores mean most frequent or severest cognitive difficulties). All participants provided written informed consent at enrolment.

Randomisation and masking

We randomly allocated participants in a 1:1 ratio to standardised ginkgo biloba extract 120 mg (EGb761; Cara-Partners, County Cork, Ireland) twice per day in tablet form or placebo of identical appearance. Randomisation was computer-generated and stratified by centre with block sizes of four. Randomisation numbers were provided to study centres via a secure website. Participants and study investigators and personnel were masked to study group assignment. To mask the taste and smell of ginkgo biloba, placebo and active tablets were coated with the same excipients, and the placebo tablets contained quinine hydrochloride to mimic the bitter taste of ginkgo biloba (in case patients sucked or chewed the tablets rather than swallowing them with water as prescribed).

Procedures

Ginkgo biloba extract was purified and standardised to 24% ginkgo flavone glycosides and 6% terpene lactones (ginkgolides and bilobalide). We chose a 240 mg daily dose of EGb761 on the basis of suggested effectiveness in patients with dementia.[31,32]

Study drugs were supplied by the sponsor and provided to participants at follow-up visits with the recruiting doctor every 3 months. Concomitant diseases and treatments and spontaneously reported adverse events were also recorded during these visits. Unused medication was returned at the following visit. Adherence, assessed by tablet count, was defined as consumption of 75–150% of study drug during study participation. Participants were given more than 3 months worth of study drug to ensure they would be able to continue taking their study drug in the event that the next follow-up visit was delayed for any reason. Participants were asked to return any unused tablets at the following visit to estimate compliance (on the basis of the number of study tablets returned and the number of days elapsed since the previous visit). When participants did not return a sufficient number of unused tablets, their compliance level could be more than 100%.

Participants underwent annual cognitive, functional, and dementia assessments at their nearest participating memory centre. Investigators were trained by an expert

neurologist (P-JO), who was a member of the study's scientific committee, before study start and once per year thereafter to ensure standardisation of dementia diagnoses and cognitive testing.

The primary efficacy outcome was incidence of probable Alzheimer's disease according to DSM-IV[28] and NINCDS-ADRDA[29] criteria at 5 years. We assessed a combined outcome of Alzheimer's disease or mixed dementia (ie, Alzheimer's disease with a vascular component) as a secondary outcome. The vascular component was assessed on the basis of clinical history, neuropsychiatric profile, the progressive nature of symptoms, and in particular on the basis of imaging data, which was requested for all cases. All participants were assessed according to diagnostic criteria once per year (or more frequently if requested by PCPs) for all participants at memory centres. All diagnoses of dementia were reviewed by an independent primary outcome committee, made up of three neurologists and a neuropsychiatrist who were masked to group assignment and investigator identity. In cases of disagreement between the independent primary outcome committee and the memory centre investigator, the latter made the final decision. The independent primary outcome committee ensured that all diagnoses made by the memory centres complied with internationally recognised diagnostic criteria. When necessary, the committee could ask for further information about the patient, or suggest that complementary examinations be done to verify the diagnosis. In most cases, these procedures enabled consensus about the diagnosis to be reached between the memory centre investigator and the primary outcome committee. For several rare cases, when consensus could not be reached, the clinical diagnosis made by the memory centre investigator was prioritised, because the primary outcome committee did not physically see the patient. The main issue in these rare cases was the final aetiological diagnosis, especially determining the presence of a vascular component. Participants who were definitively diagnosed with dementia were subsequently excluded from the study.

We assessed cognitive, functional, and depressive statuses every year with the following tests: MMSE,[23] CDR,[27] FCSRT,[26] trail making test,[33] verbal fluency,[34] visual analogue scales, instrumental activities of daily living,[35] and geriatric depression scale.[25]

Participants who withdrew from the trial before the end of follow-up were asked to attend a retrieved dropout visit at a memory centre 5 years (±6 months) after their inclusion date to undergo cognitive assessments. Such participants were also asked to attend a visit to their PCPs, during which it was recorded whether they had been diagnosed with dementia since withdrawal from the study. If neither of these visits was done, PCPs were asked to complete a questionnaire detailing whether or not the participant had been diagnosed with Alzheimer's disease since discontinuation of the study.

We assessed safety every 3 months on the basis of monitoring of vital signs, physical and neurological examinations, and assessment of adverse events. We coded adverse events with the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0.

Statistical analysis

In the placebo group, we assumed Alzheimer's disease incidence would be 2·4% in the first year[19,36] and would increase by 10% in subsequent years, leading to a 5 year cumulative incidence of 13·8%. Assuming an annual dropout rate of 5% (including deaths), and proportional hazards, the target sample size was 2800 participants to detect a 25% reduction in incidence of Alzheimer's disease in individuals receiving standardised ginkgo biloba extract, with type I error of 0·05 and 80% power.

We included all participants who received at least one dose of study drug in the efficacy and safety analyses. For the primary analysis, we compared the incidence of Alzheimer's disease between the ginkgo and placebo groups with the log-rank test and produced hazard curves with the Kaplan-Meier method. We defined time to event as the time from drug delivery to the date of Alzheimer's disease diagnosis. Participants who were not diagnosed with Alzheimer's disease were censored

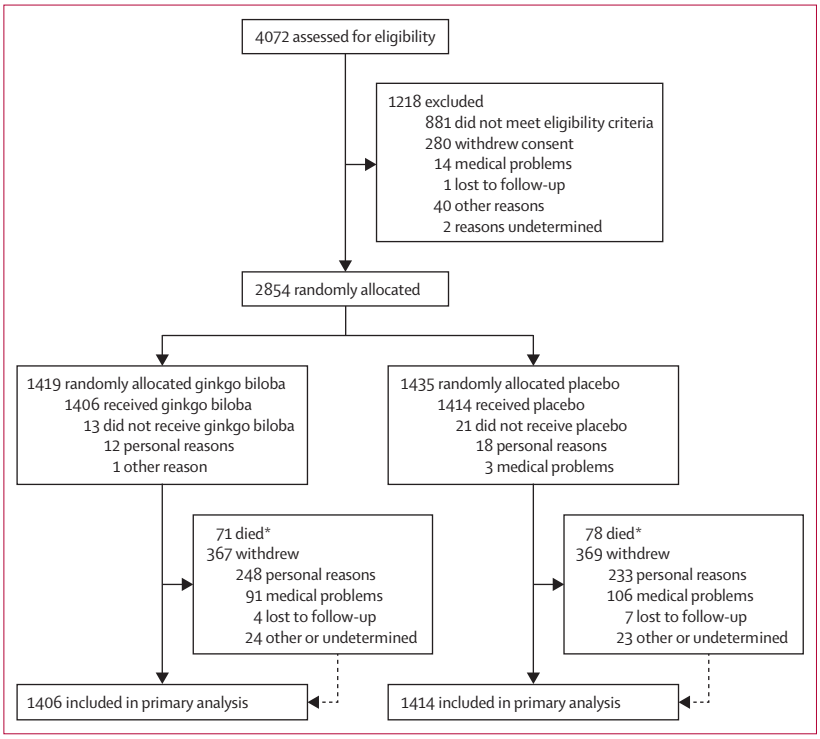

Figure 1: **Trial profile**
*Five additional deaths in the ginkgo biloba group and four additional deaths in the placebo group occurred within 30 days of the last intake of study drug, but after the participant had either completed or withdrawn from the study for another reason.

at the date of their last memory centre visit. We calculated hazard ratios with the Cox proportional hazards model. The proportional hazards assumption was verified by testing the treatment-by-time interaction in the Cox model.

Cases of Alzheimer's disease diagnosed according to retrieved dropout visits were included in sensitivity analyses, but not the primary analysis, because PCP reports of Alzheimer's disease diagnoses could not be validated in the same way as those obtained during study follow-up visits.

We also assessed the incidence of a diagnosis of dementia in 13 planned subgroups defined in the statistical analysis plan, which was finalised before data were unmasked and analysis began. Several subgroups were defined by the presence of potential Alzheimer's disease risk factors (*APOE* ε4 genotype, poor cognitive function [MMSE ≤27 or CDR 0·5], physical status [unable to do the one leg balance test], advanced age [>80 years], male sex, and no alcohol consumption), or cardiovascular risk factors (hypertension, diabetes, hypercholesterolaemia, and overweight) at baseline, because differences in the risk of a poor outcome and differences in underlying pathophysiology might give rise to heterogeneity of effects.[37] We investigated whether efficacy differed by CDR status and so we assessed efficacy in those who were cognitively normal at baseline (CDR 0) and those with some form of cognitive impairment (CDR 0·5). Also, because we postulated that a specific period of exposure would be needed for the ginkgo extract to have an effect,[14] we compared the risk of Alzheimer's disease in participants who took either standardised ginkgo biloba extract or placebo for at least 4 years. This cut-off was chosen and prespecified by the scientific committee. Interactions between subgroup variables and intervention group were tested in Cox models (including all participants with non-missing subgroup data at baseline). For

	Standardised ginkgo biloba extract (n=1406)	Placebo (n=1414)
Age, years	76·3 (4·4)	76·3 (4·4)
Sex, female	926 (66%)	954 (67%)
Education level*		
No formal education	188 (13%)	200 (14%)
Primary school certificate	532 (38%)	506 (36%)
Secondary education, no high-school diploma	324 (23%)	348 (25%)
High-school diploma (baccalaureate) or higher	360 (26%)	358 (25%)
Medical history		
Hypertension	794 (56%)	773 (55%)
Diabetes	143 (10%)	120 (8%)
Hypercholesterolaemia	439 (31%)	419 (30%)
Duration of memory complaint, months	39·7 (22·9–63·7)	39·0 (22·6–61·8)
McNair and Kahn Scale score (out of 80)	26·9 (12·1)	26·1 (11·9)
VAS: memory functioning (out of 100)	58·2 (16·7)	58·6 (17·3)
VAS: consequences of memory problems in everyday life (out of 100)	68·3 (22·0)	68·5 (22·8)
Mini-mental state examination	27·6 (1·9)	27·6 (1·9)
Clinical dementia rating		
0	642 (46%)	665 (47%)
0·5	762 (54%)	746 (53%)
>0·5	1 (<1%)	0
≥1 limitation in instrumental activities of daily living (out of 4)	110 (8%)	122 (9%)
Free and cued selective reminding test		
Free recall (out of 48)	24·7 (6·9)	25·2 (7·2)
Total recall (out of 48)	44·3 (3·8)	44·3 (4·1)
Delayed free recall (out of 16)	9·6 (3·2)	9·7 (3·3)
Delayed total recall (out of 16)	15·2 (1·3)	15·2 (1·5)
Trail making test, s		
Part A	55·1 (23·2)	54·5 (24·3)
Part B	133·4 (67·3)	135·2 (73·6)
Verbal fluency, 2 min score		
Categorical fluency	26·6 (7·5)	26·9 (7·7)
Lexical fluency	17·4 (7·2)	17·5 (7·2)
Geriatric depression scale (out of 30)	6·7 (4·1)	6·6 (3·9)
Covi anxiety scale (out of 12)		
0	515 (37%)	554 (39%)
1	332 (24%)	316 (22%)
2	251 (18%)	219 (15%)
3	180 (13%)	192 (14%)
4	92 (7%)	103 (7%)
≥5	34 (2%)	29 (2%)
Systolic blood pressure	134·4 (11·3)	134·2 (11·1)
Diastolic blood pressure	76·6 (7·2)	76·7 (7·2)
Body mass index, kg/m²	26·1 (4·1)	26·0 (4·1)
Smoking status		
Never	1033 (73%)	1048 (74%)
Current	54 (4%)	39 (3%)
Former	319 (23%)	327 (23%)
Alcohol consumption, g per day	0 (0–10)	0 (0–10)
Able to carry out the 5 s one-leg balance test	1159 (82%)	1166 (82%)
APOE ε4†	215 (22%)	242 (25%)

Data are mean (SD), n (%), or median (IQR). VAS=visual analogue scale. *Level of education was measured in terms of the highest diploma obtained. †Data for 1960 participants (985 participants were analysed in the ginkgo biloba group, and 975 in the placebo group).

Table 1: **Baseline characteristics**

interaction tests with an unadjusted p<0·05, we calculated the hazard ratio (HR) for the different values of the covariate considered. p values shown are not corrected for multiple comparisons. These analyses were not adjusted because they were classed as exploratory subgroup analyses.

We used marginal Cox models to estimate HRs for treatment-emergent adverse events (apart from deaths, which were analysed with a standard Cox model) occurring up to 30 days after the last dose of study drug or placebo. Participants without adverse events were censored at date of death or 30 days after last intake of study drug or placebo. Marginal Cox models took into account within-participant correlations via the robust sandwich estimate for the covariance matrix.[38]

Initial statistical analyses were done by Biotrial (Rennes, France) and reviewed by Bruno Scherrer (Bruno Scherrer Conseil, Saint Arnoult en Yvelines, France). The analyses were repeated by an independent statistician (Christelle Cantet, Gérontopôle, Toulouse University Hospital, Toulouse, France) who had access to all of the raw data. The results of the analyses of the independent statistician, which were concordant with the initial analyses, are presented in this article. All analyses were done with SAS version 9.1.

This study is registered with ClinicalTrials.gov, number NCT00276510.

Role of the funding source

The study sponsor was involved in study centre set-up and monitoring, preparation and distribution of ginkgo biloba (EGb761) and placebo, yearly organisation of training sessions for memory centre investigators, and data collection and monitoring, working closely with the investigators. Data analysis for this manuscript was done by an independent, publicly funded statistician employed by Toulouse University Hospital. No private funding or compensation for these analyses was received. BV, NC, SA, PG, and HM-F had full access to the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile and table 1 shows baseline characteristics for the 2820 patients who received at least one dose of study drug or placebo.

2835 (99%) of 2854 eligible participants were recruited by a PCP, and 19 were recruited by a memory centre. Compared with included participants, individuals who refused to participate were older (mean 77·8 years [SD 5·2] for non-participants *vs* 76·3 years [4·4] for participants; p<0·0001), had lower MMSE scores (27·3 [1·8] *vs* 27·8 [1·7]; p<0·0001), had lower values for body-mass index (25·4 [4·0] *vs* 26·1 [4·1]; p=0·0084), consumed less alcohol (4·5 g per day [8·1] *vs* 7·5 g per day [11·9]; p<0·0001), had higher anxiety Covi scores (p<0·0001), had a shorter duration of memory complaints (43·5 months [41·0] *vs* 51·7 months [50·1]; p=0·0013), and were more likely to be never smokers (p=0·0057) or women (202 women [75%] *vs* 1900 women [67%]; p=0·0060).

The median duration of follow-up was 5·0 years (IQR 2·9–5·1). Proportions of participants withdrawing from the study and their reasons for doing so were much the same in both groups (figure 1). The most common explanations were personal reasons, such as withdrawal of informed consent, relocation, or change of PCP.

Participants who completed the trial did not differ from those individuals who did not complete the study for the following baseline variables: sex, level of education, vascular risk factors, instrumental activities of daily living scale scores, anxiety, smoking status, alcohol consumption, *APOE* genotype, body-mass index, duration of memory problems, or subjective cognitive measures. However, patients who did not complete the study were older than were study completers (77·3 years [SD 4·7] for non-completers *vs* 75·7 years [4·2] for completers; p<0·0001) and had worse baseline cognitive scores (MMSE 27·4 [SD 2·0] *vs* 27·8 [1·8], p<0·0001;

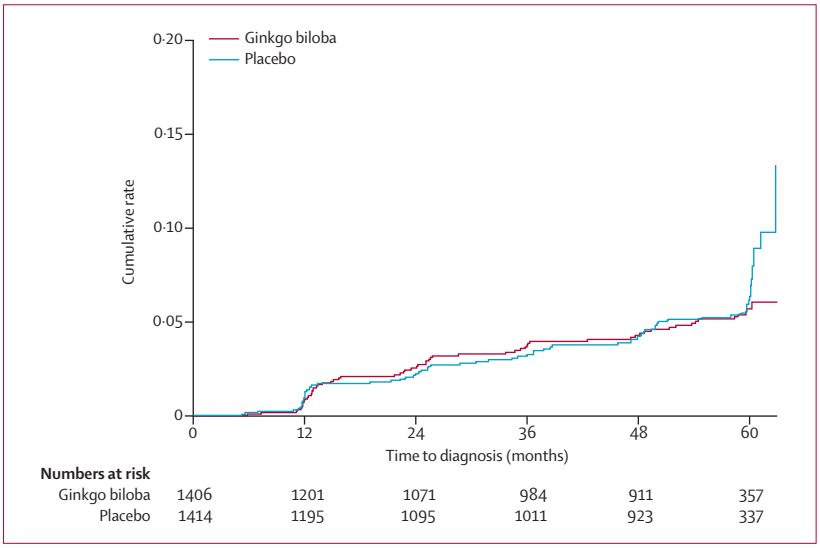

Figure 2: **Cumulative incidence of Alzheimer's disease**

	Standardised ginkgo biloba extract		Placebo		Hazard ratio (95% CI)	p value*
	Cases (number exposed)	Incidence per 100 person-years	Cases (number exposed)	Incidence per 100 person-years		
1 year	10 (1406)	0·80	14 (1414)	1·12	0·72 (0·32–1·61)	0·416
2 years	20 (1201)	1·78	12 (1195)	1·07	1·66 (0·81–3·40)	0·159
3 years	13 (1071)	1·27	12 (1095)	1·15	1·11 (0·51–2·43)	0·796
4 years	5 (984)	0·53	9 (1011)	0·94	0·57 (0·19–1·69)	0·302
≥5 years†	13 (911)	1·51	26 (923)	3·01	0·49 (0·25–0·96)	0·034

*Log-rank analysis. †Diagnoses up to 63 months, because the final assessment could be within 3 months either side of 5 years.

Table 2: **Incidence of probable Alzheimer's disease, by year of study**

FCSRT free recall 23·9 [7·1] *vs* 26·1 [6·6], p<0·0001; trail making test part A 57·8 [25·5] *vs* 52·4 [21·8], p<0·0001; categorical verbal fluency 25·8 [7·3] *vs* 27·6 [7·6], p<0·0001) and CDR status (CDR 0·5 for 521 non-completers [59%] *vs* 843 [48%] completers, p<0·0001).

Overall, 2487 (95%) patients adhered to their allocated intervention. (1228 [95%] in the treated group and 1259 [95%] in the placebo group). We did not identify any breaks in masking.

See Online for appendix

	Patients	Standardised ginkgo biloba extract	Placebo	Hazard ratio (95% CI)*	p value†
APOE ε4 positive	457	12 (215)	14 (242)	1·05 (0·49–2·28)	0·237
Hypertension at baseline	1567	28 (794)	41 (773)	0·65 (0·40–1·04)	0·120
Diabetes at baseline	263	10 (143)	8 (120)	1·05 (0·41–2·66)	0·589
Hypercholesterolaemia at baseline	858	21 (439)	21 (419)	1·02 (0·56–1·86)	0·455
Aged >80 years at baseline	497	17 (244)	16 (253)	0·97 (0·49–1·92)	0·580
Sex, male	940	14 (480)	32 (460)	0·43 (0·23–0·80)	0·011‡
MMSE ≤27 at baseline	1188	40 (579)	44 (609)	0·95 (0·62–1·46)	0·540
Body-mass index ≥27 at baseline	1059	19 (532)	32 (527)	0·59 (0·34–1·05)	0·110
No alcohol consumption at baseline	1523	46 (761)	41 (762)	1·09 (0·72–1·67)	0·028§
CDR 0·5 at baseline	1508	50 (762)	57 (746)	0·87 (0·59–1·27)	0·745
CDR 0 at baseline	1307	11 (642)	15 (665)	0·75 (0·35–1·64)	0·745
Unable to do one leg balance test at baseline	466	12 (235)	18 (231)	0·60 (0·29–1·25)	0·302
Study treatment intake ≥4 years	1911	15 (948)	28 (963)	0·53 (0·28–0·99)	0·049¶

Data are number of events (number at risk), unless otherwise stated. MMSE=mini-mental state examination. CDR=clinical dementia rating. *Ginkgo biloba *vs* placebo in subgroups of participants. †Treatment interaction test; p values are not adjusted for multiple comparisons. ‡For women (unplanned analysis; n=1880), the hazard ratio was 1·16 (95% CI 0·76–1·76). §For patients who consumed >0 g alcohol per day at baseline (unplanned analysis; n=1273) the hazard ratio was 0·47 (95% CI 0·25–0·88). ¶For patients who received study treatment for ≤4 years (unplanned analysis; n=907), the hazard ratio was 1·07 (95% CI 0·71–1·62).

Table 3: **Subgroup analyses**

	Standardised ginkgo biloba extract (n=1406)	Placebo (n=1414)	Hazard ratio (95% CI)	p value
Death	76	82	0·94 (0·69–1·28)	0·68
Stroke, overall	65	60	1·12 (0·77–1·63)	0·57
Ischaemic (transient ischaemic attack and ischaemic stroke)	37	37	1·03 (0·64–1·65)	0·90
Haemorrhagic stroke	5	3	1·72 (0·41–7·22)	0·46
Other	23	20	1·19 (0·64–2·19)	0·59
Haemorrhagic events, overall	148	164	0·93 (0·73–1·18)	0·55
Gastrointestinal	29	32	0·93 (0·54–1·62)	0·81
Vascular	26	38	0·70 (0·42–1·18)	0·19
Nervous system (including haemorrhagic stroke)	9	5	1·85 (0·62–5·56)	0·27
Cardiac disorders	341	354	0·99 (0·82–1·20)	0·93
Cardiac failure	46	51	0·93 (0·58–1·48)	0·76
Angina pectoris	33	34	1·00 (0·59–1·71)	0·99
Myocardial infarction	13	18	0·74 (0·36–1·55)	0·43

Data are number of events, not number of patients with an event, except for the numbers in the column headings.

Table 4: **Adverse events**

For the primary outcome, 61 of 1406 participants who received standardised ginkgo biloba extract were diagnosed with probable Alzheimer's disease compared with 73 patients who received placebo (HR 0·84, 95% CI 0·60–1·18; p=0·306). Incidence of disease was 1·2 per 100 person years in the ginkgo group compared with 1·4 per 100 person-years in the placebo group. Figure 2 shows the cumulative incidence of Alzheimer's disease. We noted a significant treatment-by-time interaction for the incidence of probable Alzheimer's disease (p=0·043), suggesting that the proportional hazards assumption was violated and that there was a non-constant HR over time (table 2), as suggested in the survival curve (figure 2). Table 3 presents results of the exploratory subgroup analyses.

70 participants receiving ginkgo biloba extract were diagnosed with pure Alzheimer's disease or mixed dementia (combined outcome; 1·4 per 100 person-years) compared with 84 participants receiving placebo (1·6 per 100 person-years). The between-group difference was not significant (p=0·267) and the proportional hazards assumption was not met (treatment-by-time interaction p=0·019).

A sensitivity analysis including cases of Alzheimer's disease identified through retrieved dropout visits (from 41 visits) and PCP reports (from 62 visits and 202 questionnaires) produced much the same results as the primary analysis; we noted 69 cases of Alzheimer's disease in the ginkgo biloba extract group and 85 cases in the placebo group (p=0·202). The proportional hazards assumption was not met (treatment-by-time interaction p=0·010).

Incidence of adverse events was much the same in both groups, with no significant difference in the incidence of serious adverse events, including death, haemorrhagic events, stroke (ischaemic or haemorrhagic), or cardiac disorders (table 4). Long-term administration of standardised ginkgo biloba extract at 240 mg daily did not affect vital signs, physical function, or neurological function.

The appendix contains further details of the post-hoc analyses of treatment-by-time interaction.

Discussion

Effective and safe prevention strategies are urgently needed to tackle the growing public health burden of Alzheimer's disease, and the efficacy of any such intervention needs to be shown through randomised controlled trials. GuidAge is only the third dementia prevention trial to be completed and is the first to be done outside of the USA (panel). We aimed to assess the efficacy of 5 years' administration of a standardised ginkgo biloba extract, which is widely used by patients with cognitive disorders in several countries,[13] in lowering the risk of Alzheimer's disease. However, we were unable to show a protective effect in this setting.

Our trial was unique in that the study population was made up of more than 2500 individuals aged 70 years

and older, who were free of dementia at baseline, and who had spontaneously reported subjective memory complaints to their PCP. Study drug or placebo were provided by PCPs, who also recorded adverse events; annual dementia assessments were done in specialist memory centres, and all dementia diagnoses were verified by an independent adjudication committee.

In GuidAge, as in another preventive trial,[41] the risks of Alzheimer's disease in the ginkgo biloba extract group compared with the placebo group were not proportional with time. Assessment of the survival curves suggests that the difference arose mainly at the 5 year assessment. Although incidence estimates at the last assessment might have been inflated by the decreasing number of participants at risk, we analysed similar proportions of participants in each group.

We also assessed efficacy in 13 planned subgroups. Because of the number of subgroup analyses, the absence of adjustment for multiple testing, and the absence of a significant difference in the primary analysis, significant differences in Alzheimer's disease incidence reported in men, people who consumed alcohol at baseline, and individuals who received ginkgo biloba extract for at least 4 years should be interpreted with caution. Further exploratory analysis could be considered to assess the potential effects of ginkgo biloba on particular subsets of patients (eg, according to the level of anxiety).

One previous study of the efficacy of standardised ginkgo biloba extract for the prevention of dementia reported no effect on all-cause dementia or Alzheimer's disease incidence in 3069 elderly participants, despite reaching the required number of dementia events after an extended follow-up period (median 6·1 years).[8] In that trial, no suggestion of a violation of the proportional hazards assumption was noted, and participants were recruited from the general population, but were older and slightly less impaired than were participants in GuidAge. Men were also over-represented compared with the general population. A 3 year randomised trial of ginkgo biloba extract in 118 individuals aged 85 years or older with no cognitive impairment at baseline (CDR 0) showed a non-significant protective effect of ginkgo biloba extract on cognitive decline (progression to CDR 0·5), which became significant after drug adherence was controlled for.[40]

The GuidAge findings are generalisable to elderly patients consulting their physician for memory complaints in a European setting. To our knowledge, no data exist to compare whether or not spontaneously reported memory complaints are comparable across different sociocultural settings.

A key strength of our study was the active involvement of PCPs in recruitment and follow-up of participants. This involvement might have decreased selection bias during recruitment in comparison with population-based recruitment, which risks selection of healthier and more educated participants owing to self-selection. Recruitment by PCPs could have also increased study compliance and ensured that other drugs or supplements containing ginkgo biloba extract were not used during trial participation. Furthermore, we used a target population focusing on subjective memory complaints, which are a significant risk factor for dementia.[42–44]

The main limitation of our study was that the number of dementia events was much lower than expected, leading to a lack of statistical power to detect effects. Over-recruitment of healthy volunteers is a frequent concern in prevention trials,[45] and an examination of baseline data from previous studies suggested that the participants of such trials are healthier and better educated than the general population.[46] Some evidence of selection bias exists in our trial too, because although at risk for Alzheimer's disease, the individuals who agreed to

Panel: Research in context

Systematic review

We searched the PubMed database to March, 2012, without language restrictions, for articles, systematic reviews, or meta-analyses reporting randomised controlled trials with at least 1 year of follow-up on the efficacy of ginkgo biloba extract for the prevention of dementia or cognitive decline in older adults (aged 60 years or older). We used the following search terms: "ginkgo biloba" OR "Egb 761" AND "prevent*" with the limits: "meta-analysis", "randomized controlled trial", or "review". We identified two randomised controlled trials. The Ginkgo Evaluation of Memory (GEM) study reported that treatment with standardised ginkgo biloba extract for a median of 6·1 years was not effective for prevention of dementia[6] and cognitive decline[39] in 3069 individuals aged 75 years or older with normal cognition or mild cognitive impairment. The other study[40] reported no effect of use of ginkgo biloba extract for 42 months on the prevention of cognitive decline in the primary analysis of a trial of 185 cognitively intact patients aged 85 years and older, although a secondary analysis adjusted for drug adherence suggested a possible protective effect of ginkgo biloba extract against cognitive decline.

Interpretation

The 5 year GuidAge trial assessed the same preparation and dose of standardised ginkgo biloba extract as the two other trials,[6,40] but in a study population aged 70 years and older who had spontaneously complained of memory problems to a primary care practitioner. Primary care practitioners were actively involved in recruitment and follow-up of the GuidAge study, which could explain the high level of treatment compliance in this trial. Overall, the GuidAge trial was unable to reach our primary endpoint criterion (decreased conversion to Alzheimer's disease in 5 years of follow-up). Conclusions from this trial were restricted by the lower than expected incidence of Alzheimer's disease. Further studies about long-term exposure to standardised ginkgo biloba extract might be warranted.

participate in this long-term dementia-prevention trial had a higher level of education than the general elderly population[47] on which our sample size was based. Furthermore, compared with included participants, individuals who refused to take part were, in particular, older, with lower MMSE and higher anxiety scores. Thus, selection bias could partly explain the lower than expected rate of Alzheimer's disease. In addition, the exclusion of individuals with marked objective memory impairment (to exclude prodromal Alzheimer's disease), major depression, or generalised anxiety at baseline could also have restricted incidence of Alzheimer's disease.

Attrition bias during follow-up is also likely to have contributed to the low incidence of Alzheimer's disease that we noted. We had a higher than expected dropout rate, especially at the beginning of the trial. Individuals who did not complete the study might have been those most at risk of development of Alzheimer's disease, and we noted that non-completers had poorer cognitive scores at baseline than did study completers. However, there was no indication of differential dropout between the two groups, and so non-completers should not affect the overall study result beyond the problem of decreased statistical power.

We offered retrieved dropout visits to participants who withdrew, although few cognitive assessments were done, and contacted family doctors to record any evidence of dementia diagnoses after study discontinuation. Sensitivity analyses including this information did not alter the overall result of the trial. Future trials should use new methods, such as less burdensome cognitive assessments or home visits, to reduce the number of non-completers,[48] and should include new biomarker and imaging surrogate outcomes when these have been developed and validated.

Overall, the GuidAge trial showed that recruitment of a large population of elderly individuals with subjective memory complaints is possible and that most individuals adhere to use of ginkgo biloba extract for 5 years. However, our study did not show that ginkgo biloba was protective for incidence of Alzheimer's disease. The effect of long-term exposure to ginkgo biloba extract could be clarified through further investigation.

Contributors

BV, P-JO, GB, J-FD, BD, HG, FPa, FPi, PR, JT, PG, HM-F, and SA designed the study. BV, P-JO, GB, J-FD, BD, FPa, FPi, PR, and JT obtained data. BV, NC, P-JO, J-FD, PG, HM-F, and SA analysed and interpreted data. BV, NC, J-FD, and SA drafted the report. All authors critically revised the report. All authors commented on drafts of the manuscript and approved the final report.

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Conflicts of interest

HM-F and PG are employees of Ipsen. NC was supported by a CIFRE PhD studentship (grant number 2007/189), jointly funded by Ipsen and the French National Association of Technical Research. Other authors received pro-rata fees from the sponsor for their participation in the study's Scientific Committee.

Acknowledgments

The study was sponsored by Ipsen, Boulogne, France, which markets the ginkgo biloba extract EGb761. We gratefully acknowledge the generosity of the study participants and the nursing staff and study investigators.

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