Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomised, double-blind, placebo-controlled, multicentre trial

Christos Haritoglou, Joachim Gerss*, Cristina Sauerland, Anselm Kampik, Michael W Ulbig, for the CALDIRET study group†*

Lancet 2009; 373: 1364–71
See Comment page 1316

*These authors contributed equally
†Members listed at end of paper
Department of Ophthalmology, Ludwig-Maximilians-University, Munich, Germany (C Haritoglou MD, A Kampik MD, M W Ulbig MD); **and Department of Medical Informatics and Biomathematics, University of Münster, Münster, Germany** (J Gerss PhD, C Sauerland MSc)
Correspondence to: Dr Christos Haritoglou, Department of Ophthalmology, Ludwig-Maximilians-University, 80336 Munich, Germany
christos.haritoglou@med.uni-muenchen.de

Summary

Background **Medical treatment for diabetic retinopathy could have an important role in prevention of complications such as visual loss. We aimed to assess the effect of calcium dobesilate on occurrence of diabetic macular oedema.**

Methods **We undertook a randomised, double-blind, placebo-controlled, multicentre study in 40 centres in 11 countries. We enrolled outpatients with adult-onset type 2 diabetes and mild-to-moderate non-proliferative diabetic retinopathy, and randomly allocated them via sealed envelopes either calcium dobesilate (1500 mg per day) or placebo. The primary endpoint was development of clinically significant macular oedema (CSME) within a follow-up period of 5 years. Patients who dropped out of the study early were censored. Analysis was by intention to treat.**

Findings **We enrolled 635 patients. 324 were randomly allocated calcium dobesilate and 311 were assigned placebo. In the calcium dobesilate group, 86 patients developed CSME compared with 69 in the placebo group. Accounting for censored cases, estimated cumulative 5-year CSME probability was 35% and 28%, respectively (hazard ratio 1·32, 95% CI 0·96–1·81; p=0·0844). Adverse events did not differ between treatment groups (78 [24%] on calcium dobesilate and 90 [29%] with placebo). No relevant drug-related complications were noted. Nine patients (3%) died in the calcium dobesilate group and eight (3%) deaths were recorded on placebo.**

Interpretation **Calcium dobesilate did not reduce the risk of development of CSME.**

Funding **Sanofi; OM Pharma; and Synthelabo.**

Introduction

Diabetic retinopathy is the most important cause of blindness in people of working age,[1,2] and is a major socioeconomic problem. About 90% of patients with type 1 diabetes become legally blind because of proliferative diabetic retinopathy or development of macular oedema, despite availability of several effective treatment options, such as laser therapy or vitreoretinal surgery.[3]

Development of diabetic retinopathy is a multifactorial process. Much of the damage results from leakage of retinal blood vessels and inadequate retinal perfusion.[4] Sustained hyperglycaemia in diabetes affects various vasoactive factors, such as vascular endothelial growth factor (VEGF).[5] These factors, which are all interrelated, contribute to development of structural and functional changes in diabetic retinopathy, such as breakdown of the blood–retina barrier.[6]

Prevention of visual loss depends on timely detection of diabetic fundus changes, and instant treatment with laser photocoagulation. Therefore, stopping occurrence and progression of sight-threatening complications remains an important task. However, particularly in macular oedema, laser treatment is still suboptimum because it only reduces risk of visual deterioration and rarely reverses visual loss once it happens. Additionally, timely and tight glycaemic control, with near normal concentrations of glycosylated haemoglobin (HbA_{1c}), and blood pressure lower than 130/80 mm Hg, cannot be achieved in all patients, despite the benefits of these strategies.

In addition to the present standards of care for diabetic retinopathy, several medical treatment strategies are under investigation, which are aimed at suppression of neoangiogenesis, stabilisation of the blood–retina barrier to reduce vascular leakage and macular oedema, and lowering of serum lipid concentrations.[7–9] Medical treatment for diabetic retinopathy could also have an important role in prevention of diabetic retinal complications, such as development of macular oedema.

Calcium dobesilate, a venotonic drug, has beneficial effects in vascular diseases such as chronic venous insufficiency[10] and haemorrhoids[11] and is prescribed in more than 60 countries.[11] It seems to be safe, with infrequent complications including fever, gastrointestinal disorders, skin reactions, arthralgia, and very rarely, agranulocytosis (0·32 cases per million).[11] In general, pharmacological data for calcium dobesilate indicate its ability to decrease capillary permeability, platelet aggregation, and blood viscosity.[12,13]

How might calcium dobesilate reduce diabetic retinopathy? Postulated mechanisms include reduction of microvascular permeability (attributable to antioxidant properties) and augmentation of endothelium-dependent relaxation through synthesis of nitric oxide.[14,15]

Antioxidant and angioprotective effects have been shown by in-vivo and in-vitro approaches, such as diminished peritoneal permeability in rats induced by pro-oxidant substances and decreased vascular permeability in a reperfusion model in rats with streptozotocin-induced diabetes.[16–19] Moreover, experimental data indicated an inhibition of formation of sorbitol and reduction of overexpression of VEGF by calcium dobesilate.[20,21] Pharmacological evidence suggests that calcium dobesilate might stabilise the blood–retina barrier in patients with diabetic retinopathy by an antioxidant mechanism.[22]

The primary objective of the present investigation was to assess the efficacy of calcium dobesilate compared with placebo in prolonging time between diagnosis of mild-to-moderate diabetic retinopathy at enrolment, and development of clinically significant macular oedema (CSME) in patients with adult-onset type 2 diabetes. We further aimed to compare the risk and benefit of calcium dobesilate, compared with placebo, over a long follow-up period.

Methods

Patients

The calcium dobesilate in diabetic retinopathy (CALDIRET) study is a multicentre, double-blind, randomised, placebo-controlled trial in 40 centres in 11 countries. We included outpatients (men and women) with diagnosed adult-onset type 2 diabetes, aged 40–69 years, who showed mild-to-moderate non-proliferative diabetic retinopathy[23] in at least one eye, and who presented at hospital with microproteinuria (diagnosed with a urine dipstick microalbumin test [Bayer, Leverkusen, Germany]).

We excluded any individuals who had received treatment with calcium dobesilate within the past 12 months. Further exclusion criteria included: neovascularisation of the optic disc; neovascularisation elsewhere; preretinal haemorrhage; any signs of macular oedema (eg, retinal thickening or hard exudates within the vascular arcades); cataract or other opacities precluding retinal examination and high-quality photography; other retinal diseases; glaucoma; unauthorised (by the protocol) concomitant drugs (aspirin or other anticoagulant drugs, aldose reductase inhibitors, and other investigational drugs [ie, from participation in another medical study]); unauthorised (by the protocol) interventional treatment for diabetic retinopathy (eg, laser, cryocoagulation, vitrectomy); pregnancy; breastfeeding; history of drug or alcohol abuse; known allergic hypersensitivity to calcium dobesilate or any similar drug; participation in another clinical trial; malignant hypertension; hepatic or renal failure; and malignant or other life-threatening diseases.

All participants gave written informed consent. The study was approved by the ethics committee of Ludwig-Maximilians-University, Munich, Germany, and the local ethics committee of every site.

Procedures

We randomly allocated patients to receive either capsules of calcium dobesilate (1500 mg per day in three divided doses of 500 mg) or placebo. Placebo tablets had exactly the same appearance and taste as calcium dobesilate capsules. Randomisation was done by Synthelabo (Paris, France) using the block method; all centres were unaware of block size. Every investigator received a sealed opaque envelope for every patient's number. This envelope could only be decoded in case of an emergency by the investigator, according to German drug law. Drugs were provided by Synthelabo and stored and handed over by the local examiner, who was not further involved in the trial (eg, with reading, etc). Patients and treating doctors were unaware of the random allocation. All outcome assessments were undertaken by examiners who were unaware of treatment allocation.

We used metabolic control (indicated by HbA_{1c} amount) and diabetes type as strata for randomisation. Four groups were used: (1) HbA_{1c} less than 9% and insulin-dependent diabetes mellitus (IDDM); (2) HbA_{1c} less than 9% and non-insulin-dependent diabetes mellitus (NIDDM); (3) HbA_{1c} 9% or more and IDDM; and (4) HbA_{1c} 9% or more and NIDDM.

We initiated treatment at visit 1, with a placebo-controlled run-in period of 2 weeks. During this time, every patient took one capsule of placebo in the morning, at 12:00 h, and in the evening. We tested adherence using tablet containers with an incorporated computer chip: opening and closing of the box became visible on a computer-based timetable. If a patient did not open the box regularly, and therefore was not adhering to the regimen, they could be withdrawn.

We did the random allocation at visit 2 (day 0). At this visit, we counted and recorded remaining capsules in containers returned by patients to the study centre. Patients were regularly followed up every 6 months, for a total of 12 visits. At every study visit, we supplied patients with sufficient tablets for the following period.

We did not exclude patients because of non-adherence. Instead, we used all available information as far as possible—eg, if a patient adhered to the regimen up to the 2-year visit but not beyond, the observation period was censored at that timepoint and we judged them to have dropped out of the trial. Further data for the patient were not gathered, but any data that had been obtained were used in statistical analyses.

At visit 1 (run-in), we recorded patients' bodyweight, height, blood pressure, and concomitant medication. We also did a complete physical examination.

We did full laboratory analyses at one central laboratory at visit 1 and then once a year. We obtained a list of normal ranges for all variables before initiation of the study. Laboratory analysis included HbA_{1c} concentration, red-blood-cell count, white-blood-cell count (with differential), platelet amount, haemoglobin

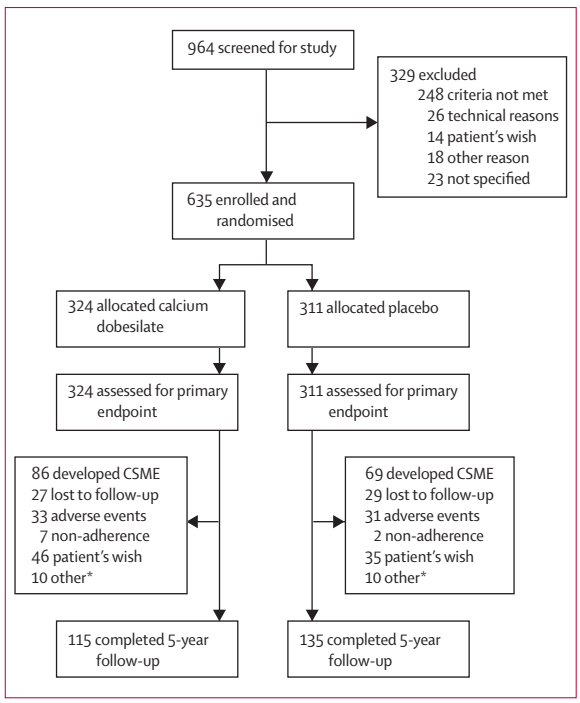

Figure 1: **Trial profile**
*Death or any laser treatment or surgical intervention due to diabetic retinopathy.

concentration, and packed-cell volume. Blood chemistry measurements were done for alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, creatine kinase, creatine, urea, and uric acid. We also measured concentrations of electrolytes (sodium, potassium, and calcium) and fibrinogen. We analysed urine with a dipstick test for glucose, total protein, and bilirubin. We assessed metabolic control by measuring concentrations of blood glucose, after an overnight fast, and HbA_{1c}. Lipid fractionation showed amounts of total cholesterol, HDL, LDL, and triglycerides.

At every study visit, patients underwent complete bilateral eye examination, which included best corrected visual acuity as tested with Early Treatment Diabetic Retinopathy Study (ETDRS) charts,[24] slit-lamp examination, intraocular pressure, and stereoscopic biomicroscopy (ophthalmic examination technique). We took seven-field stereoscopic fundus photographs (colour images, 30° field), according to criteria described in the ETDRS protocol.[23] Fluorescein angiography at study initiation and termination was optional, and done according to the ETDRS scheme.[25] Assessment of fundus photographs was always done by examiners who were unaware of treatment allocation, at the CALDIRET central reading centre in Munich, Germany, under the guidance of one of us (MWU). If we detected CSME, its occurrence was reported immediately to the appropriate study centre; the patient was then given laser treatment, and excluded from further follow-up.

Study endpoints

Our primary endpoint was development of CSME in one eye at least, which required laser treatment. Secondary endpoints were development of either neovascularisation elsewhere or neovascularisation of the optic disc. Adverse events had to be reported, whether or not they were thought to be caused by study drugs.

Statistical analysis

The basic design of the CALDIRET study constituted a group sequential plan, using the O'Brien-Fleming approach[26] and the Lan-DeMets α spending function method for unequally spaced intervals between interim analyses.[27] Two interim analyses were done (after 90 and 120 CSMEs) and a final analysis was scheduled. This report presents results of the final analysis.

We analysed the primary endpoint with a global log-rank test, comparing all patients in both treatment groups. This particular hypothesis test provides confirmatory statistical evidence and constitutes the primary study result. To control for an overall type I error of $\alpha=0{\cdot}05$ (two-sided), we used $\alpha=0{\cdot}005$ in the first and second interim analyses and $\alpha=0{\cdot}047$ in the final analysis. From power calculations, we anticipated a difference of 15% in cumulative CSME probability—ie, 50% and 65% event-free patients after a period of 5 years in the calcium dobesilate and placebo groups, respectively. Hence, we calculated a required sample size of 630 patients (315 per group), resulting in 90% power.

For secondary analyses, we used univariate logistic regression to calculate raw CSME rates (ie, disregarding time of occurrence), subject to the potential predictors of sex, CSME preventive treatment (calcium dobesilate *vs* placebo), blood pressure, duration of diabetes, and baseline HbA_{1c} amount. To account for enhancement of the type I error due to multiple testing, we judged results of secondary analyses significant at $p<0{\cdot}01$.

We did additional post-hoc subgroup analyses in an exploratory manner (these were not prespecified in the study protocol). To assess the effect of CSME preventive treatment in different subgroups of patients (defined by baseline variables), we undertook a multivariate analysis of time to CSME development. Covariates included strata used in the randomisation—ie, metabolic control (HbA_{1c} ≥9% *vs* <9%) and diabetes type (IDDM *vs* NIDDM)—and patients' sex and systolic blood pressure (≥140 mm Hg *vs* <140 mm Hg), which is known to be an important predictive factor in people with diabetes. Because multiplicity of comparisons undertaken might yield false-positive chance findings, we did not interpret results of post-hoc analyses with a significance test with controlled type I error. However, we judged findings noticeable if $p<0{\cdot}05$, particularly in case of associated pronounced effect estimates (ie, a detected effect worth mentioning because of its size).

We did all statistical analyses by intention to treat—ie, we analysed patients according to their allocated

	Calcium dobesilate (n=324)	Placebo (n=311)
Demographics		
Women	140 (43%)	159 (51%)
Age (years)	57·5 (7·1)	57·7 (6·6)
Diabetic retinopathy level*		
13	1	3
20	0	1
35	303	286
43	14	15
61	3	1
65	0	1
Diabetes type		
IDDM	137 (42%)	140 (45%)
NIDDM	187 (58%)	171 (55%)
Median (IQR) duration of diabetes mellitus (years)	10·3 (4·9–16·0)	10·7 (6·1–15·4)
Randomisation stratum		
HbA_{1c} <9%, IDDM	87 (27%)	95 (31%)
HbA_{1c} <9%, NIDDM	128 (40%)	116 (37%)
HbA_{1c} ≥9%, IDDM	50 (15%)	45 (14%)
HbA_{1c} ≥9%, NIDDM	59 (18%)	55 (18%)

Data are number (%) or mean (SD), unless otherwise indicated. *Data missing for three patients in calcium dobesilate group and four in placebo group.

Table 1: **Baseline characteristics of total study population**

	Calcium dobesilate (n=324)	Placebo (n=311)
Risk factors for cardiovascular disease		
Arterial hypertension	197 (61%)	186 (60%)
Current smoker	50 (15%)	58 (19%)
Disorder of lipid metabolism	79 (24%)	64 (21%)
Obesity	139 (43%)	143 (46%)
Current consumption of alcohol	125 (39%)	103 (33%)
Concomitant diseases		
Endocrine or metabolic disease	105 (32%)	92 (30%)
Disorders of the nervous or sensory system	71 (22%)	80 (26%)
Cardiovascular diseases	235 (73%)	218 (71%)
Diseases of the gastrointestinal tract	73 (23%)	62 (20%)
Musculoskeletal disorders	85 (26%)	77 (25%)
Concomitant treatments		
Antidiabetic drugs	288 (93%)	298 (92%)
β-adrenergic blockers	39 (12%)	47 (15%)
Angiotensin-converting-enzyme inhibitors	94 (29%)	94 (30%)
Lipid-lowering drugs	26 (8%)	25 (8%)

Table 2: **Cardiovascular risk factors and concomitant diseases and treatments recorded at baseline in total study population**

treatment arm, irrespective of any later protocol deviations. Unless otherwise specified, we used Pearson's χ^2 test to compare ordinal data, including crude rate of events, and assessed continuous data with Student's *t* test. To analyse occurrence of CSME events, we plotted Kaplan-Meier curves and did the log-rank test, accounting for censored cases (who only provided limited information on the 5-year event rate). We calculated hazard ratios and 95% CIs with Cox's proportional-hazards model when appropriate, to show differences between Kaplan-Meier curves. Associated p values of hazard ratios were derived by Wald-type significance tests. We undertook statistical analyses with SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Role of the funding source

Synthelabo, a co-sponsor of the CALDIRET study, did the randomisation. Otherwise, the sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. A senior author (MWU) had full access to all the data in the study and, with the corresponding author (CH), had final responsibility for the decision to submit for publication.

Results

Between September, 1996, and January, 1999, 635 patients were enrolled in the present study. 324 were randomly allocated calcium dobesilate, and 311 placebo (figure 1). The last patient completed 5-year follow-up on June 17, 2004. Median duration of follow-up was 5·0 years (IQR 2·1–5·0) in the calcium dobesilate group and 5·0 years (2·8–5·0) in the placebo group.

Table 1 shows baseline characteristics for the study population. In all participants, mean HbA_{1c} was 8·25% (SD 1·68), and this value did not differ by treatment group (8·22% [1·68] for calcium dobesilate *vs* 8·28% [1·68] for placebo). In patients with HbA_{1c} of 9% or more, HbA_{1c} decreased over time, as did albuminuria, which could constitute a confounding factor. Table 2 presents a list of cardiovascular risk factors, concomitant diseases, and current treatments recorded in the study population at baseline.

Insulin administration became necessary during follow-up in 92 (28%) patients allocated calcium dobesilate and in 100 (32%) assigned placebo. Other treatments used included oral antidiabetic drugs (74 [23%] *vs* 66 [21%]), β-adrenergic blockers (48 [15%] *vs* 58 [19%]), angiotensin-converting-enzyme inhibitors (105 [32%] *vs* 95 [31%]), and lipid-lowering drugs (42 [13%] *vs* 38 [12%]). Arterial hypertension and hyperlipidaemia needing therapeutic intervention were recorded in 73 (23%) and 16 (5%) patients in the calcium dobesilate arm and in 81 (26%) and 18 (6%) allocated to placebo, respectively, but differences were not significant.

86 patients assigned calcium dobesilate compared with 69 allocated placebo reached the primary endpoint of CSME requiring laser treatment. Accounting for censored cases, the estimated cumulative 5-year CSME probability was 35% and 28%, respectively (hazard ratio 1·32 [95% CI 0·96–1·81]; log-rank p=0·0844; figure 2, A). In most patients, only one eye was affected (seven bilateral cases *vs* 74 unilateral cases for each eye).

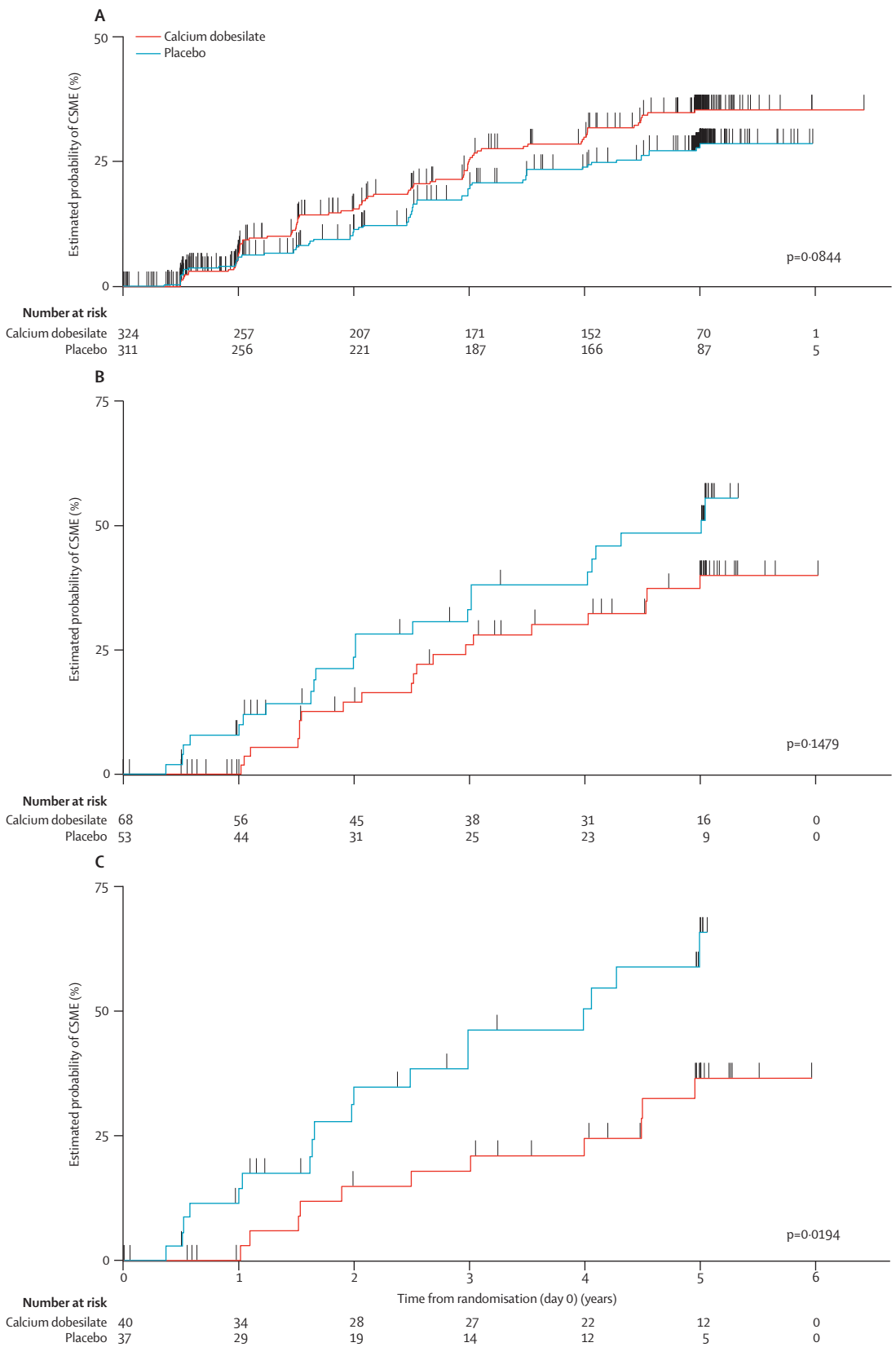

Figure 2: **Estimated cumulative 5-year event probability**
The log-rank test was used to calculate p values. (A) Total population (intention-to-treat analysis). (B) Subpopulation with HbA_{1c} concentrations 9% or higher and systolic blood pressure of 140 mm Hg or more (post-hoc analysis). (C) Women with HbA_{1c} concentrations 9% or higher and systolic blood pressure of 140 mm Hg or more (post-hoc analysis).

We looked for univariate predictors of CSME development. In the total study population, 74 of 336 (22%) men and 81 of 299 (27%) women developed CSME during follow-up (odds ratio 1·32 [95% CI 0·92–1·89]; p=0·138). Therefore, patients' sex was not a significant predictor of CSME development. Preventive treatment was also not predictive (1·27 [0·88–1·82]; p=0·2014), and neither were duration of diabetes (1·02 [0·99–1·04]; p=0·1506), baseline systolic blood pressure (1·00 [0·99–1·01]; p=0·4038), nor diastolic blood pressure (0·99 [0·97–1·01]; p=0·1777). HbA_{1c} was the only baseline covariate providing significant predictive capacity for CSME development (1·19 [1·07–1·33]; p=0·0013).

We undertook an exploratory post-hoc multivariate analysis of time to CSME development. We included the baseline covariates sex, HbA_{1c} (≥9% *vs* <9%), diabetes type (IDDM *vs* NIDDM), systolic blood pressure (≥140 mm Hg *vs* <140 mm Hg), and CSME preventive treatment. Additionally, interaction terms of any of the above baseline covariates with CSME preventive treatment were included. The fitted model indicated noticeable interactions of the baseline covariates systolic blood pressure, HbA_{1c}, sex, and diabetes type with CSME preventive treatment. The treatment effect differed markedly in particular subgroups of patients defined by baseline covariates. Of note, not only did the size of the treatment effect differ between subgroups but also the sign varied—ie, positive effects of calcium dobesilate treatment and reverse effects favouring placebo. Table 3 shows emergence of a possible pattern: some might say that accumulation of risk factors tended to favour treatment with calcium dobesilate, and absence of risk factors tended to favour placebo. Women with high systolic blood pressure, high HbA_{1c} fractions, and IDDM may have been more likely than other patients to benefit from calcium dobesilate (Wald χ^2 p=0·0494). However, it is noteworthy that the number of patients in this subgroup was rather small (n=40). Figure 2 (B and C) shows Kaplan-Meier estimates of the cumulative CSME probability in subgroups of patients who possibly benefited from calcium dobesilate treatment.

More men were assigned to the calcium dobesilate group than to the placebo group. Exploratory post-hoc analyses to ascertain the effect of the sex bias showed positive results in the calcium dobesilate group for a subgroup of women with inadequate glycaemic control, indicated by HbA_{1c} amounts of 9% or more. In this subgroup, 18 of 63 patients (29%) developed CSME compared with 26 of 61 (43%) in the corresponding placebo group (Pearson's χ^2 p=0·1021). When only female patients with HbA_{1c} amounts of 9% or more and poorly controlled arterial hypertension (systolic blood pressure ≥140 mm Hg) were included, 11 of 40 (28%) in the calcium dobesilate group developed CSME compared with 18 of 37 (49%) in the placebo group (Pearson's χ^2 p=0·0557). No such effect was recorded either in men with systolic blood pressure of 140 mm Hg or greater or in men and women with blood pressure less than 140 mm Hg.

	Calcium dobesilate	Placebo	Hazard ratio (95% CI)	p
No risk factors	34	29	3·63 (1·77–7·45)	0·0004
IDDM	137	140	3·08 (1·45–6·52)	0·0034
Female sex	140	159	2·65 (1·19–5·86)	0·0166
HbA_{1c} ≥9%	109	100	1·86 (0·83–4·16)	0·1295
Systolic blood pressure ≥140 mm Hg	200	168	1·64 (0·86–3·15)	0·1349
Systolic blood pressure ≥140 mm Hg, HbA_{1c} ≥9%	68	53	0·84 (0·40–1·79)	0·6558
Systolic blood pressure ≥140 mm Hg, HbA_{1c} ≥9%, IDDM	33	23	0·71 (0·32–1·57)	0·4030
Systolic blood pressure ≥140 mm Hg, HbA_{1c} ≥ 9%, female sex	40	37	0·61 (0·32–1·19)	0·1484
Systolic blood pressure ≥140 mm Hg, HbA_{1c} ≥ 9%, female sex, IDDM	20	20	0·52 (0·27–1·00)	0·0494

Data derived from Wald approach, based on Cox's proportional-hazards model.

Table 3: **Multivariate analysis of time to CSME development**

Concomitant antihypertensive drugs (such as β blockers or angiotensin-converting-enzyme inhibitors) at study entry seemed to enhance the treatment effect for patients with HbA_{1c} fractions of 9% or more and with systolic blood pressure of 140 mm Hg or greater (men and women). In this subgroup, one of 24 (4%) patients in the calcium dobesilate group developed CSME versus ten of 24 (42%) in the placebo group (Pearson's χ^2 p=0·0020).

Baseline rating of albuminuria seemed to affect the response to treatment as far as event probability was concerned. In women with high albuminuria and HbA_{1c} fractions of 9% or more, three of 15 (20%) in the calcium dobesilate group developed CSME, compared with ten of 19 (53%) in the placebo group (Pearson's χ^2 p=0·0519).

Neovascularisation was seen in only three patients during the 5-year follow-up period. Calcium dobesilate had no effect on occurrence of the secondary endpoints of neovascularisation elsewhere (0/324 calcium dobesilate *vs* 1/311 placebo; odds ratio 0·32 [95% CI 0·01–7·86]) or neovascularisation of the optic disc (1/324 *vs* 2/311; 0·48 [0·04–5·30]). Formation of retinal haemorrhages, hard exudates, cotton-wool spots, microaneurysms, or intraretinal microvascular anomalies was unaffected by calcium dobesilate treatment, as was retinal thickening. Furthermore, no effect was recorded on the appearance of the venous vascular system (such as venous beading). No effects on intraocular pressure were attributed to calcium dobesilate. The extent (severity) of diabetic retinopathy did not change significantly during 5-year follow-up.

We did not record any relevant drug-related complications. However, adverse events—as defined by the study protocol—arose in 78 (24%) of 324 patients

assigned calcium dobesilate and in 90 (29%) of 311 allocated placebo. The most frequent events were cardiovascular and vision disorders. All adverse events could be accounted for by the underlying pathology, patient's age, and long study duration. During 5-year follow-up, nine of 324 patients (3%) in the calcium dobesilate group and eight of 311 (3%) in the placebo group died.

Discussion

Our findings showed that calcium dobesilate could neither prevent occurrence of CSME nor reduce probability of developing CSME during the 5-year follow-up period in patients with type 2 diabetes and mild-to-moderate non-proliferative diabetic retinopathy. We recorded no lowering effect on intraocular pressure, as described previously in 41 treated patients followed up for 6 months.[28] Also, no effect was seen on frequency of neovascularisation or formation of intraretinal microvascular anomalies.

Clinical use of calcium dobesilate was encouraged in the late 1980s by studies showing a positive effect on blood flow and microcirculation in patients with peripheral and cerebral diseases,[29] enhancement of photocoagulation in people with diabetes,[30] reduced blood hyperviscosity and lowered intraocular pressure in individuals with diabetic retinopathy and glaucoma,[28] and stabilisation of permeability of the blood–retina barrier.[31] However, these studies included rather small groups of patients. In a double-blind, placebo-controlled study of 2000 mg calcium dobesilate daily for 2 years, a positive effect of the drug was recorded on progression of early diabetic retinopathy in terms of significantly better activity than placebo for prevention of blood–retina barrier disruption, as measured by fluorescein leakage using fluorophotometry every 6 months. The described effect was independent of diabetes control.[32]

In our study, we undertook post-hoc analyses to find out whether a future trial might be warranted in a subgroup of patients, and to identify potential inclusion and exclusion criteria. Findings of such analyses should be interpreted with great caution, owing to low strength of evidence, not least because the numbers in each subgroup were small. Of note, we saw no effect of study drug in men and women with good glycaemic control and blood pressure in the normal range, and in specific subgroups of patients, placebo was significantly better than calcium dobesilate (table 3). Our data suggest that women with risk factors for vascular disease might benefit from treatment with calcium dobesilate, although this interpretation remains speculative.

Contributors

CH wrote the report and participated in grading of patients. JG wrote the report and participated in statistical analysis of data. CS participated in statistical analysis of data. AK was a principal study investigator. MWU designed the study and was head of the central reading centre.

The CALDIRET study group

Western European centres—Berlin, Germany (M H Foerster); Bonn, Germany (M Spitznas); Düsseldorf, Germany (K D Lemmen); Frankfurt, Germany (F Koch); Geneva, Switzerland (P Leuenberger); Graz, Austria (J Faulborn); Greifswald, Germany (S Clemens); Hamburg, Germany (W Kypke); Hanover, Germany (B Wiechens); Heidelberg, Germany (H E Völcker); Heidenheim, Germany (J Schön); Homburg/Saar, Germany (K W Ruprecht); Koblenz, Germany (P Schmitz-Valkenberg); Leipzig, Germany (P Wiedemann); Munich, Germany (A Kampik); Central Reading Centre, Munich, Germany (M W Ulbig, C Haritoglou, S Fröhlich, A Kollias, T Ring); Passau, Germany (C von Düring); Regensburg, Germany (D Spiegel); Rostock, Germany (N Schulz); Starnberg, Germany (T Hamacher); Vienna, Austria (M Stur); Wuppertal, Germany (E Gerke). *Eastern European centres*—Sofia, Bulgaria (P I Vassileva); Zagreb, Croatia (V Profozic); Rijeka, Croatia (B Vojnikovic); Hradec, Czech Republic (P Rozival); Brno, Czech Republic (S Synek); Prague, Czech Republic (P Soucek, P Kuchynka); Tallin, Estonia (K Noor, Ü Aamer); Tartu, Estonia (R Kuiv); Riga, Latvia (G Laganovska); Lodz, Poland (J Nawrocki); Poznan, Poland (K Pecold); Szeczecin, Poland (O Palacz); Bucharest, Romania (A Barnea, B Carstocea, M Pop); Cluj-Napoca, Romania (M Calugaru); Iasi, Romania (D Chiselita); Kiev, Ukraine (N M Sergienko, M Tronko).

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

The CALDIRET study was financed by Sanofi, France, OM Pharma, Switzerland, and Synthelabo, France.

References

1 Harris MI. Diabetes in America: epidemiology and scope of the problem. *Diabetes Care* 1998; **21** (suppl 3)**:** C11–14.
2 The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000; **342:** 381–89.
3 Klein R, Klein BEK, Moss SE. Prevalence of diabetes mellitus in southern Wisconsin. *Am J Epidemiol* 1984; **119:** 54–61.
4 Joussen AM, Poulaki V, Le ML, et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. *FASEB J* 2004; **18:** 1450–52.
5 Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol* 1994; **118:** 445–50.
6 Ishida S, Usui T, Yamashiro K, et al. VEGF164 is proinflammatory in the diabetic retina. *Invest Ophthalmol Vis Sci* 2003; **44:** 2155–62.
7 PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: thirty-month results of the randomized PKC-DMES clinical trial. *Arch Ophthalmol* 2007; **125:** 318–24.
8 Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007; **370:** 1687–97.
9 Lang GE. [Therapy of diabetic retinopathy with somatostatin analogues]. *Ophthalmologe* 2004; **101:** 290–93.
10 Casley-Smith JR. A double-blind trial of calcium dobesilate in chronic venous insufficiency. *Angiology* 1988; **39:** 853–57.
11 Allain H, Ramelet AA, Polard E, Bentue-Ferrer D. Safety of calcium dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids. *Drug Saf* 2004; **27:** 649–60.
12 Tejerina T, Ruiz E. Calcium dobesilate: pharmacology and future approaches. *Gen Pharmacol* 1998; **31:** 357–60.
13 Michal M, Gotti C. Effect of calcium dobesilate on platelet function. *Thromb Res* 1988; **51:** 593–605.
14 Berthet P, Farine JC, Barras JP. Calcium dobesilate: pharmacological profile related to its use in diabetic retinopathy. *Int J Clin Pract* 1999; **53:** 631–36.
15 Tejerina T, Ruiz E, Sanz M, Ganado P. Study of calcium dobesilate in diabetic rats. *Int J Angiol* 1999; **8:** 16–20.
16 Brunet J, Farine JC, Garay RP, Hannaert P. Angioprotective action of calcium dobesilate against reactive oxygen species-induced capillary permeability in the rat. *Eur J Pharmacol* 1998; **358:** 213–20.

17 Brunet J, Farine JC, Garay RP, Hannaert P. In vitro antioxidant properties of calcium dobesilate. *Fundam Clin Pharmacol* 1998; **12:** 205–12.

18 Szabo ME, Haines D, Garay E, et al. Antioxidant properties of calcium dobesilate in ischemic/reperfused diabetic rat retina. *Eur J Pharmacol* 2001; **428:** 277–86.

19 Padilla E, Ganado P, Sanz M, et al. Calcium dobesilate attenuates vascular injury and the progression of diabetic retinopathy in streptozotocin-induced diabetic rats. *Diabetes Metab Res Rev* 2005; **21:** 132–42.

20 Schmidt M, Michal M. Inhibition of sorbitol formation in human erythrocytes by calcium dobesilate. *Arzneimittelforschung* 1989; **39:** 493–95.

21 Lameynardie S, Chiavaroli C, Travo P, Garay RP, Pares-Herbute N. Inhibition of choroidal angiogenesis by calcium dobesilate in normal Wistar and diabetic GK rats. *Eur J Pharmacol* 2005; **510:** 149–56.

22 Garay RP, Hannaert P, Chiavaroli C. Calcium dobesilate in the treatment of diabetic retinopathy. *Treat Endocrinol* 2005; **4:** 221–32.

23 Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic colour fundus photographs: an extension of the modified Airlie House classification—ETDRS report number 10. *Ophthalmology* 1991; **98** (5 suppl)**:** 786–806.

24 Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985; **103:** 1796–806.

25 Early Treatment Diabetic Retinopathy Study Research Group. Classification of diabetic retinopathy from fluorescein angiograms: ETDRS report number 11. *Ophthalmology* 1991; **98** (5 suppl): 807–22.

26 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35:** 549–56.

27 Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983; **70:** 659–63.

28 Vojnikovic B. Doxium (calcium dobesilate) reduces blood hyperviscosity and lowers elevated intraocular pressure in patients with diabetic retinopathy and glaucoma. *Ophthalmic Res* 1991; **23:** 12–20.

29 Költringer P, Eber O, Rothlauer W, et al. Calcium dobesilate and its effects on hemorheology and microcirculation. *Int J Clin Pharmacol Ther Toxicol* 1988; **26:** 500–02.

30 Dittmar P. [Photocoagulation given additional benefit by calciumdobesilate (author's transl)]. *Klin Monatsbl Augenheilkd* 1979; **174:** 753–55.

31 Leite EB, Mota MC, de Abreu JR, Cunha-Vaz JG. Effect of calcium dobesilate on the blood-retinal barrier in early diabetic retinopathy. *Int Ophthalmol* 1990; **14:** 81–88.

32 Ribeiro ML, Seres AI, Carneiro AM, et al. Effect of calcium dobesilate on progression of early diabetic retinopathy: a randomised double-blind study. *Graefes Arch Clin Exp Ophthalmol* 2006; **244:** 1591–600.