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Naturalistic, prospective study of glaucoma and ocular hypertension treatment in France: Strategies, clinical outcomes, and costs at 2 years

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PURPOSE. To prospectively observe second-line treatment strategies, their clinical outcomes, and treatment costs in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH) in France.
METHODS. Second-line patients were recruited from September 14, 1998, to December 20, 2000, in 37 centers and were followed for up to 2 years. Outcomes were numbers of and reasons for treatment changes, changes in clinical parameters (intraocular pressure (IOP) levels, visual field defects, and optic nerve excavation), and direct medical costs associated with glaucoma management. This article reports results of the final analysis of 2-year follow-up data for patients with at least two contacts with a study ophthalmologist.
RESULTS. Data were analyzed for 346 patients and 672 treated eyes. Monotherapy was used as first-line therapy in 92.0% of eyes. Second-line treatment was initiated an average of 2.8±0.2 years after diagnosis, primarily due to insufficient IOP control (60.3%) and adverse drug reactions (18.3%). Relative risk (RR) (95% CI) for adverse drug reactions (ADR) under monotherapy was 1.00 (1.00-1.00) under beta blockers (n=116) versus 0.40 (0.16-0.64) under latanoprost (n=21), 2.30 under carbonic anhydrase inhibitors (n=29), and 2.90 under adrenergics (n=38); RR for ADR under combination therapy was 1.00 (1.00-1.00) for unfixed combinations without latanoprost (n=66) versus 0.11 (0.00-0.22) for unfixed combinations of latanoprost + timolol (n=3). Cardiac or pulmonary problems have been reported in 26.9% of patients. Persistency on initial therapy was 62.5% (95% CI 53.0-72.0) for latanoprost monotherapy versus 41.1% (34.8-47.4) for beta-blocker monotherapy and 43.6% (26.6-60.6) for the latanoprost + timolol combination versus 29.8% (15.2-44.4) for combination therapies that did not include latanoprost. Average daily cost for latanoprost monotherapy was similar to that for patients who failed beta-blocker monotherapy: latanoprost + timolol did not cost more than therapeutic combinations without latanoprost.
CONCLUSIONS. Insufficient IOP control and adverse drug reactions are the two main reasons for changing first-line treatment in patients with POAG or OH. After 2 years, second-line treatment with latanoprost, as monotherapy or combined with timolol, provides superior safety and persistency to treatment at an acceptable cost. (Eur J Ophthalmol 2005; 15: 562-80)

KEY WORDS. Adverse drug reactions, Costs, IOP, Ocular hypertension, Persistency, Primary open-angle glaucoma, Treatment strategy

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INTRODUCTION

In France, about 1 million people may be at risk for primary open-angle glaucoma (POAG) (1), a condition characterized by chronic neuropathy of the optic nerve that, when uncontrolled, eventually leads to the progressive and irreversible destruction of the visual field (2). French authorities estimate that 650,000 persons are being treated for chronic glaucoma (2% of people above 40 years of age) and that 400,000 persons do not know of the disease due to absence of functional signs until a very aggravated stage. In its terminal form, glaucoma is the first cause of total blindness in France (1). Advanced age is a major risk factor for POAG (3). The prevalence of the condition is estimated to be between 2% and 5% in persons over 70 years old, making POAG the third leading cause of visual deficiency in this age group (4) and severely limiting the daily lives of those affected. Systematic screening for POAG is difficult because it is an asymptomatic disease, and an estimated 20% to 50% of optic nerve fibers may be lost before any damage is detected by conventional perimetry techniques (5).

Patients with elevated intraocular pressures (IOPs) are at increased risk for the development of POAG (3, 5). Conversely, reduced IOP levels impede visual field defect progression in patients with glaucoma (6-9), and it has been argued that an IOP reduction of 3 mmHg reduces the relative risk of glaucoma progression by 50% (5). As a result, current treatment focuses on lowering IOP levels in order to preserve vision (3). Although no firm IOP threshold has been established because it seems more appropriate to tailor IOP control to individual patients, the European Glaucoma Society has set a target IOP range of 8 mmHg to 21 mmHg depending on the IOP level at which the initial visual deficit was detected (2). In general, the initial IOP must be reduced by at least 30% in order to achieve a pressure within this target range (2).

Ocular hypertension (OH) is characterized by an IOP of >21 mmHg but no optic nerve damage (3). The true prevalence of the condition is unknown due to poor systematic screening. Up to 10% of persons older than 40 years of age may have OH (3). Although this value may seem high, reported prevalence rates in other studies may reflect country-specific differences in the way OH is perceived and managed. In France, ophthalmologists used to treat OH very early, without waiting for visual field defects to occur, as other countries would treat later. A recent modelling study estimates risk of progression from OH to unilateral blindness from 1.5% to 10.5% in untreated patients and 0.3% to 2.4% in treated patients over 15 years. From these estimates, between 12 and 83 patients with OH would require treatment to prevent one patient from progressing to unilateral blindness over a 15-year period (10). In addition to larger cup-to-disc ratios and thinner central corneal measurements, elevated IOP levels also predict progression of OH to POAG (11). As a result, OH treatment aims at reduc-

TABLE I - UNIT COSTS OF AMBULATORY EXAMINATIONS

Procedures	**UCANSS tariff quotation (key letters and coefficients)**	**Cost** €
Diurnal IOP	K13	25.00
Fluorescein angiography	K32	61.50
Gonioscopy	K9	17.30
Ophthalmoscopy	K11	21.10
Optic nerve head evaluation	Performed during an ophthalmoscopy	—
Pachymetry	K9	17.30
Photography of anterior segment	Performed during an ophthalmoscopy	—
Photography of axon fibers	K9	17.30
Photography of papilla	K9	17.30
Scan laser	Z19 + technical fee	130.80
Visual evoked potentials	K28	53.80
Visual field evaluation	K13	25.00

UCANSS = Union des Caisses Nationales de Sécurité Sociale; IOP = Intraocular pressure

TABLE II - UNIT COSTS OF SURGICAL STAYS

Type of surgery	Setting	Surgery	Unit cost, €	Quotation
In-patient surgery	Public hospitals	Trabeculectomy or combined cataract-trabeculectomy	2,956.13	Other intraocular surgery (GHM 054)
		Cataract (10% of actual costs)	182.01	Surgery of the crystalline with or without vitrectomy (GHM 051)
Ambulatory surgery	Public hospitals	Trabeculectomy or combined cataract-trabeculectomy	1,281.33	Ambulatory surgery of the crystalline (GHM 762)
		Cataract (10% of actual costs)	128.13	Ambulatory surgery of the crystalline (GHM 762)
	Private hospitals	Combined cataract-trabeculectomy	296.57	UCANSS general nomenclature of professional procedures + surgical theater fee
		Laser	129.49	
		Cataract (10% of actual costs)	29.64	
	Private practice	Trabeculectomy	292.40	UCANSS general nomenclature of professional procedures
		Laser	125.31	
		Iridectomy	83.54	

GHM = Groupe Homogène de Malades; UCANSS = Union des Caisses Nationales de Sécurité Sociale

TABLE III – PATIENT CHARACTERISTICS AT INCLUSION (FIRST TREATMENT CHANGE)

	Characteristics	Values
Demographic data	No. of patients followed at 2 years	346
	No. of treated eyes	672
	Mean age, yr	64.8±12.9
	Men	159 (46.0)
	Women	187 (54.0)
Diagnosis, n=672	Primary open-angle glaucoma	452 (67.3)
	Ocular hypertension	153 (22.7)
	Normal pressure glaucoma	36 (5.4)
	Exfoliative glaucoma	17 (2.5)
	Pigmentary glaucoma	8 (0.9)
	Other (not documented)	8 (1.29)
Intraocular pressure, n=591	Mean ± SD	20.1 ± 4.1
	CI 95%	19.7 to 20.3
	Median	20.0
	Minimum	8.0
	Maximum	32.0

Values are n, mean ± SD, or n (%)

TABLE IV - FIRST-LINE TREATMENT STRATEGIES

Strategy	No.	%
Monotherapy	621	92.4
Beta-blockers	518	77.0
Adrenergics	45	6.7
Carbonic anhydrase inhibitors	30	4.5
Latanoprost	26	3.9
Myotics	2	0.3
Combination therapy	39	5.8
Fixed combinations	4	0.6
Non-fixed combinations with latanoprost	26	3.9
Non-fixed combinations without latanoprost	9	1.3
No treatment	12	1.8
Total	672	100

TABLE V - REASONS FOR FIRST-LINE TREATMENT CHANGE

Reason for change	No.	%
IOP insufficiently controlled	405	60.3
Adverse drug reactions	123	18.3
Visual field deterioration	63	9.4
Suspected aggravation of optic nerve head excavation	18	2.7
IOP well controlled	12	1.8
Patient wish	7	1.0
Poor observance	5	0.8
Treatment stop or modification prior to surgery	4	0.5
Contraindication	2	0.3
Other reasons	33	4.9
Total	672	100

IOP = Intraocular pressure

TABLE VI - SECOND-LINE TREATMENT STRATEGIES

Strategy	No.	%
Monotherapy	415	61.8
Beta-blockers	248	36.9
Latanoprost	112	16.6
Adrenergics	28	4.1
Carbonic anhydrase inhibitors	27	4.0
Combination therapy	189	28.1
Combinations without latanoprost	94	14.0
Latanoprost + timolol	39	5.8
Other combinations with latanoprost	54	8.0
Fixed combinations without latanoprost	2	0.3
No treatment	48	7.1
Surgery	20	3.0
Total	672	100

ing such levels (2), and intraocular instillation of hypotensive agents has been shown to effectively delay and prevent the onset of POAG in patients with OH (12). Topical beta-blockers are often used as first-line medical therapy in both POAG and OH, followed in case of failure by a change to another monotherapy or to treatment with a combination of therapies.

When IOP control requires more than two topical therapies, surgical treatments may be considered (2). In recent years, the introduction of new ocular hypotensive drugs, particularly latanoprost and brimonidine, has been associated with important reductions in rates of trabeculum surgery. Baudouin C, Rouland JF, Piriou E, Le Pen C, Kenigsberg PA. (Evolution des traitements médicaux et chirurgicaux du glaucome entre 1997 et 1999. 108ème Congrès de la Société Française d'Ophtalmologie; 2002; Communication 62 55, 283). (13-15).

Compliance with medical therapeutic regimens is low in glaucoma patients, however (16), and noncompliance plays an important role in the progression of glaucoma to blindness. In addition, age and concomitant diseases may impair the ability of patients with glaucoma to instill drops into their eyes (2). Therefore, the preferred pharmacologic strategy must be the simplest treatment that maintains the target IOP level.

The French Ministry of Health recently considered setting up quantitative targets concerning glaucoma management for the years 2004 to 2008. Objectives are to reduce by 20% the unknown visual troubles in the adult population, to reach 0% unknown visual trouble in children, to reduce unknown visual trouble by 30% and unknown damage of the second eye by 70% in the elderly, to reduce the frequency of troubles leading to visual impairment, to reduce the frequency of blindness and low vision associated with diseases accessible to treatment, and to maintain remaining visual capacity in the elderly with low vision.

Public health initiatives considered involve glaucoma screening from age 40, with systematic IOP control upon examinations for eyeglasses prescriptions, and periodic follow-up examinations of people above 55 years old. Some of these objectives have been officially annexed to the 2004 Public Health Law (Law 2004-2005 of August 9; 2004; Jo185 of August 11, 2004, Sext 4 (1).

The present research prospectively observed second-line treatment strategies, their clinical outcomes, and associated costs in patients with POAG or OH in France. Comparisons between patients treat-

ed with the prostaglandin analogue latanoprost and those receiving a topical beta-blocker were of particular interest given latanoprost's demonstrated superior effectiveness and safety in comparison with timolol, a widely used beta-blocker (17-20).

MATERIALS AND METHODS

Centers and patients

This naturalistic study recruited patients prospectively from September 14, 1998, to December 20, 2000, from 37 centers located in 14 administrative regions in France. The distribution of practice types (74% private ophthalmologist offices, 26% hospital centers) was representative of ophthalmology practices in France as reported by the ICOMED panel (4,400 private ophthalmologists offices for 1,000 hospital ophthalmologists, ratio 81%:19%). Inclusion criteria were age ≥ 18 years; a diagnosis of POAG or OH in at least one eye; a clinical change in therapy, i.e., either treatment was changed or stopped for the treated eye, treatment of the other eye was begun, or surgery was performed on one of the eyes; and data concerning IOP level, visual field, and optic nerve head were available from the visit at which the clinical change in therapy occurred (inclusion visit). Patients hospitalized

TABLE VII - EVOLUTION OF INTRAOCULAR PRESSURE AFTER 2 YEARS OF FOLLOW-UP

Initial second-line strategy	Eyes treated	Mean IOP at inclusion (95% CI)	Mean IOP after 2 years (95% CI)	Mean IOP reduction after 2 years (95% CI)
Monotherapies	415	19.82 (19.42-20.22)	17.03 (16.74-17.33)	2.79 (2.68-2.89)
Beta-blockers	248	19.69 (19.27-20.12)	17.10 (16.76-17.45)	2.59 (2.51-2.67)
Adrenergics	28	19.05 (17.39-20.71)	16.36 (15.05-17.68)	2.69 (2.34-3.03)
Carbonic anhydrase inhibitors	27	21.28 (19.19-23.37)	18.90 (17.68-20.12)	2.38 (1.51-3.25)
Latanoprost	112	19.91 (19.03-20.79)	16.64 (16.08-17.20)	3.27 (2.95-3.59)
Combination therapies	189	21.15 (20.49-21.82)	17.04 (16.59-17.49)	4.11 (3.90-4.33)
Timolol + latanoprost	39	20.51 (18.01-23.01)	16.11 (13.61-18.61)	4.40 (4.40-4.40)
Non-fixed combinations without latanoprost	94	20.72 (19.85-21.59)	17.05 (16.49-17.62)	3.67 (3.36-3.97)
Non-fixed combinations with latanoprost	54	22.36 (20.93-23.79)	17.75 (16.74-18.76)	4.61 (4.19-5.03)
Fixed combinations	2	26.00 (ND)	18.50 (ND)	7.50 (ND)
No treatment	48	17.78 (16.49-19.08)	17.85 (16.51-19.19)	-0.07 (-0.02,-0.11)
Surgery	20	22.00 (18.21-25.79)	17.24 (15.78-19.01)	4.76 (2.73-6.78)
Total	672	20.08 (19.74-20.42)	17.10 (16.86-17.35)	2.98 (2.88-3.07)

IOP = Intraocular pressure; CI = Confidence interval

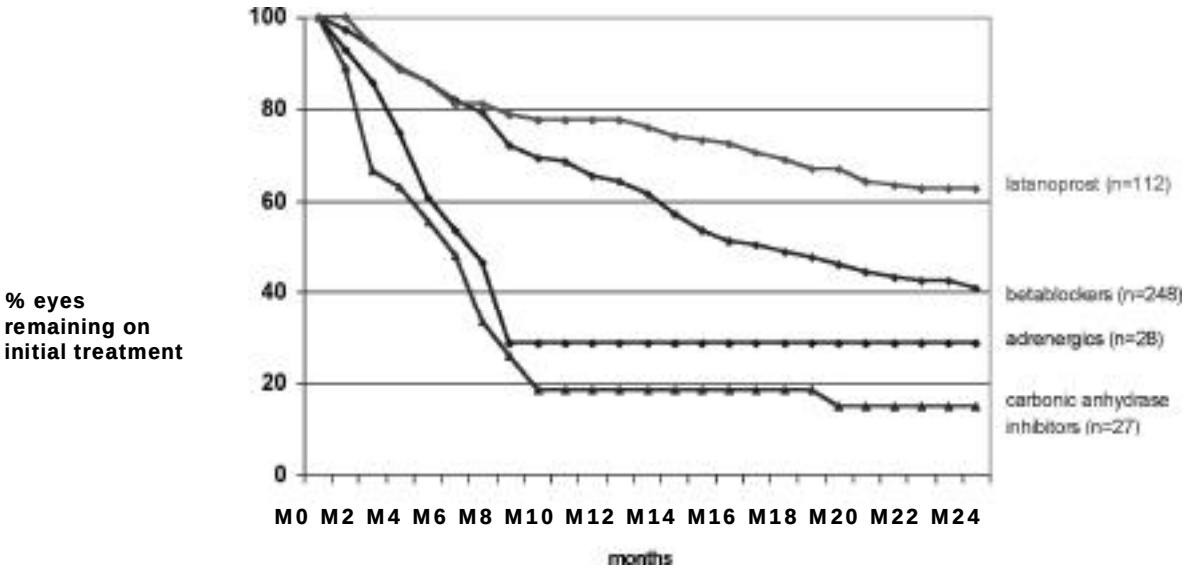
for >30 days and those enrolled in a clinical trial for OH treatment were excluded. Because the design was naturalistic, no effort was made to alter current medical practice. For example, it has been observed during patient recruitment that few physicians actually kept track of data concerning visual field and optic nerve head in patient files.

As these data concerned secondary outcomes, it was decided to proceed with inclusion and that no attempt should be made to retrieve such information in order to respect current medical practice. Patients were followed for up to 2 years, and each event, defined as any patient contact with a study ophthalmologist, was recorded.

As this naturalistic study did not introduce any modification of the patient-physician relationship, ethical committee advice was not requested. Patients were informed that they had been selected for an observational study in order to describe glaucoma management, that their medical data would be anonymous and collected over a 2- year period, and that they were free to accept or refuse the use of their medical data for statistical analysis. In compliance with the French law 78-17 of January 6, 1978, a declaration concerning data management and use has been made to the Commission Nationale de l'Informatique et des Libertés.

Patients were declared lost to follow-up when they could not be reached by the study ophthalmologist. Most common reasons for declaring a patient lost to follow-up included patient relocation, ophthalmologist relocation, repeated patient no-show at appointment with study ophthalmologist, patient referral to another ophthalmologist not participating in the study, and patient file lost. Patients regularly seen by the study ophthalmologist but who did not complete the 2-year follow-up were censored for the analysis.

TABLE VIII - PERSISTENCY WITH MONOTHERAPY (proportion of patients remaining on initial treatment)



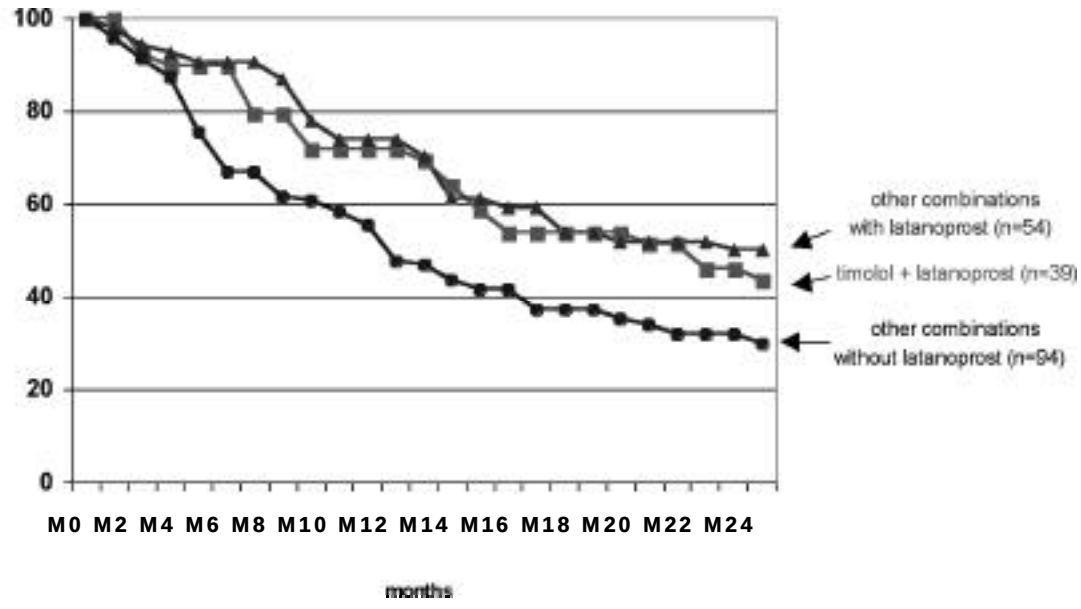
Initial second-line strategy (monotherapy)	No. of eyes treated	% Eyes remaining on initial treatment at 2 years (95% CI)
Latanoprost	112	62.5 (53.0-72.0)
Beta-blockers	248	41.1 (34.8-47.4)
Adrenergics	28	28.6 (9.8-47.4)
Carbonic anhydrase inhibitors	27	14.8 (0-38.3)

CI = Confidence interval

Outcomes evaluated in the final analysis

The present article reports results of the final analysis of 2-year follow-up data for patients having at least two events. The principal outcomes were numbers of and reasons for treatment changes. Secondary outcomes included changes in clinical parameters (IOP levels, visual field defects, and optic nerve excavation) and costs associated with patient management. The unit of measurement was treated eyes. Costs were reported in 2003 Euros (€). Only direct medical costs specific to glaucoma management were considered. These included costs associated with visits to an ophthalmologist, medical procedures (measuring the IOP or visual field, etc.), ocular hypotensive drugs, and surgery (trabeculoplasty, trabeculectomy, cataract, combined cataract-trabeculectomy, iridotomy). Indirect and intangible costs, non-reimbursed medical expenditures, and direct non-medical costs (such as patient transportation) were not collected or estimated. Resource use was evaluated from the perspective of the National Health Insurance (Caisse Nationale d'Assurance Maladie des Travailleurs Salariés), the major, non-governmental, third party payer in France. Unit costs of visits, surgery, and ambulatory care procedures were valued according to Union des Caisses Nationales de Sécurité Sociale (UCANSS) fees (Nomenclature Générale des Actes Professionnels et Nomenclature Générale des Actes de Biologie Médicale, Paris. Paris: Union des Caisses Nationales de Sécurité Sociale (UCANSS); 2002). For multiple procedures performed during the same visit on the same patient by the same physician (such as procedures on both eyes), the cost of the most expensive procedure plus 50% of the cost of the next most expensive procedure was used according to UCANSS guidelines. If the procedure cost

TABLE IX - PERSISTENCY WITH COMBINATION THERAPY (proportion of patients remaining on initial treatment)



Initial second-line strategy (combination therapy)	No. of eyes treated	% Eyes remaining on initial treatment at 2 years (95% CI)
Timolol + latanoprost	39	43.6 (26.6-60.6)
Other combinations with latanoprost	54	50.0 (35.6-64.4)
Combinations without latanoprost	94	29.8 (15.2-44.4)

CI = Confidence interval

was less than the cost of a visit to the ophthalmologist (€ 23), only the visit cost was used. Unit costs used in calculations are presented in Table I. Surgeries performed in public hospitals were valued using the 2001 relative cost scale of the French Diagnosis Related Group system (Programme de Médicalisation des Systèmes d'information) (21). Surgeries performed in private hospitals were valued using UCANSS and National Health Insurance fees. Unit costs of surgical hospital stays are presented in Table II. Because cataract surgery was considered an indirect glaucoma treatment strategy, only 10% of the total cost was included (22). The cost of combined cataract-trabeculectomy was valued as cost of trabeculectomy only.

Ocular hypotensive drugs were valued using public prices and reflect the value-added tax, current reimbursement rates, the shelf life of eye drop solutions, and defined daily dosages for tablets.

Statistical analyses

Analyses were performed using common statistical calculations for qualitative and quantitative variables. Group comparisons were made using appropriate statistical tests including the Student t test, the χ^2 test, the log rank test for survival, and the Wilcoxon test for cost variables (non-normal distributions). Significance levels were set at $p \leq 0.05$.

Statistical uncertainty concerning the costs and effectiveness of monotherapies was evaluated with a bootstrap method (24). Using observations for patients treated with latanoprost or beta-blocker monotherapy, confidence intervals for costs and IOP levels were estimated for a random sample of 1,000 patients. This iterative procedure consisted of the following steps:

Resampling with replacement of average total medical cost and IOP change in the latanoprost branch

Resampling with replacement of average total medical cost and IOP change in the beta-blocker branch

Calculation of total medical cost and IOP change in both latanoprost and beta-blocker branches

Calculation of the cost-effectiveness ratio: absolute value (latanoprost cost minus beta-blocker cost)/absolute value (change IOP latanoprost minus change IOP beta-blockers)

Repeat of steps 1 to 4 for n = 1,000.

Analysis of the distribution of the 1,000 ratios.

RESULTS

A total of 498 patients were included in the study. A total of 110 patients (22%) were lost to follow-up and 42 patients regularly seen by the ophthalmologist did not reach 2 full years of follow-up and were censored.

Although the rate of patients lost to follow-up may appear relatively high when compared to rates usually observed in controlled clinical trials, the present study is a naturalistic study, with a protocol forbidding actively researching patients lost to follow-up or identifying reasons for drop-out, as any intervention would alter real medical practice.

Two-year follow-up data were available for 346 pa-

TABLE X - FREQUENCY OF ADVERSE EVENTS

Initial second-line strategy	No. of adverse events	Frequency of adverse events, %	95% CI
Monotherapies (n=415)	204	49.2	42.1-56.3
Beta-blockers (n=248)	116	46.8	37.2-56.4
Adrenergics (n=28)	38	135.7	ND
Carbonic anhydrase inhibitors (n=27)	29	107.4	ND
Latanoprost (n=112)	21	18.8	0-38.3
Combination therapies (n=189)	96	50.8	40.2-61.4
Timolol + latanoprost (n=39)	3	7.7	0-61.3
Non-fixed combinations without latanoprost (n=94)	66	70.2	58.3-82.1
Non-fixed combinations with latanoprost (n=54)	25	46.3	24.4-68.2
Fixed combinations (n=2)	2	100	75.0-125.0
Total (n=604)	300	49.7	43.9-55.5

TABLE XI - RELATIVE RISK OF ADVERSE EVENTS ACCORDING TO INITIAL SECOND-LINE STRATEGY

Initial second-line strategy: monotherapies (n = number of adverse events)	**Relative risk vs latanoprost**	**Relative risk vs beta-blockers (95% CI)**
Beta-blockers (n=116)	2.49	1.00 (0.996-1.004)
Adrenergics (n=38)	7.21	2.90 (95% CI ND)
Carbonic anhydrase inhibitors (n=29)	5.71	2.30 (95% CI ND)
Latanoprost (n=21)	1.00	0.40 (0.16-0.64)
Initial second-line strategy: combination therapies (n = number of adverse events)	**Relative risk vs latanoprost + timolol combination**	**Relative risk vs combinations without latanoprost (95% CI)**
Timolol + latanoprost (n=3)	1.00	0.11 (0-0.22)
Non-fixed combinations without latanoprost (n=66)	9.11	1.00 (0.995-1.005)
Non-fixed combinations with latanoprost (n=25)	6.01	0.66 (0.52-0.80)
Fixed combinations (n=2)	13.00	1.42 (95% CI ND)

CI = Confidence interval

TABLE XII – TOTAL TREATMENT COSTS

Resource	**Mean cost per eye per 2 years,** €	**95% CI**	**% Of total cost**
Drugs	285.83	273.67-298.00	54.0
Visits and medical procedures	122.43	117.95-126.90	23.1
Surgery	121.32	81.48-161.16	22.9
Total cost	529.58	487.66-571.51	100

CI = Confidence interval

TABLE XIII - TOTAL TREATMENT COSTS BY TREATMENT STRATEGY

Initial second-line therapy	**No.**	**Mean cost per eye per 2 years**	**95% CI**
Monotherapy	415	451.46	406.67-496.25
Beta-blockers	248	379.33	321.10-437.57
Adrenergics	28	353.07	309.22-396.93
Latanoprost	112	557.72	486.08-629.36
Carbonic anhydrase inhibitors	27	775.18	491.23-1059.14
Combination therapy	257	655.74	575.30-736.17
Latanoprost + timolol	39	730.29	550.91-909.68
Non-fixed combinations without latanoprost	94	621.64	543.54-699.74
Non-fixed combinations with latanoprost	54	844.92	626.61-1063.23
Fixed combinations	2 4	05.49	—
No treatment	48	202.13	160.39-243.87
Surgery	20	1273.47	686.98-1859.96
Total	672	529.58	487.66-571.51

CI = Confidence interval

tients (672 treated eyes) having at least two events. Patient characteristics at inclusion are summarized in Table III. Overall, 67% of eyes were diagnosed with POAG, 23% with OH, 10% with another form of glaucoma, and the average IOP was 20.1 ± 4.1 mmHg. Visual field defects observed at first treatment change were none or minor (54.7% of eyes examined), moderate (27.0%), or severe (18.3%).

First-line treatment strategies

As might be expected given European guidelines for the management of POAG and OH, monotherapy with an ocular hypotensive was used as the first-line treatment strategy in 92.4% of eyes switching to second line (Tab. IV). Combination therapy was used initially in 5.8% of eyes, while 1.8% received no treatment. Beta-blockers were the most widely prescribed monotherapy (77.0% of eyes).

Mean IOP levels at inclusion did not differ between patients treated with latanoprost versus beta-blocker monotherapy (19.9 ± 0.9 mmHg versus 19.6 ± 0.4 mmHg, respectively) or between those treated with latanoprost + timolol versus those treated with a combination that did not include latanoprost (20.5 ± 2.5 mmHg versus 20.7 ± 0.9 mmHg, respectively).

Second-line treatment strategies

Second-line treatment was initiated an average of 2.8 ± 0.2 years after diagnosis. Reasons for treatment change (Tab. V) were insufficient IOP control (60.3%), adverse drug reactions (18.3%), visual field deterioration (9.4%), or other reasons (12.0%). The largest absolute proportions of adverse drug reactions (n=300) were associated with beta-blockers (38.7%) followed by adrenergics (12.7%), carbonic anhydrase inhibitors (9.7%), and latanoprost (7.0%). Second-line treatment strategies (Tab. VI) consisted primarily of ocular hypotensive monotherapy (61.8% of eyes) or combination drug therapy (28.1% of eyes), although a few eyes underwent surgery (3.0%) or received no treatment (7.1%).

Medical treatment intensification patterns beyond second-line

All treatment strategies considered, overall failure rate of second-line treatment was high. For 672 eyes entering second-line treatment, 399 eyes (59.4%) were switched to a third-line treatment.

As the two main reasons for switching treatment were insufficient IOP control and adverse drug reactions, treatment intensification schemes favored more effective and/or safer treatment options, while using the simplest treatment scheme available.

After failure of second-line monotherapy, the preferred option remained monotherapy with another drug; bitherapy was introduced very gradually, mostly after fourth-line treatment, and with a high proportion of treatment stops presumably due to adverse events.

After failure of second-line combination therapy, selection of an effective treatment option was the result of a trial-and-error process, alternating monotherapy and bitherapy as preferred medical treatments.

Proportion of eyes switching from second to third-line medical treatment was two times lower for eyes under latanoprost monotherapy (25.0%; 95% CI 6.9-43.1%; n=28) than for eyes under beta-blocker monotherapy (53.0%; 95% CI 44.0-62.0%; n=131) (Fig. 1). In combination therapy (Fig. 2), the proportions of eyes switching from second to third-line medical treatment were also lower for eyes under timolol + latanoprost combination (44.0%; 95% CI 16.7-71.3%; n=17) than for combinations that did not include latanoprost (68.0%; 95% CI 55.7-80.3%; n=64).

Eyes under latanoprost + timolol combination (n=39) received latanoprost once daily plus timolol once daily in 69.2% of the eyes (n=27) or timolol twice daily in 30.8% of cases (n=12).

Clinical changes after 2 years of second-line treatment

Mean IOP reductions 2 years after inclusion were 3.3 mmHg (95% CI 3.0-3.6 mmHg; from 19.9 ± 0.9 mmHg to 16.6 ± 0.6 mmHg) in eyes treated with latanoprost monotherapy versus 2.6 mmHg (95% CI 2.5-2.7 mmHg; from 19.7 ± 0.4 to 17.1 ± 0.3 mmHg) in those receiving beta-blocker monotherapy (Tab. VII).

In eyes receiving combination therapy, mean IOP reductions from time of inclusion were 4.4 mmHg (95% CI 4.4-4.4 mmHg; from 20.5 ± 2.5 mmHg to 16.1 ± 2.5 mmHg) in eyes treated with the latanoprost + timolol combination versus 3.7 mmHg (95% CI 3.4-4.0 mmHg; from 20.7 ± 0.9 mmHg to 17.1 ± 0.5 mmHg) in those receiving combination therapies that did not

include latanoprost (Tab. VII).

Thirty-five percent of the 259 eyes with follow-up information concerning visual field deterioration or optic nerve excavation showed moderate or severe impairment after 2 years, representing relative stability from time of inclusion. Proportions of eyes remaining on the same second-line treatment after 2 years were 62.5% (95% CI 53.0-72.0%) under latanoprost monotherapy (n=112) versus 41.1% (95% CI 34.8-47.4) under beta-blocker monotherapy (n=248), 28.6% (95% CI 9.8-47.4%) under adrenergic monotherapy (n=28), and 14.8% (95% CI 0.0-30.3) under carbonic anhydrase inhibitor monotherapy (n=27, Tab. VIII).

In combination therapy (Tab. IX), proportions of eyes remaining on the same second-line treatment after 2 years were 43.6% (95% CI 26.6-60.6%) in eyes receiving latanoprost + timolol (n=39) versus 29.8% (15.2-44.4%) in those treated with a combination therapy that did not include latanoprost (n=94).

Eyes receiving second-line latano-prost monotherapy remained on treatment for an average of 548 days compared with 450 days for eyes treated with beta-blocker monotherapy; eyes receiving second-line latanoprost + timolol combination therapy remained on treatment for an average of 485 days compared with 374 days for those treated with combinations that did not include latanoprost.

Adverse events during the first 2 years of second-line treatment

During the first 2 years of second-line treatment, 300 adverse events were reported in 145 patients (271 eyes); 68.0% of the events occurred under monotherapy (n=204) and 32.0% under combination therapy (n=96) (Tab. X).

Relative risk for adverse drug reactions under monotherapy was 1.00 (95% CI 1.00-1.00) under beta-blockers (n=116) versus 0.40 (0.16-0.64) under latanoprost (n=21), 2.30 under carbonic anhydrase inhibitors (n=29), and 2.90 under adrenergics (n=38). Relative risk for adverse drug reactions under combination therapy was 1.00 (1.00-1.00) for unfixed combinations without latanoprost (n=66) versus 0.11 (0.00-0.22) for unfixed combinations of latanoprost + timolol (n=3) and 0.66 (0.52-0.80) for non-fixed combinations with latanoprost (n=25) (Tab. XI).

Cardiac or pulmonary problems have been reported in 39 of the 145 patients with an adverse drug reaction (26.9% of patients).

Health care resource use and patient management

During the first 2 years of second-line treatment, patients averaged 6.3 ± 0.2 visits to an ophthalmologist (95% CI 6.09 to 6.53). The very narrow CI reflects the consensus among French ophthalmologists regarding the appropriate delay between visits (3 months) and excellent patient compliance with regard to making and keeping appointments. Mean delay between visits was 107±83 days in private practices (median 97 days, min 0 days, max 670 days, 95% CI 103 to 111 days) and 92 ± 91 days in public hospitals (median 64 days, min 0 days, max 646 days, 95% CI 84 to 101 days). Delays between visits vary according to the availability of ophthalmologists. The shortest delay between visits was observed in the Languedoc-Roussillon region (64 days) and the longest in the Nord-Pas-de-Calais region (168 days). Differences in numbers of visits over time reflected treatment intensification. For example, medical treatment following failure of beta-blocker monotherapy required an average of 6.5 visits in 2 years (n=134) versus 5.0 visits for a successful beta-blocker monotherapy (n=99); surgical treatment required 9.6 visits in 2 years (n=20).

Visual field measurements were performed in only 44.0% of eyes after 2 years of treatment (296/672). The two mostly used systems for visual field measurement were the Humphrey (67%) and Octopus (21%) perimeters (reference equipment). Overall, patients underwent an average of 2.1 visual field examinations, 3.7 ophthalmoscopies, and 0.6 gonioscopies in 2 years. The failure rate of second-line treatments was high, with 49.9% of eyes requiring a third-line medical therapy (335/672), 3.0% stopping treatment (20/672), and 6.5% having surgery (44/672). Surgery mainly remains a last-resort strategy, concerning only 14% of eyes treated at 2 years; time to procedure is summarized in Figure 3. Argon laser trabeculoplasty was the most frequently performed procedure (38%), followed by cataract surgery (14%), combined cataract + trabeculectomy surgery (13%), trabeculectomy (7%), iridotomy (4%), and other procedures (24%).

Evaluation of daily doses prescribed showed excellent

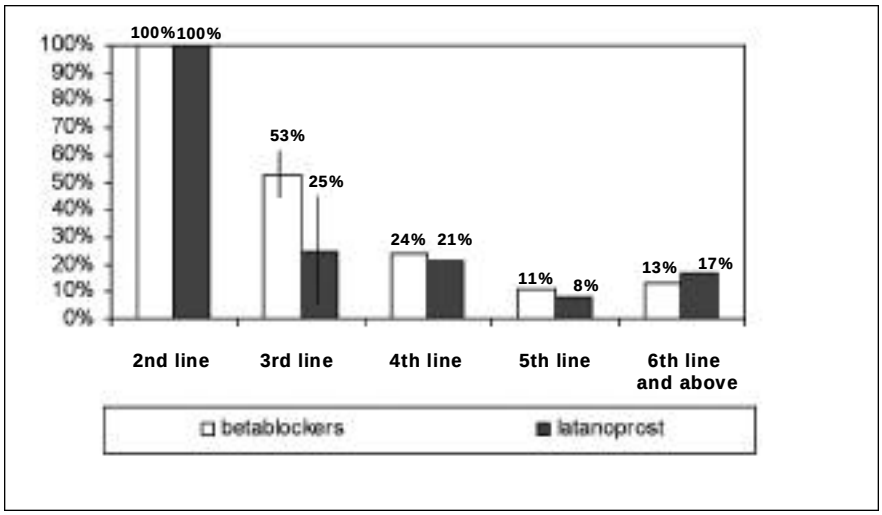


Fig. 1 - Proportion of eyes switching treatment beyond second line (reflects rate of treatment failure): monotherapy.

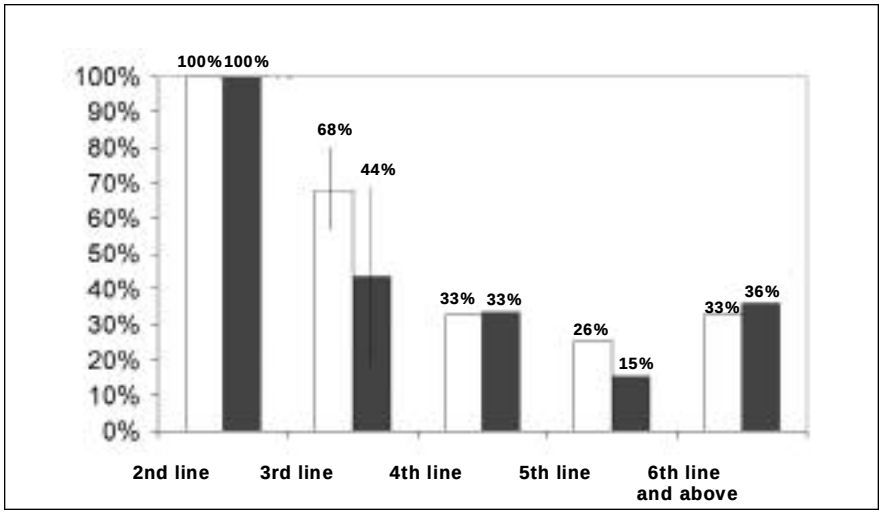


Fig. 2 - Proportion of eyes switching treatment beyond second line (reflects rate of treatment failure): combination therapy.

adherence to drug labeling: once-a-day treatment was observed in 99.3% of latanoprost prescriptions, and 40.7% of beta-blockers; twice-daily treatment was observed in 59.3% of beta-blockers, 93.4% of adrenergics, 85.6% of carbonic anhydrase inhibitors, 100.0% of the fixed combination of dorzolamide and timolol, and 92.3% of myotics.

Economic evaluation

On average, the total treatment cost of second-line therapy for POAG and OH was € 530 (95% CI: € 488 to € 572) per eye for the first 2 years of treatment (€ 0.72 per day). This cost included drugs (the main cost driver, accounting for 54.0% of the total), visits and medical procedures (23.1% of the total), and surgery (22.9% of the total) (Tab. XII). Distribution of total medical cost was multimodal, reflecting a high variability in patient treatment patterns; three major eye groups may be identified: one with a mean treatment cost between € 201 and 250, the second with a mean treatment cost between € 451 and 500, and a third group of 31 eyes with a treatment cost above € 1000 in the first 2 years of treatment (Fig. 4). Most surgeries (76%) were performed on an ambulatory basis. The average cost per operated eye was € 1210 (95% CI: € 995 to € 1425). Total treatment cost was lower to manage OH (€ 421, 95% CI: € 364 to € 479) than to manage glaucoma (€ 559, 95% CI: € 509 to € 610). Total treatment costs also varied according to treatment strategy: on average, combination therapies were 1.4 times more expensive than monotherapies. In return for better safety and persistency to treatment, latanoprost monotherapy cost an average of €

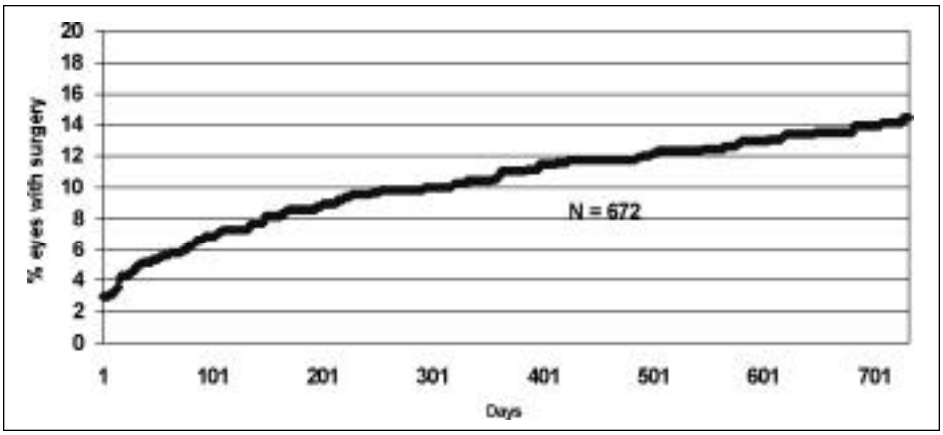


Fig. 3 - Time to surgery (proportion of patients undergoing surgery vs time). As medical treatments are usually preferred to surgery, surgical rates increase slowly over time, reaching only 14% of the eyes at 2 years.

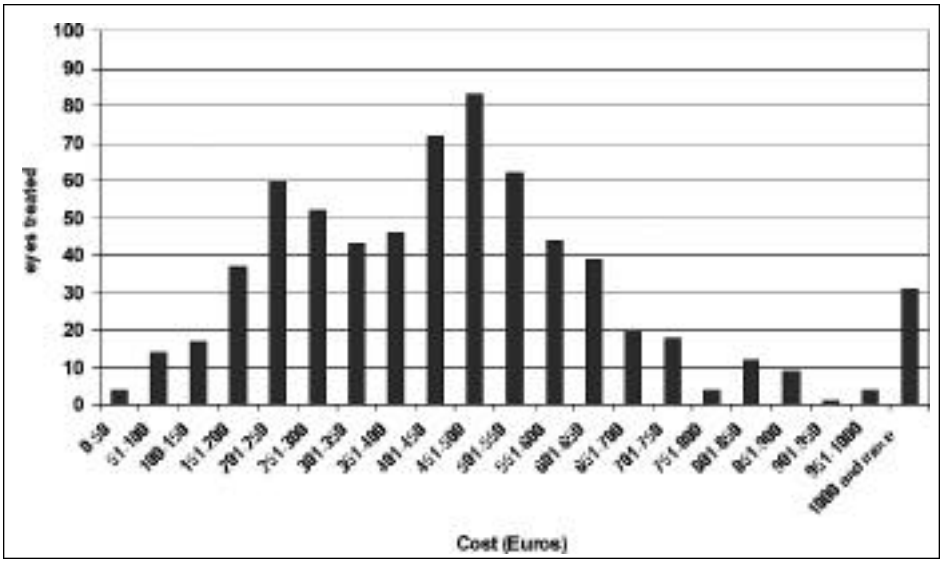


Fig. 4 - Multimodal distribution of treatment costs, reflecting variability in patient treatment pattern.

178 (95% CI: € 165 to € 192) more than beta-blocker monotherapy in the first 2 years of second-line treatment (Tab. XII-XIII).

The combination of latanoprost + timolol (€ 730 for 2 years) did not cost more than combinations that did not include latanoprost (€ 622 for 2 years). Statistical uncertainty concerning the costs and effectiveness of latanoprost versus beta-blocker monotherapy was evaluated using a bootstrap method (23). The resulting cost-effectiveness scatter plot (Fig. 5) reflects individual variability in IOP levels and patient management costs and illustrates differences in these variables for the two strategies.

Overall, the position of points indicates that latanoprost monotherapy is both more effective and more costly than beta-blocker monotherapy in 94% of cases. Two decision trees (Tabs. XIV and XV) present estimated treatment costs associated with various therapeutic outcomes for treated eyes included in the final analysis. The daily treatment cost for eyes starting a second-line treatment and persisting with this treatment for 2 years was lower for those receiving beta-blocker monotherapy than for those treated with latanoprost monotherapy (€ 0.33 per day (95% CI: € 0.31 to € 0.35) versus € 0.63 per day [95% CI: € 0.61 to € 0.64], respectively). However, the daily cost for latanoprost monotherapy (successful therapy: € 0.63 per day; therapy with failure: € 0.72 per day) was comparable to the cost of failed beta-blocker monotherapy (€ 0.62 per day (95% CI: € 0.49 to € 0.75)).

For treated eyes that began second-line treatment with a combination therapy and that persisted with this treatment for 2 years, the treatment cost for successful drug combinations that did not include latanoprost

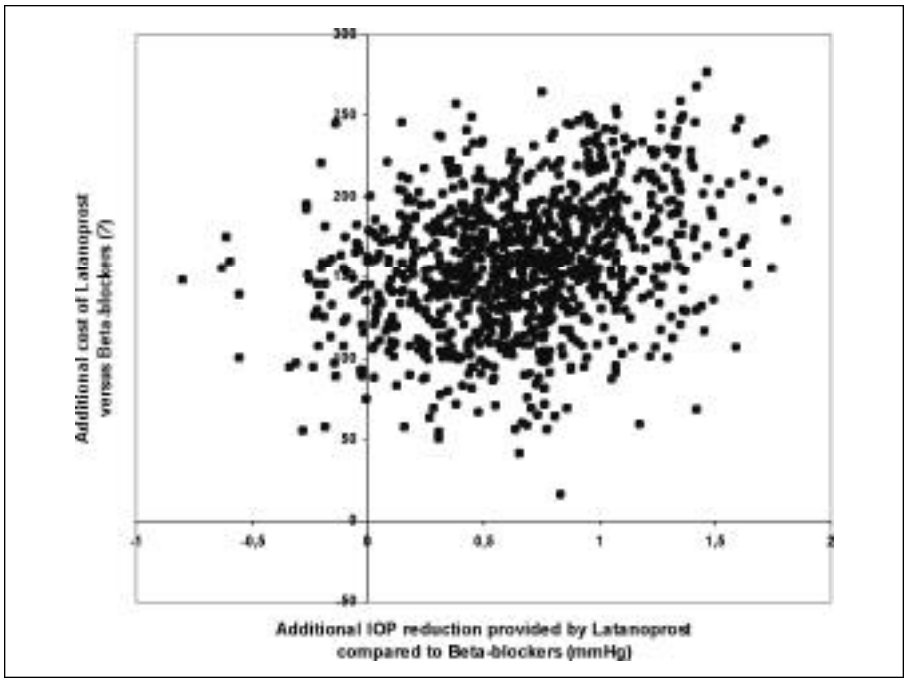


Fig. 5 - Difference of cost and effectiveness of latanoprost monotherapy compared to beta-blocker monotherapy (cost per mmHg gained): IOP=Intraocular pressure. Point distribution in scatterplot reflects individual variability of treatment for each eye treated in terms of cost and effectiveness. As 94% of points fall into the upper right quadrant, latanoprost monotherapy is almost always more effective and more costly than beta-blocker monotherapy.

(€ 0.64 per day (95% CI: € 0.60 to € 0.69)) was similar to the cost for the latanoprost + timolol combination (€ 0.80 (95% CI: € 0.75 to € 0.85)).

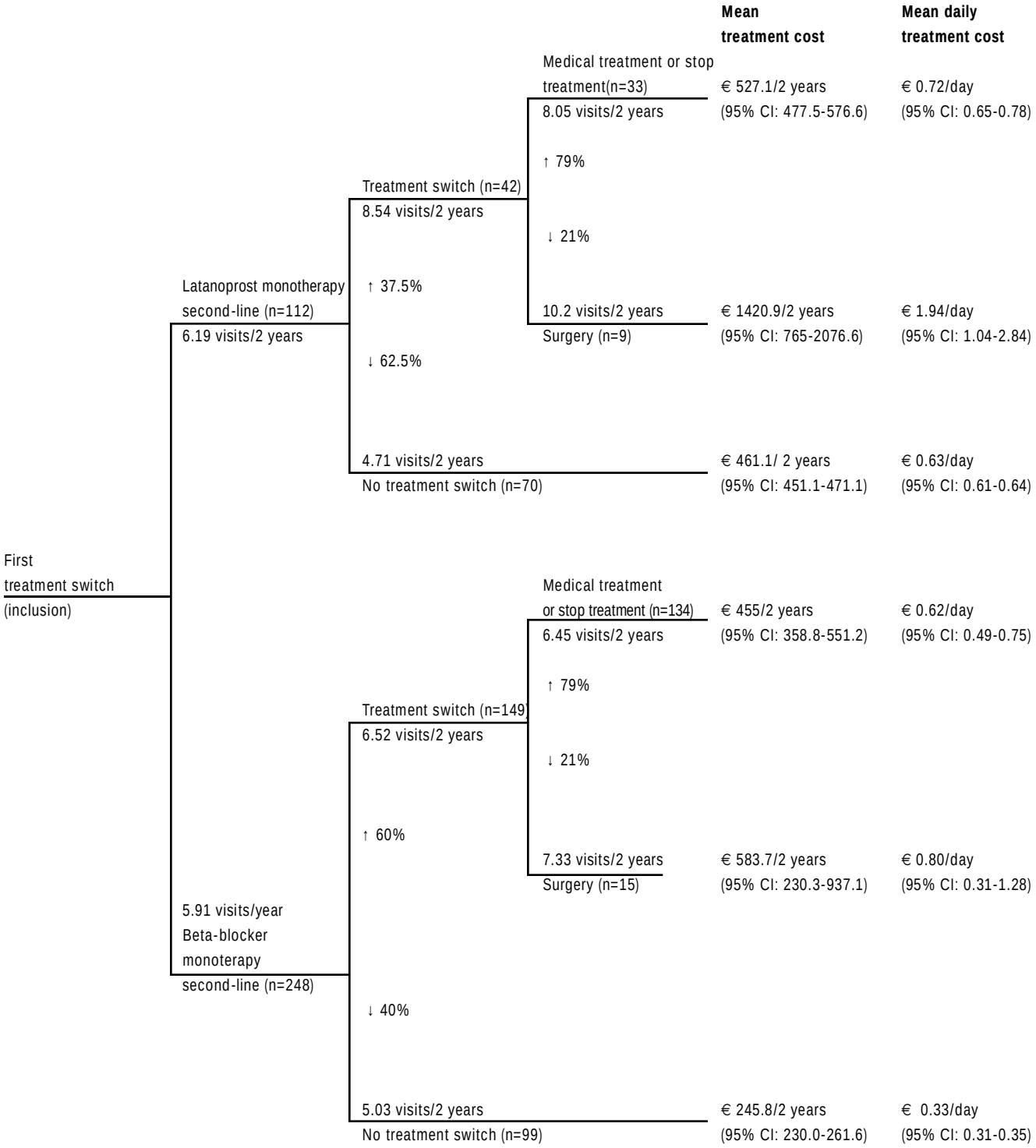
The numbers of eyes in other treatment categories (failed latanoprost monotherapy or latanoprost + timolol combination therapy, or required surgery) were insufficient to support further statistical analyses.

DISCUSSION

Although double-blind, randomized, controlled clinical trials are the standard for evaluating drugs prior to marketing, their efficacy and safety results may have limited applicability to actual medical practices. In controlled trials, patients are selected from relatively homogeneous populations, ones that are often very different from the populations of future users with regard to patient diagnoses, ages, histories, risk factors, comorbidities, and concomitant medications. While the standardized conditions of clinical trials firmly establish dose, duration of therapy, and follow-up regimens, these factors are heterogeneous in routine practice settings. Moreover, the efficacy and safety of any given drug is rarely compared in controlled trials with those for a variety of treatment strategies in patients with various diagnoses. Finally, the cost relative to medical value of a new drug and its added value in comparison to existing alternatives are not apparent at the controlled clinical trial stage; analyses of these variables require reasonably wide utilization of a therapy over a long period of time.

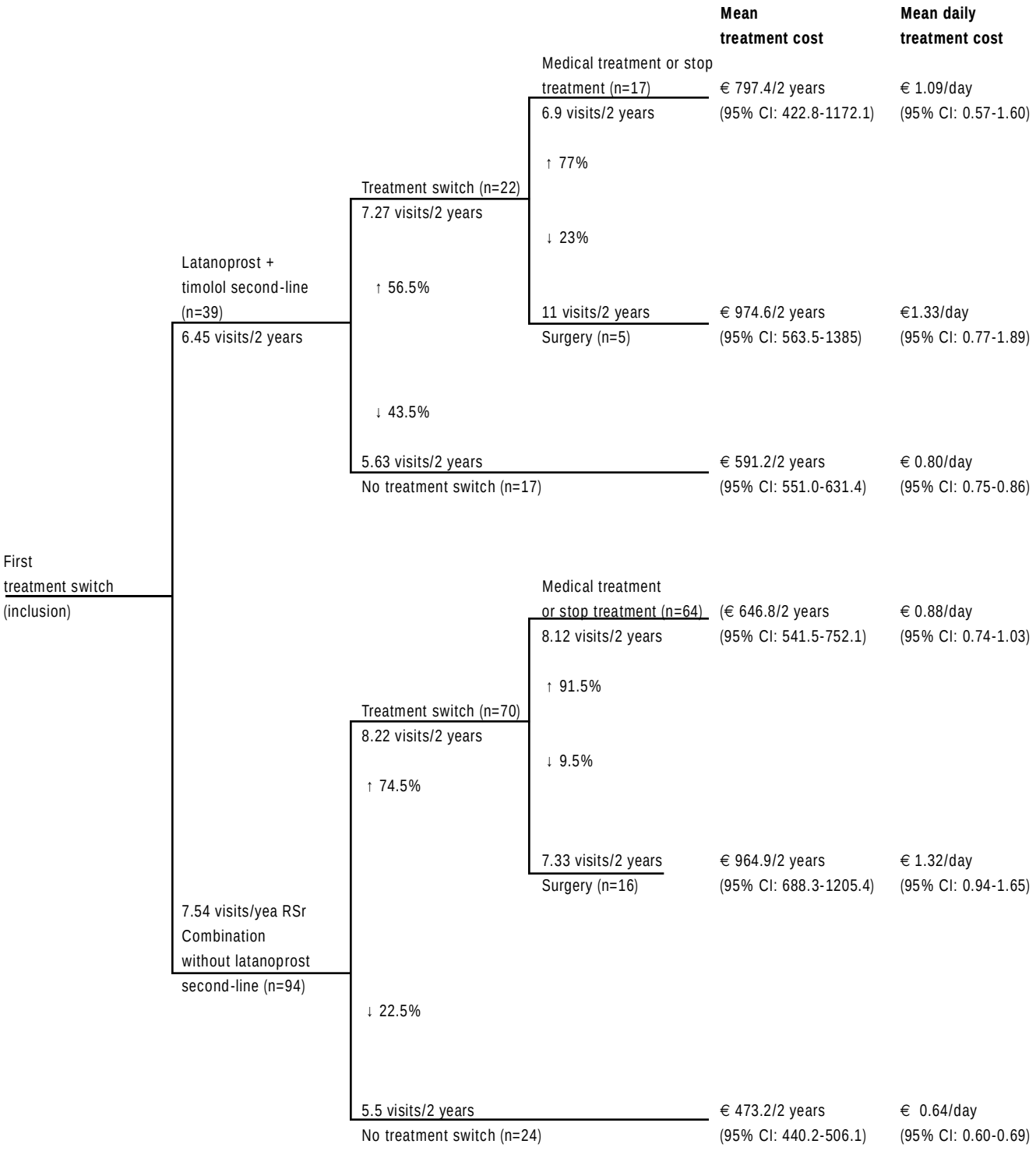
This observational study, which complements a previously published retrospective, observational study of the cost of the first 2 years of treatment in patients with POAG and OH (22), compared the effectiveness, safety, and utilization costs of latanoprost as monotherapy or in combination therapy to those of alternative treatments available in France. Data for the retrospective study were collected between January 1990 and June 1995, while data for the present prospective study were recorded prospectively between September 1998 and December 2000. Glaucoma management in France has changed markedly during the last 10 years, notably with the introduction of new drugs (such as latanoprost, brimonidine, and brinzolamide) that have been associated with reductions in glaucoma-related surgery (13-15). Reimbursement was granted to latanoprost in April 1998 (second-line indication) and September 2003 (first-line indication), to brimonidine in September 1998, and brinzolamide in June 2000. More recently, two new fixed combination therapies were also launched in France during the study period: dorzolamide + tim-

TABLE XIV - COST OF TREATMENT OPTIONS AFTER SECOND-LINE COMBINATION MONOTHERAPY
(N = number of treated eyes)



Minimum and maximum values are given instead of CIs where n's are small; CI= Confidence interval

TABLE XV - COST OF TREATMENT OPTIONS AFTER SECOND-LINE COMBINATION THERAPY
(N = number of treated eyes)



Minimum and maximum values are given instead of CIs where n's are small; CI= Confidence interval;

olol, reimbursed since February 2001, and latanoprost + timolol, reimbursed since August 2002. Travoprost was reimbursed in March 2002 and bimatoprost in May 2003. As the use of travoprost was still marginal upon study completion by the end of December 2002, we did not observe any use of this drug in the 346 patients having completed the 2 years of follow-up. Other factors, such as the development of new surgical techniques, the expansion of ambulatory surgery, the increased use of generic drugs, and the emergence of new, more expensive pharmacologic agents also have altered the costs of glaucoma management.

Because center selection and patient sampling were different in the two studies, their results cannot be directly compared. For example, more hospital centers participated in the retrospective study, which may have favored inclusion of patients with more severe disease who required more surgery and hospitalizations. In the present prospective study, centers were selected according to current glaucoma patient management in France (74% private offices, 26% hospital centers). Nevertheless, the studies yielded comparable results. For example, in both the present 2-year prospective and previous 2-year retrospective studies, the primary reason for treatment change was insufficient IOP control (60% versus 78%, respectively) and persistency of treatment with beta-blocker monotherapy diminished markedly over time (to 41% and 58%, respectively). Results also confirmed that French ophthalmologists prefer monotherapy as first-line treatment (92% of eyes). Beta-blockers were the principal treatment in France, as prostaglandins did not have first-line indication during most of the study period (latanoprost obtained a first-line indication in September 2002 and a reimbursement in this indication in September 2003). In the United States, a large percentage of patients are treated with prostaglandins (12, 24).

With regard to economic value, latanoprost monotherapy provided significantly better safety at an average incremental cost of € 89 per patient per year over beta-blocker monotherapy, and the combination of latanoprost + timolol was significantly safer than combination therapies that did not include latanoprost.

Treatment costs for patients receiving latanoprost monotherapy who persisted with treatment for 2 years were found to be comparable to those for patients who failed beta-blocker therapy. Importantly, eyes receiving latanoprost, either as monotherapy or in combination with timolol, were significantly more likely to remain on second-line treatment at the end of 1 year than were those receiving beta-blocker monotherapy or combination therapies that did not include latanoprost. Previous research has demonstrated that patients initially treated with latanoprost monotherapy remain on therapy significantly longer than those receiving beta-blockers, sympathomimetics, or carbonic anhydrase inhibitors (24-31). Changes in therapy themselves been associated with periods of intense resource utilization and increased costs (32-34).

The majority of treatment changes occur due to reduced IOP control and adverse drug reactions, which may lead to disease progression, more difficult patient management, and increased expenses. Given these interactions, it is reasonable to suggest that the early use of the most effective and safest glaucoma treatments, in the simplest possible regimens, may be not more costly over time than other ocular hypotensives.

CONCLUSIONS

In patients with POAG or OH, the high rate of treatment failure and the adverse drug reactions associated with beta-blocker therapy combined with the relatively poor medication compliance observed in patients with these conditions suggest that the simplest (one daily dose–no titration) and most effective treatment be the preferred option. Based on 2-year prospective data from current medical practice in France, we report that second-line treatment of these patients with latanoprost, as monotherapy or combined with timolol, provides superior safety and persistency to treatment at an acceptable cost.

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