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Naturalistic, prospective study of glaucoma and ocular hypertension treatment in France: Strategies, clinical outcomes, and costs at 1 year

J-F. ROULAND[1], C. LE PEN[2] AND THE OPHTHALMOLOGISTS OF THE GLAUCOMA STUDY

[1]Ophthalmology Service, Regional and University Hospital Center, Claude Huriez Hospital, Lille
[2]Dauphine University of Paris, Paris - France

PURPOSE. *To prospectively observe second-line treatment strategies, their clinical outcomes, and treatment costs in patients with glaucoma or ocular hypertension (OH) in France.*
METHODS. *Patients were recruited between 1998 and 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 in patients receiving monotherapy or combination therapy. This article reports results of an interim analysis of 1-year follow-up data for patients having at least two contacts with a study ophthalmologist.*
RESULTS. *Data were analyzed for 283 patients and 549 treated eyes. Ocular hypotensive monotherapy was used as first-line therapy in 92.0% of eyes. Second-line treatment was initiated an average of 3.4 ± 0.5 years after diagnosis, primarily due to insufficient IOP control (62.8%). Mean IOP reductions after 1 year of second-line therapy were 3.0 mmHg in eyes treated with latanoprost monotherapy versus 2.1 mmHg in those receiving beta-blocker monotherapy (p=0.02) and 5.4 mmHg in eyes treated with the latanoprost + timolol combination versus 4.1 mmHg in those receiving combination therapies that did not include latanoprost (p=0.01). Although second-line treatment with latanoprost was more costly than treatment with beta blockers, the average daily cost for latanoprost monotherapy was similar to that for patients who failed beta-blocker monotherapy, and latanoprost + timolol was less costly than therapeutic combinations without latanoprost.*
CONCLUSIONS. *Insufficient IOP control is the main reason for changing first-line treatment in patients with glaucoma or OH. After 1 year, second-line treatment with latanoprost, as monotherapy or combined with timolol, provides superior IOP control at an acceptable cost.*
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KEY WORDS. *Glaucoma, Health economics, Intraocular pressure, Ocular hypertension, Treatment strategy*

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INTRODUCTION

In France, approximately 1 million people may be at risk for glaucoma (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). In 2003, French authorities estimated that 650,000 persons were being treated for chronic glaucoma (2% of people over 40 years of age) and that 400,000 affected people were unaware that they had the disease due to an absence of functional signs until an advanced stage (1). In its terminal form, glaucoma is the leading cause of total blindness in France (1). Ageing may be a risk factor for glaucoma (3). The prevalence of the condition is estimated to be between 2% and 5% in people over 70 years old, making glaucoma the third leading cause of visual deficiency in this age group (4) and severely limiting the daily lives of those affected. Systematic screening for glaucoma is difficult because it is an asymptomatic disease, and an estimated 20% to 50% of optic nerve fibres may be lost before any damage is detected by conventional perimetry techniques (5).

Patients with elevated intraocular pressure (IOP) are at increased risk of developing primary open-angle glaucoma (POAG), the most common type (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 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.

Ocular hypertension (OH) is characterized by an IOP of >21 mmHg but no optic nerve damage (3). Up to 10% of people over 40 years of age may have OH (3), although the true prevalence of the condition is unknown due to poor systematic screening. In addition to larger cup-to-disc ratios and thinner central corneal measurements, elevated IOP levels also predict progression of OH to POAG (10). As a result, OH treatment aims at reducing such levels, and intraocular instillation of hypotensive agents has been shown to effectively delay and prevent the onset of POAG in patients with OH (11).

Topical beta-blockers often are 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 treatment frequently is 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 (12-15). Compliance with medical therapeutic regimens is low in glaucoma patients (16), however, and noncompliance plays an important role in the progression of glaucoma to blindness (2). In addition, age and concomitant diseases may impair the ability of glaucoma patients to instill drops into their eyes. Therefore, the preferred pharmacologic strategy must be the simplest treatment that maintains the target IOP level.

The French Ministry of Health recently established quantitative targets concerning glaucoma management for the years 2002 to 2007 (1). Objectives include: reduction of undiagnosed visual conditions by 20% in adults; diagnosis of all visual conditions in children; reductions in the frequency of diseases that lead to visual impairment and in the numbers of cases of blindness and visual impairment that result from treatable diseases; and preservation of visual capacity in elderly individuals with decreased vision. Recommended public health initiatives involve glaucoma screening for individuals 40 years of age and older, IOP measurements as part of examinations for eyeglass prescriptions, and periodic follow-up examinations in people over 55 years of age (1).

The present naturalistic, prospective study evaluated second-line treatment strategies, their clinical outcomes, and associated costs in patients with glaucoma or OH in France.

Comparisons between patients treated 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 (17-19).

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 was representative of ophthalmology practices in France (74% private ophthalmologist offices, 26% hospital centers). Inclusion criteria were age ≥18 years; a diagnosis of glaucoma (POAG, normal pressure glaucoma, exfoliative glaucoma, or pigmentary glaucoma) or OH in at least one eye; a clinical change in therapy, ie, 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 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. Patients were followed for up to 2 years, and each event, defined as any patient contact with a study ophthalmologist, was recorded.

Outcomes evaluated in the interim analysis

The present article reports results of an interim analysis of 1-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 IOP levels, visual field defects, and optic nerve excavation. Visual field defects, measured by perimetry, were evaluated by study ophthalmologists and were classified as minor (mean deviation [MD] ≤5 db), moderate (MD ≥5 db and ≤12 db), or severe (MD ≥12 db). Optic nerve head degradation level was based on the presence of an excavation with an early impact on the neuroretinian border (NRB) and was classified as normal (NRB not affected), moderate (localized or limited notch on the NRB), or severe (extended impact on the NRB). Costs associated with patient management were calculated and reported in 2001 euros (€). The unit of measurement was treated eyes.

Only direct medical costs specific to glaucoma management were considered. These included costs associated with visits to an ophthalmologist, medical procedures (such as measuring the IOP or visual field), ocular hypotensive drugs, and surgery (trabeculoplasty, trabeculectomy, cataract, combined cataract-trabeculectomy, iridotomy). Indirect and intangible costs, nonreimbursed medical expenditures, and direct nonmedical costs (such as transportation and home nursing) 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), a major nongovernmental, third-party payer in France. Unit costs of visits, surgery, and ambulatory care procedures were evaluated according to Union des Caisses Nationales de Sécurité Sociale (UCANSS) fees (20). 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 were used according to UCANSS guidelines. If the procedure cost was less than the cost of a visit to the ophthalmologist (€ 22.87), only the visit cost was used. Unit costs used in calculations are presented in Table I.

The cost of surgery performed in public hospitals was evaluated using the 2001 relative cost scale of the French Diagnosis Related Group system (21). Surgery performed in private hospitals was evaluated 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 calculated as cost of trabeculectomy only.

The cost of ocular hypotensive drugs was calculated using public prices and reflects the value-added tax, current reimbursement rates, the shelf life of eyedrop solutions, and defined daily dosages for tablets (23).

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 log rank test for survival, and the Wilcoxon test

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

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

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	

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

for cost variables (nonnormal distributions). Significance levels were set at p≤0.05.

Statistical uncertainty concerning the costs and effectiveness of monotherapies was evaluated using 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 1000 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 the first four steps for n=1000 and analysis of the distribution of the 1000 ratios.

RESULTS

A total of 500 patients has been included in the study. The current preliminary analysis included the 283 patients (549 treated eyes) with at least two events for whom 1-year follow-up data were available. Patient characteristics at inclusion are summarized in Table III. Overall, 70% of eyes were diagnosed with POAG, and the average IOP was 20.0 ± 4.3 mmHg.

First-line treatment strategies

As one might expect given European guidelines for the management of glaucoma and OH, monotherapy with an ocular hypotensive was used as the first-line treatment strategy in 92.0% of eyes (Tab. IV). Combination therapy was used initially in 5.6% of eyes while 0.4% of eyes were treated surgically and 2.0% received no treatment. Beta-blockers were the most widely prescribed monotherapy (79.1% of eyes). Mean IOP levels at inclusion did not differ significantly between patients treated with latanoprost versus beta-blocker monotherapy (19.3 ± 4.7 mmHg versus 19.5 ± 3.9 mmHg,

TABLE III - CHARACTERISTICS AT INCLUSION (First treatment change)

Demographic data	Number of patients followed at 1 year	283
	Number of treated eyes	549
	Mean age (years)	65 ± 1.5
	Women	128 (45.2%)
	Men	155 (54.8%)
Diagnosis (n=543)	Primary open-angle glaucoma	380 (70.0%)
	Ocular hypertension	118 (21.7%)
	Normal-pressure glaucoma	26 (4.8%)
	Exfoliative glaucoma	15 (2.8%)
	Pigmentary glaucoma	4 (0.7%)
Intraocular pressure (n=517)	Mean	20.0 ± 4.3 mmHg
	Confidence interval 95%	19.6 mmHg to 20.4 mmHg
	Median	20.0 mmHg
	Minimum	8.0 mmHg
	Maximum	38.0 mmHg

TABLE IV - FIRST-LINE TREATMENT STRATEGIES

Strategy	n	%
Monotherapy	*505*	*92.0*
Beta-blockers	434	79.1
Adrenergics	31	5.6
Carbonic anhydrase inhibitors	22	4.0
Latanoprost	16	2.9
Myotics	2	0.4
Combination therapy	*31*	*5.6*
Fixed combinations	4	0.7
Nonfixed combinations with latanoprost	6	1.1
Nonfixed combinations without latanoprost	21	3.8
No treatment	*11*	*2.0*
Surgery	*2*	*0.4*
Total	*549*	*100*

TABLE V - REASONS FOR FIRST-LINE TREATMENT CHANGE

Reason for change	n	%
IOP insufficiently controlled	345	62.8
Adverse drug reactions	94	17.1
Visual field deterioration	52	9.5
Suspected aggravation of optic nerve head excavation	14	2.6
IOP well controlled	14	2.6
Poor compliance	7	1.3
Patient's wish	3	0.5
Contraindication	2	0.4
Treatment discontinued or modified prior to surgery	2	0.4
Other reasons	16	2.9
Total	549	100

IOP=Intraocular pressure

TABLE VI - SECOND-LINE TREATMENT STRATEGIES

Strategy	n	%
Monotherapy	*337*	*61.4*
Beta-blockers	209	38.1
Latanoprost	90	16.4
Adrenergics	28	5.1
Carbonic anhydrase inhibitors	10	1.8
Combination therapy	*165*	*30.1*
Latanoprost + timolol	39	7.1
Other combinations with latanoprost	51	9.3
Combinations without latanoprost	75	13.7
No treatment	*34*	*6.2*
Surgery	*13*	*2.4*
Total	*549*	*100*

respectively; p=0.76) or between those treated with the unfixed combination of latanoprost + timolol versus those treated with a combination that did not include latanoprost (20.9 ± 3.7 mmHg versus 21.3 ± 3.9 mmHg, respectively; p=0.66).

Second-line treatment strategies

Second-line treatment was initiated an average of 3.4 ± 0.5 years after diagnosis. Primary reasons for treatment change (Tab.V) were insufficient IOP control (62.8%), adverse drug reactions (17.1%), and visual field deterioration (9.5%). The largest proportion of adverse drug reactions (n=94) was associated with beta-blockers (61.7%) followed by adrenergics (21.3%), carbonic anhydrase inhibitors (12.8%), or other drugs (4.2%). Second-line treatment strategies (Tab. VI) consisted primarily of ocular hypotensive monotherapy (61.4% of eyes) or combination drug therapy (30.1% of eyes), although a few eyes underwent surgery (2.4%) or received no treatment (6.2%).

Clinical changes after 1 year of second-line treatment

Mean IOP reductions 1 year after inclusion were 3.0 mmHg (from 19.3 ± 4.7 mmHg to 16.3 ± 3.8 mmHg) in eyes treated with latanoprost monotherapy versus 2.1 mmHg (from 19.5 ± 3.9 mmHg to 17.4 ± 3.0 mmHg) in those receiving beta-blocker monotherapy (p=0.02) (Fig. 1). In eyes receiving combination therapy, mean

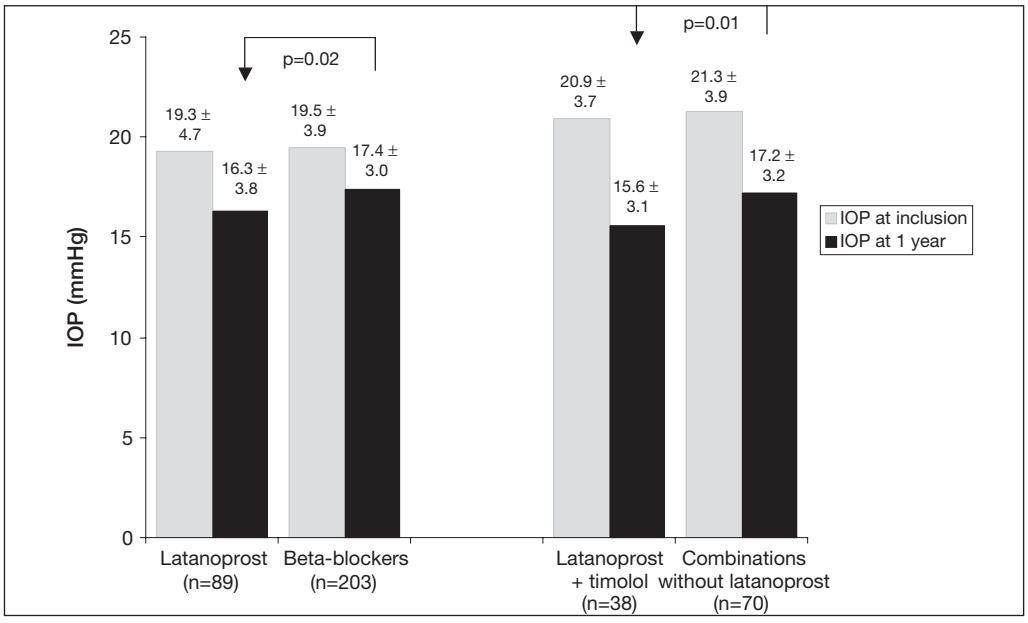

Fig. 1 - *Mean intraocular pressure (IOP) reduction 1 year after inclusion.*

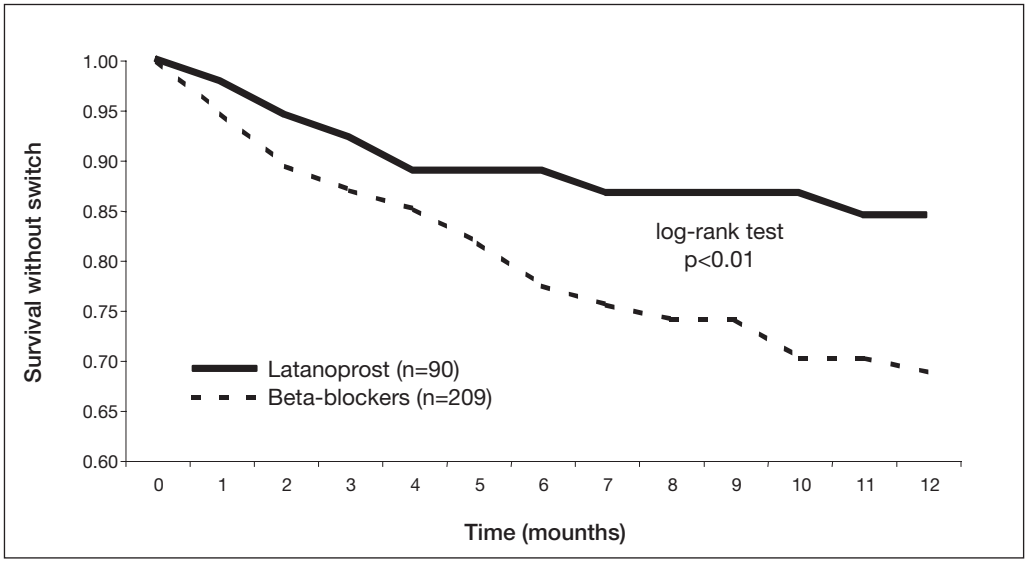

Fig. 2 - *Persistency with monotherapy. Proportion of patients remaining on initial therapy.*

IOP reductions from time of inclusion were 5.4 mmHg (from 20.9 ± 3.7 mmHg to 15.6 ± 3.1 mmHg) in eyes treated with the latanoprost + timolol combination versus 4.1 mmHg (from 21.3 ± 3.9 mmHg to 17.2 ± 3.2 mmHg) in those receiving combination therapies that did not include latanoprost (p=0.01).

Visual field measurements were performed in 43.5% of eyes after 1 year of treatment. During this period, patients underwent medians of 1.2 visual field examinations, 2.4 ophthalmoscopies, and 0.9 gonioscopies. No clinically detectable deterioration was seen in either optic nerve head excavation or visual field between inclusion and after 1 year of treatment.

Proportions of eyes remaining on the same second-line treatment after 1 year were 84.4% in those receiving latanoprost monotherapy versus 68.9% in those treated with beta-blocker monotherapy (p=0.0068; Fig. 2) and 79.5% in eyes receiving latanoprost + timolol combination therapy versus 44.0% in those treated with a combination therapy that did not include latanoprost

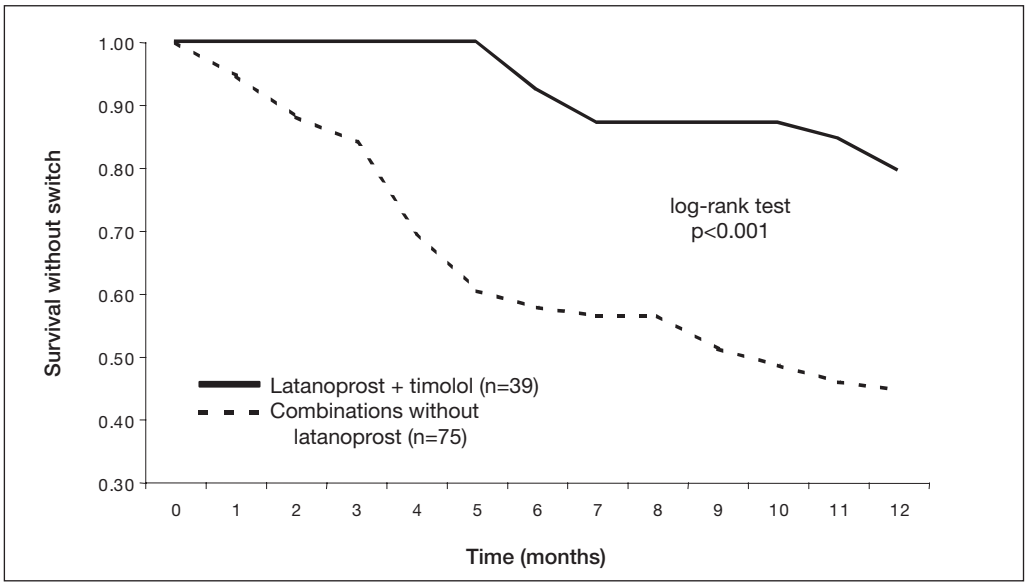

Fig. 3 - *Persistency with combination therapy. Proportion of patients remaining on initial therapy.*

(p=0.0002; Fig. 3). Eyes receiving second-line latanoprost monotherapy remained on treatment for an average of 326 days compared with 292 days for eyes treated with beta-blocker monotherapy (p=0.01); eyes receiving second-line latanoprost + timolol combination therapy remained on treatment for an average of 340 days compared with 237 days for those treated with combinations that did not include latanoprost (p<0.0001).

Health care resource use and patient management

During the first year of second-line treatment, patients averaged 4.0 (95% confidence interval [CI]: 3.8 to 4.2) visits to an ophthalmologist. The very narrow CI reflects the consensus among French ophthalmologists regarding the appropriate length of time between visits (3 months) and excellent patient compliance with regard to making and keeping appointments. Notably, just 8% of surviving patients were lost to follow-up, demonstrating high patient loyalty to their ophthalmologists. Differences in numbers of visits over time reflected treatment intensification. On average, monotherapy required fewer visits than combination therapies (3.7 visits per year, n=337, versus 4.5 visits per year, n=165; p<0.01). Medical treatment following failure of beta-blocker therapy required 4.5 visits per year (n=62).

The failure rate of second-line and subsequent treatments was high, with 40.3% of eyes requiring a third-line medical therapy, 18.4% a fourth-line therapy, 9.8% a fifth-line therapy, and 8.6% a sixth-line therapy and above (Fig. 4). Cessation of treatment was observed in 8.2% of the eyes. Surgery occurred in 12.2% of eyes overall and was performed in 65 of 534 eyes with no previous surgery; time to procedure is summarized in Figure 5. Argon laser trabeculoplasty was the most frequently performed procedure (55.4%) followed by cataract surgery (18.5%), trabeculectomy (13.8%), combined cataract + trabeculectomy surgery (9.2%), and iridotomy (3.1%).

Economic evaluation

On average, the total treatment cost of second-line therapy for glaucoma or OH was € 262 per eye for the first year of treatment (€ 0.72 per day). This cost included drugs (the main cost driver, accounting for 56.9% of the total), visits and medical procedures (26.0% of the total), and surgery (17.2% of the total) (Tab. VII). The average cost per operated eye was € 700 (95% CI: € 485 to € 915).

Total treatment costs varied according to treatment strategy, and on average, combination therapies were 1.8 times more expensive than monotherapies. In return for significantly better IOP control, latanoprost

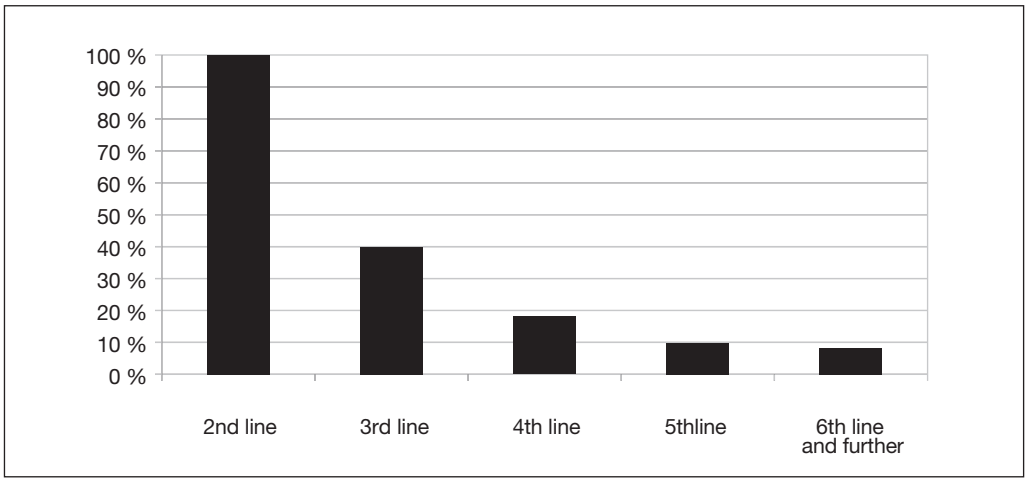

Fig. 4 - *Proportion of eyes switching treatment beyond second line, reflecting treatment failure. 2nd line n=549 (inclusion); 3rd line n=221; 4th line n=101; 5th line n=54; 6th line and further n=47.*

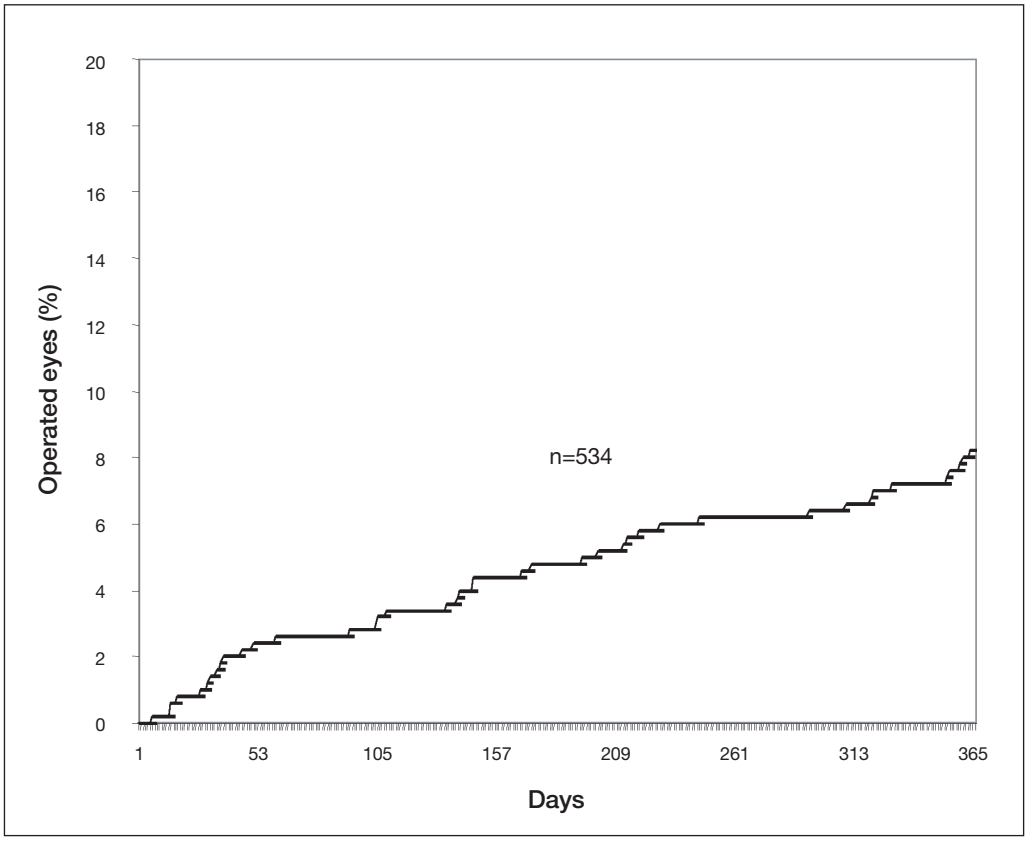

Fig. 5 - *Proportion of patients undergoing surgery versus time. As medical treatments usually are preferred to surgery, surgical rates increased slowly over time, reaching only 8% of the eyes at 1 year.*

monotherapy cost an average of € 89 (95% CI: € 74 to € 105; p<0.0001) more than beta-blocker monotherapy in the first year of second-line treatment (Tab. VIII). The combination of latanoprost + timolol was both more effective and less costly than combinations that did not include latanoprost. On average, the latanoprost + timolol combination cost € 38 less than combinations without latanoprost (p=0.014) in the first year of treatment. In addition, the latanoprost + timolol combination provided significantly better IOP control.

Statistical uncertainty concerning the costs and effectiveness of latanoprost versus beta-blocker monotherapy was evaluated using a bootstrap method (19). The re-

TABLE VII - TOTAL TREATMENT COSTS

	Mean cost per eye per year	95% CI	% of total cost
Drugs	€ 149	€ 141 - € 156	56.9
Visits and medical procedures	€ 68	€ 65 - € 71	26.0
Surgery	€ 45	€ 21 - € 69	17.2
Total cost	€ 262	€ 236 - € 287	100

CI=Confidence interval; €=Euro

TABLE VIII - TOTAL TREATMENT COSTS BY TREATMENT STRATEGY

	n	Mean total treatment cost	95% CI
Monotherapy			
Beta-blockers	209	€ 179	€ 146 - € 212
Adrenergics	28	€ 201	€ 179 - € 224
Latanoprost	90	€ 268	€ 220 - € 317
Carbonic anhydrase inhibitors	10	€ 306	€ 241 - € 370
Combination therapy			
Latanoprost + timolol	39	€ 321	€ 284 - € 358
Combinations without latanoprost	75	€ 359	€ 265 - € 453
Combinations with latanoprost	51	€ 420	€ 291 - € 548
No treatment	*34*	*€ 126*	*€ 97 - € 154*
Surgery	*13*	*€ 549*	*€ 157 - € 941*
Total	*549*	*€ 262*	*€ 236 - € 287*

CI=Confidence interval; €=Euro

sulting cost-effectiveness scatter plot (Fig. 6) reflects individual variability in IOP levels and patient management costs and illustrates differences in these variables for the two treatments. Overall, the position of points indicates that latanoprost monotherapy is both more effective and more costly than beta-blocker monotherapy in 97% of cases. On average, one would expect to pay € 102 more for latanoprost than for beta-blocker therapy per 1 mmHg of control gained after 1 year of treatment (95% CI: € 32 to € 516).

Two decision trees (Figs. 7 and 8) represent estimated treatment costs associated with various therapeutic outcomes for treated eyes included in the present interim analysis. The daily treatment cost for eyes starting a second-line treatment and persisting with this treatment for 1 year was significantly lower for those receiving beta-blocker monotherapy than for those treated with latanoprost monotherapy (€ 0.36 [95% CI: € 0.34 to € 0.38] versus € 0.65 [95% CI: € 0.64 to € 0.66], respectively; p<0.001). However, the daily cost for latanoprost monotherapy was similar to that for those who failed beta-blocker monotherapy (€ 0.68 [95% CI: € 0.47 to € 0.89]; p=0.26). For treated eyes that began second-line treatment with a combination therapy and that persisted with the treatment for 1 year, the treatment cost for drug combinations that did not include latanoprost was somewhat lower than the cost for the latanoprost + timolol combination (€ 0.75 [95% CI: € 0.69 to € 0.80] versus € 0.88 [95% CI: € 0.81 to € 0.95], respectively). The treatment cost for the latanoprost + timolol combination, however, was comparable to that in those who changed medical treatment following the failure of a combination therapy that did not include latanoprost (€ 0.87 [95% CI: € 0.74 to € 1.00]). At this stage of the study, the numbers of eyes in other treatment categories (failed latanoprost monotherapy or latanoprost + timolol combination therapy or required surgery) are insufficient to support 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, controlled clinical trials rarely compare the efficacy and safety of any given drug with the effectiveness and tolerabili-

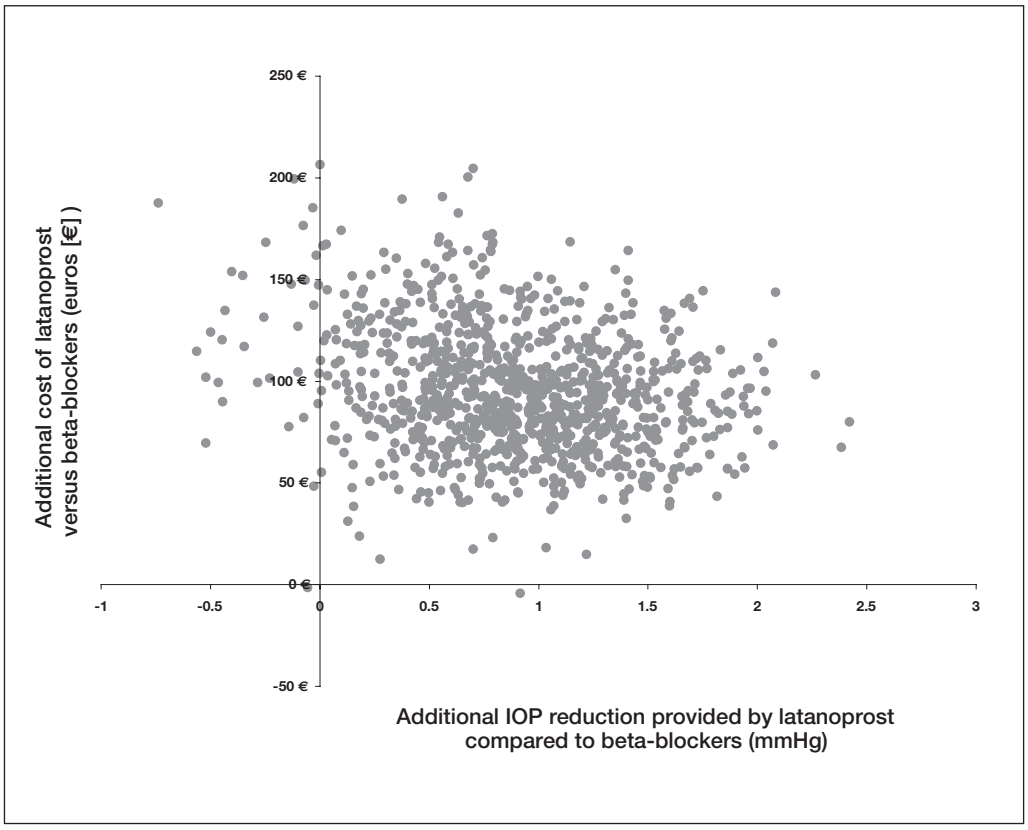

Fig. 6 - *Difference of cost and effectiveness of latanoprost monotherapy compared to beta-blocker monotherapy (cost per mmHg gained); IOP=Intraocular pressure. The point distribution in the scatter plot reflects individual variability of treatment for each eye treated in terms of cost and effectiveness. As 97% of points fall into the upper right quadrant, latanoprost monotherapy is almost always more effective and more costly than beta-blocker monotherapy.*

ty of a variety of treatment strategies. Finally, the cost relative to the 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 glaucoma or 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 previously reported study were collected between January 1990 and June 1995 while data for the present study were recorded prospectively between September 1998 and December 2000. Glaucoma management has changed markedly during these 10 years, notably with the introduction of new drugs (latanoprost was approved in France in September 1997) that have been associated with reductions in glaucoma-related surgery (12-15). 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 ophthalmologist offices, 26% hospital centers). Nevertheless, the studies yielded comparable results. For example, in both the present 1-year prospective and previous 2-year retrospective studies, the primary reason for treatment change was insufficient IOP control (62% versus 78%, respectively), and persistency of treatment

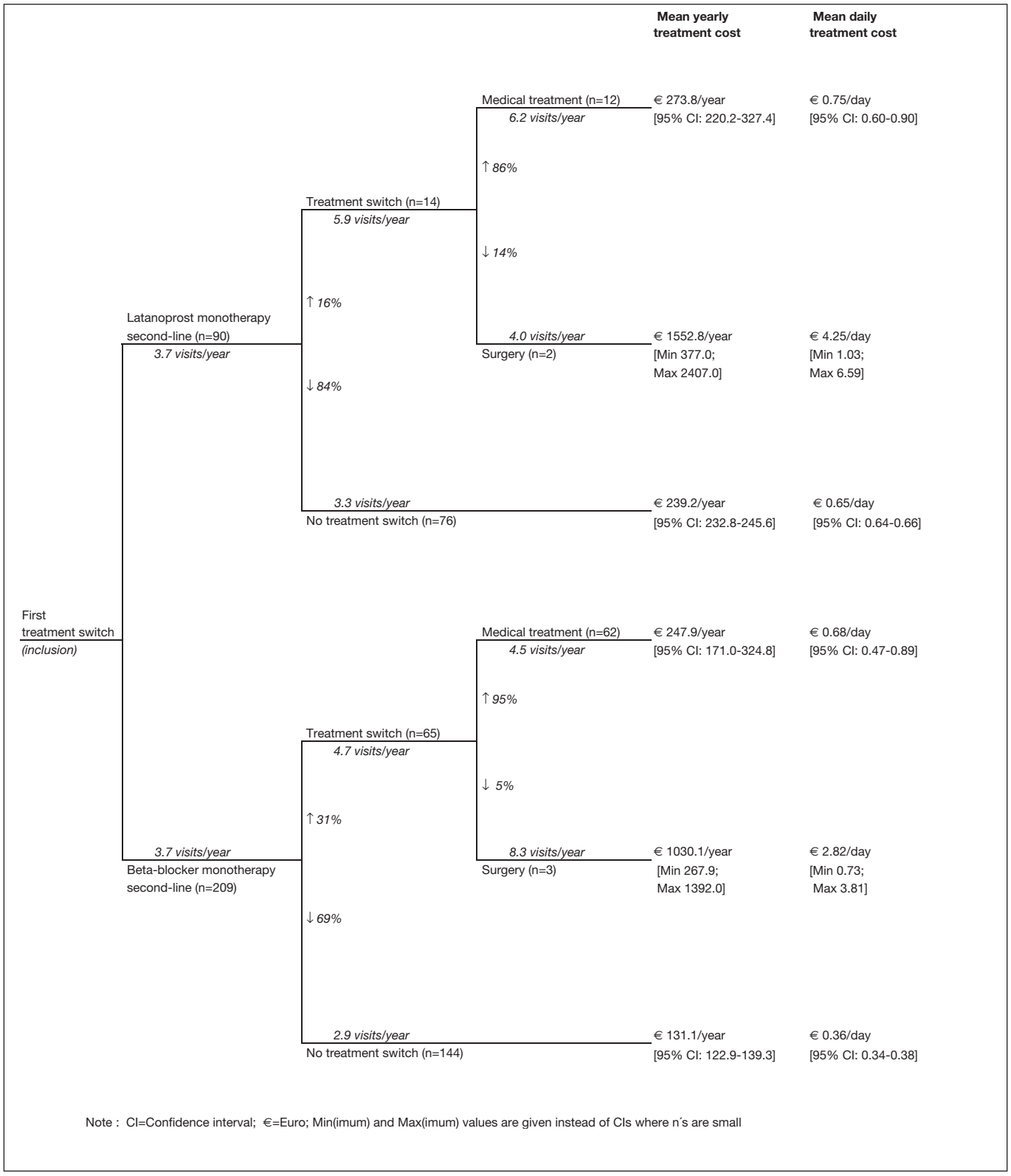

Fig. 7 - *Cost of treatment options after second-line monotherapy (n=number of treated eyes).*

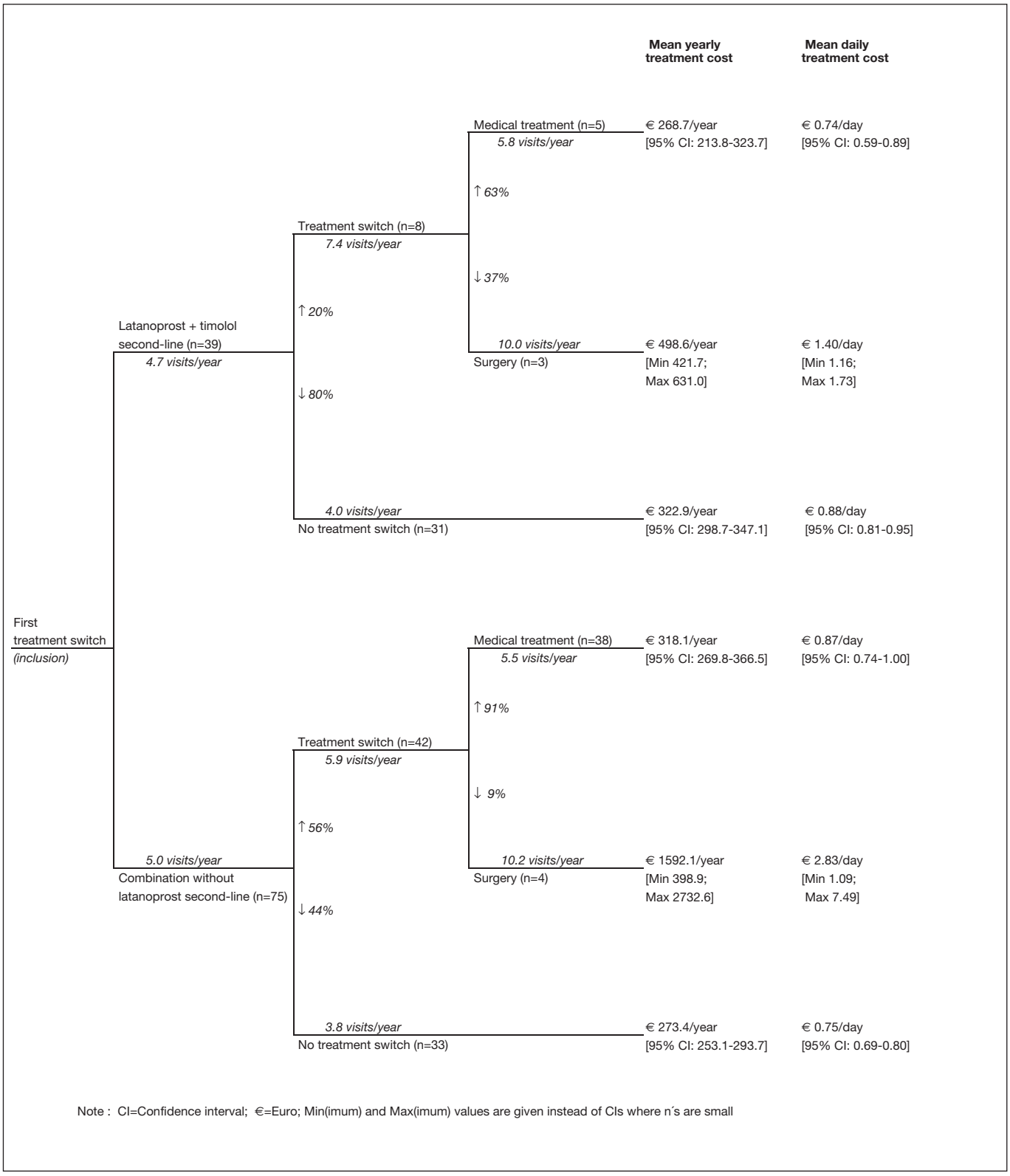

Fig. 8 - *Cost of treatment options after second-line combination therapy (n=number of treated eyes).*

with beta-blocker monotherapy diminished markedly over time (to 69% and 58%, respectively). In addition, results of the present study support the hypothesis generated in the retrospective study that a durable reduction of IOP by a single glaucoma drug reduces the number of visits required. Results also confirmed that French ophthalmologists prefer monotherapy as first-line treatment (92% of eyes). Interestingly, beta-blockers remain the principal treatment in France, although a large percentage of patients in the United States is now treated with prostaglandins (11, 25).

Evaluation of the cost of daily patient ocular hypotensive therapy has found the costs of newer adjunctive therapies, including latanoprost and brimonidine, are similar to those of more traditional regimens (26, 27). In the present naturalistic study, latanoprost monotherapy provided significantly better IOP control at an average incremental cost of € 89 per patient per year, and the combination of latanoprost + timolol was both more effective and less costly than combination therapies that did not include latanoprost. Treatment costs for patients receiving latanoprost monotherapy who persisted with treatment for 1 year were estimated 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 (25, 28, 29). Not only have changes in therapy themselves been associated with periods of intense resource utilization and increased costs (30, 31) but also the majority of treatment changes occur due to reduced IOP control, which may lead to disease progression, more intensive patient management, and increased expenses. Given these interactions, it is reasonable to suggest that latanoprost, either as monotherapy or in combination with other drugs, may be found to be less costly to use over time than other ocular hypotensives even though its use as second-line therapy is more costly in the short term than is treatment with beta-blockers. Analyses of 2-year data reflecting the full sample of more than 500 patients should further clarify these relationships and will be free of any selection bias that may be present in this analysis of a subset of 283 patients.

CONCLUSIONS

In patients with glaucoma 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 and most effective treatment be the preferred option. Based on 1-year data from current medical practices in France, we conclude that second-line treatment of these patients with latanoprost, as monotherapy or combined with timolol, provides superior IOP control at an acceptable cost.

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Reprint requests to:
Prof. Jean-François Rouland, MD
Service d'Ophtalmologie
Centre Hospitalier Régional et Universitaire de Lille
Hôpital Claude Huriez
12 avenue Oscar Lambret
59037 Lille, France
jfr3@wanadoo.fr

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