

Daily costs of prostaglandin analogues as monotherapy or in fixed combinations with timolol, in Denmark, Finland, Germany and Sweden

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Background: To compare the daily costs of 3 prostaglandin analogues (bimatoprost, latanoprost, travoprost), alone, and associated with timolol in 4 European countries (Denmark, Finland, Germany, and Sweden).

Methods: Six glaucoma products were sampled by buying 5 bottles from 1 suburban pharmacy in each of the 4 countries. Drops were weighed by a single operator at 1 site according to standardized procedures. Residual drops were then counted. Unit bottle costs were estimated from tariff lists. Eye-drop weights were entered into a nested analysis of variance comprising drug, instillation day, country, the interaction, and a sample factor nested within the country factor. Effectiveness was represented by treatment failure rates estimated from a meta-analysis and a general practitioner survey.

Results: Every drug bottle contained sufficient drops to treat 1 patient for 28/31 days. Drop-size heterogeneity between countries was observed for bimatoprost and bimatoprost/timolol. Mean travoprost and travoprost/timolol drop-sizes were the smallest, and drop-counts per bottle were the lowest for latanoprost, or latanoprost/timolol. In all 4 countries annual costs were least for travoprost and travoprost/timolol.

Conclusions: On taking into account drug costs and effectiveness, travoprost and travoprost/timolol were cheaper and more effective than latanoprost and latanoprost/timolol and were cheaper than bimatoprost and bimatoprost/timolol.

Keywords: prostaglandin analogue, economics, daily cost

Introduction

Glaucoma prevalence in industrialized countries ranges from 1% to 3% and constitutes a major cause of irreversible blindness worldwide.¹ Its most common form in adults is primary open-angle glaucoma (POAG), which is associated with increased intraocular pressure (IOP) and leads to progressive visual field loss.² To preserve visual function, it is essential to prevent optic nerve damage by decreasing intraocular hypertension.

First-line treatment in POAG aims at reducing IOP, usually with one of the following three prostaglandin analogues (PGAs): latanoprost 0.005% (Xalatan®; Pfizer Inc., New York, NY, USA), travoprost 0.004% (Travatan®; Alcon Inc., Fort Worth, Texas, USA), and bimatoprost 0.03% (Lumigan®; Allergan Inc., Irvine, CA, USA). When any of these single agents fails to control IOP sufficiently it is customary to add a beta-blocker, often in a fixed combination. Various fixed combinations have recently become available, eg, bimatoprost 0.03%/timolol (Ganfort®; Allergan Inc., Irvine, CA, USA), latanoprost 0.005%/timolol (Xalacom®; Pfizer Inc, New York, NY, USA), and travoprost 0.004%/timolol (DuoTrav®; Alcon Inc., Fort Worth, Texas, USA).

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Optimization of expenditure on medical resources first depends on evaluating efficacy and safety data, but subsequently extends to disease costs and, in particular, treatment costs. Several clinical trials have directly compared the aforementioned PGAs, in monotherapy and in fixed combinations with timolol.^{3–18} A meta-analysis by Denis et al¹⁹ found that IOP was better controlled (1 mmHg, approx) by travoprost or bimatoprost than by latanoprost, ie, the incidence rate ratio (IRR) of IOPs > 18 mmHg was 1.17 (1.00; 1.35) higher with latanoprost.

Treatment costs are important not only to health authorities but also to general practitioners responsible for their drug budgets, as in Germany. Several studies have focussed on glaucoma drug costs, using various methods and economic indicators (eg, costs per mmHg decrease; costs to attain a 20% IOP decrease).^{20–24} The number of eye-drops in a bottle (drop-count) is also a major item when estimating daily treatment costs, as the drop-count fixes the number of treatment days delivered per bottle.

According to the study conducted by Frankel in the United States, bimatoprost 0.03% had the lowest monthly and annual costs and the greatest cost effectiveness for lowering IOP compared with latanoprost 0.005% and travoprost 0.004%. The savings came from more drops in a bimatoprost bottle (113 for bimatoprost 0.03%, 84 for latanoprost 0.005%, and 83 for travoprost 0.004%), resulting in longer treatment duration per bottle. Cost effectiveness was based on an average cost per mmHg reduction IOP.

The aim of this manuscript was to check whether the above results would apply to 4 selected EU countries. This study compares the daily and annual treatment costs associated with various first-line and second-line treatments for patients with glaucoma or IOP in several European countries.

Methods

The study included 4 European countries: Denmark, Finland, Germany, and Sweden. Three first-line, single agents for IOP control were compared, ie, bimatoprost 0.03% (BP), latanoprost 0.005% (LP), and travoprost 0.004% (TP). Similarly, 3 fixed-combination agents for second-line therapy were compared, ie, bimatoprost 0.03%/timolol (BP/T), latanoprost 0.005%/timolol (LP/T), and travoprost 0.004%/timolol (TP/T).

Drop-count estimate

Each of the 6 glaucoma treatments was sampled by buying 5 new eye-drop bottles (4 bottles of travoprost 0.004% in Finland, only) from 1 suburban pharmacist in each of the 4 countries. All bottles had similar expiry dates and all

were sent to the US for centralized drop-count and drop-size evaluations, performed by a single assessor in order to reduce measurement variability.

Measurement methods followed standard operating procedures. Bottles were numbered sequentially and all outer encumbrances were removed (eg, shrink bands and obvious closure rings). Each container was weighed and its dispensing angle for drop expression was specified and recorded. A weigh boat, or suitable container, was centered on the balance pan and tared. A sample bottle was selected and shaken, as appropriate, before removing the cap. Any overflow was recorded before the bottle was held above the weigh boat, at the desired angle from horizontal, and finally 1 drop was dispensed into the weigh boat. The bottle number and drop weight ('drop-size' to the nearest 0.0001 g, 0.1 mg) were recorded. The sequence was repeated for the second drop. The cap was then replaced and the bottle stored upright for reweighing on subsequent days.

According to the relevant Summaries of Product Characteristics,²⁵ shelf-life after bottle opening ranged from 28 to 31 days, depending on the product and country. Hence a maximum of 62 measurements were performed, as above, on every bottle of all 6 drugs purchased in each of the 4 countries, to represent patients' daily instillations. On the day when the last of 62 weighings was completed, the procedure continued until the bottle was empty in order to measure the total fill of each bottle and, in due course, estimate the average number of drops in a bottle and total fill (sum of drop weights). The percentage of total product remaining in each bottle, after 62 weighings were completed, was also estimated and averaged. Observations were averaged for the total fill in grams (SD; range), drop-size in milligrams (SD; range), and total drop-count per bottle (SD; range).

Treatment cost estimation

Treatment costs, expressed as euros (2008), were estimated for each country and agent in terms of average drop count and local retail price. Annual and daily costs were calculated for each agent and country, based on local public prices^{26–29} and treatment durations of 28 and 31 days per month, as specified in the Summary of Product Characteristics of the country concerned.

Statistical analysis

The statistical analysis was performed with SAS software (SAS Institute, North Carolina, USA) Release No. 9.1. All statistical tests were interpreted two-sided with alpha fixed at 5%.

Drop-sizes (mg) for the first 62 drops per bottle of each agent were analyzed in order to evaluate experimental reliability, and drop-size variability was estimated across instillation days and between countries for each agent.

A nested analysis of variance was conducted separately for each agent comprising 'day' and 'country' factors treated as fixed effects, their possible interaction, and a 'sample factor' nested within the 'country factor'. Except for 1 missing sample (Finland: travoprost 0.004%) the design was fully balanced. Homoscedasticity and normality of the residues were checked. Graphs plotted the average daily drop-size evolution per agent for individual countries, or overall, according to observed statistical significances. Stepwise regression analyses determined effects and the best-fitting trend generated by linear, quadratic, and cubic models.

Results

The daily evolution of average drop-sizes over 1 month is shown in Figures 1 to 3 for monotherapy and Figures 4 to 6 for fixed combination agents. Statistically significant differences in drop-size were observed across simulated instillation days with all agents in all 4 countries. In particular, both the LP (Figure 2) and LP/T (Figure 5) curves differ from those of alternative agents by decreases of average drop-size over time. The TP (Figure 3) and TP/T (Figure 6) curves show slight fluctuations about steady average drop-sizes.

Significant differences between countries were observed with BP and BP/T. The BP curve for Denmark indicates a

smaller mean drop-size during the first half of the month, compared to all other countries (Figure 1; $P < 0.0001$). This is reflected in Table 1 where the mean drop-size was less than in all other countries, which were similar. The BP/T curve for Finland indicates smaller mean drop-sizes across the entire experimental period, especially in the first half of the month, compared to its curves in other countries (Figure 4; $P < 0.0001$). This conforms to the mean drop-size in Table 1. Other BP/T trend differences between countries indicate increasing mean drop-sizes over time (high at the end of the month) for Denmark and Germany, and a slow biphasic trend for Sweden (decreasing at the start of the month, then rising).

Tables 2 to 9 present the mean total fill and drop-counts of all 6 agents (monotherapy and fixed combinations) per country. Drop-counts were highest for BP/T and decreased in the sequence LP/T > TP/T in all countries. The mean drop-count *per* bottle varied from 79 to 115 across all agents, but was always least with LP and LP/T. Given the number of drops required for 62 instillations over 31 days, the remaining 'unused' drops per bottle were least for LP and LP/T (+21% to +24%) in all countries. The percentage of remaining drops was highest for TP/T (+41% to +46%) in all countries, except Finland, and slightly less for BP and BP/T (+39% to +42%).

Annual and daily costs of glaucoma treatment were calculated for each country based on public retail prices (Tables 2 to 9). Annual costs (based on 28/31 days per month)

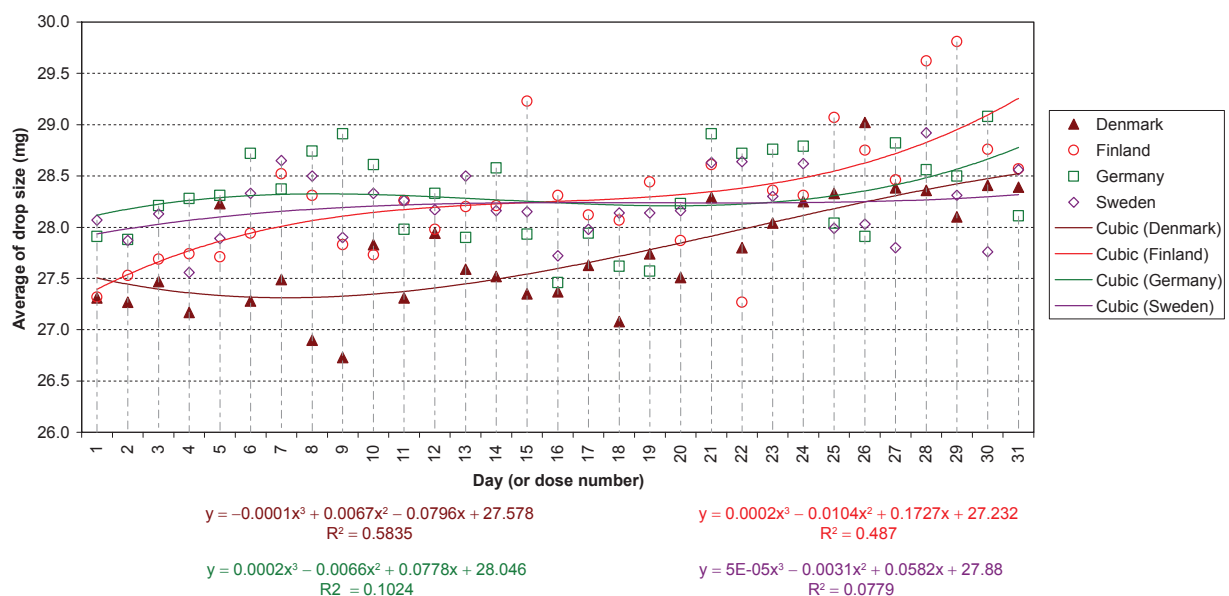


Figure 1 Bimatoprost 0.03%: daily average of drop size by country and trend fitting.

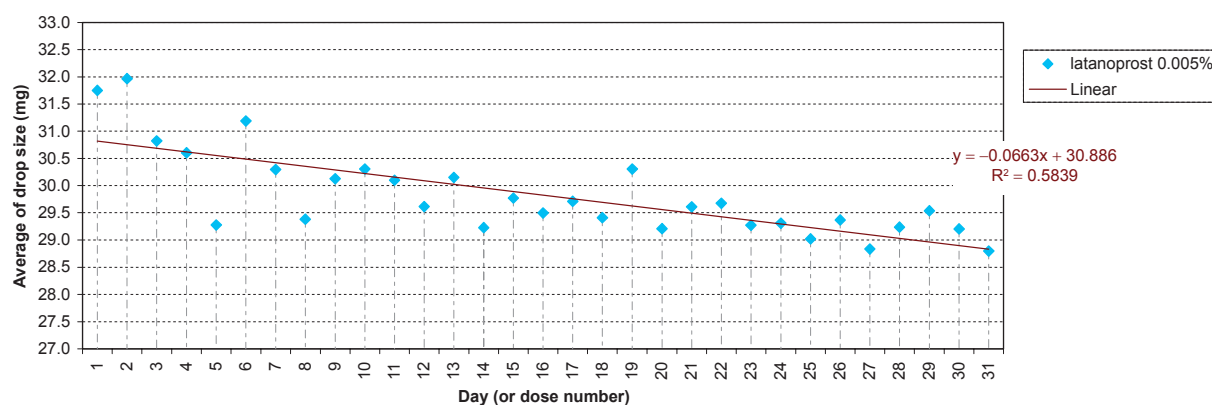


Figure 2 Latanoprost 0.005%: daily average of drop size and trend fitting.

of the three first-line monotherapy agents were higher for LP than BP (€13/€12) or TP (€22/€20) in Germany, and higher than BP (€45/€40) or TP (€45/€40) in Denmark. In Sweden, TP was cheaper than both BP and LP. For second-line fixed combinations, annual costs were more for LP/T than BP/T (€46/€41) or TP/T (€46/€41) in Sweden. Annual costs were also more for LP/T than BP/T (€12/€10) or TP/T (€41/€35) in Germany. In Finland LP/T and BP/T were equal in price, but cost more than TP/T (€12/€11). In Denmark BP/T cost more than both LP/T (€15/€14) and TP/T (€37/€34), but LP/T cost more than TP/T (€22/€19). Thus, irrespective of country and duration of treatment, the least expensive drug combination overall was TP/T followed by BP/T or LP/T, depending on the country.

Discussion

Our analysis shows that daily and annual costs of both TP and TP/T, after taking account of product shelf-life, were less than those of all corresponding glaucoma products in all four countries studied.

Our findings differ from those of Frenkel et al who considered that glaucoma products could be used until a bottle is empty.²⁰ The latter study was performed in the US, where the healthcare environment and economic analytic methods differed from those of the present study, which followed European Summaries of Product Characteristics recommendations on product shelf-life following bottle opening. Obviously, their estimates would not apply to EU countries in which patients are advised to renew their medication when shelf-life is exceeded.

Lastly, their cost-effectiveness decision rule was based on average ratio, while incremental cost-effectiveness ratio is the estimate which is recommended by most health economics guidelines, leading to inefficient resource allocation. Also, IOP, a surrogate end-point of glaucoma progression, was used as an effectiveness parameter, although it is no more than a clinical trial efficacy parameter. Health authorities are not paying to reduce IOP, but to avoid blindness.

Drop-size has economic significance, too, which may be understood as follows. The conjunctival cul-de-sac normally

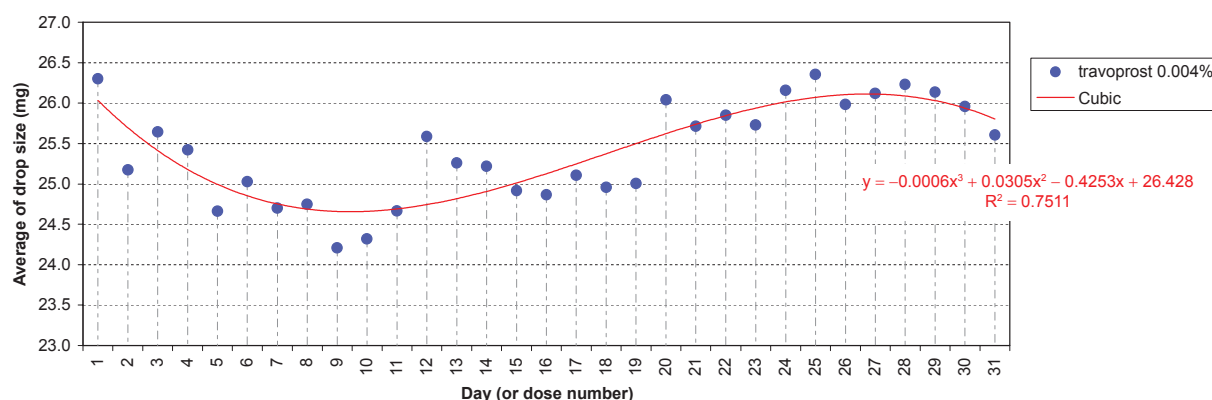


Figure 3 Travoprost 0.004%: daily average of drop size and trend fitting.

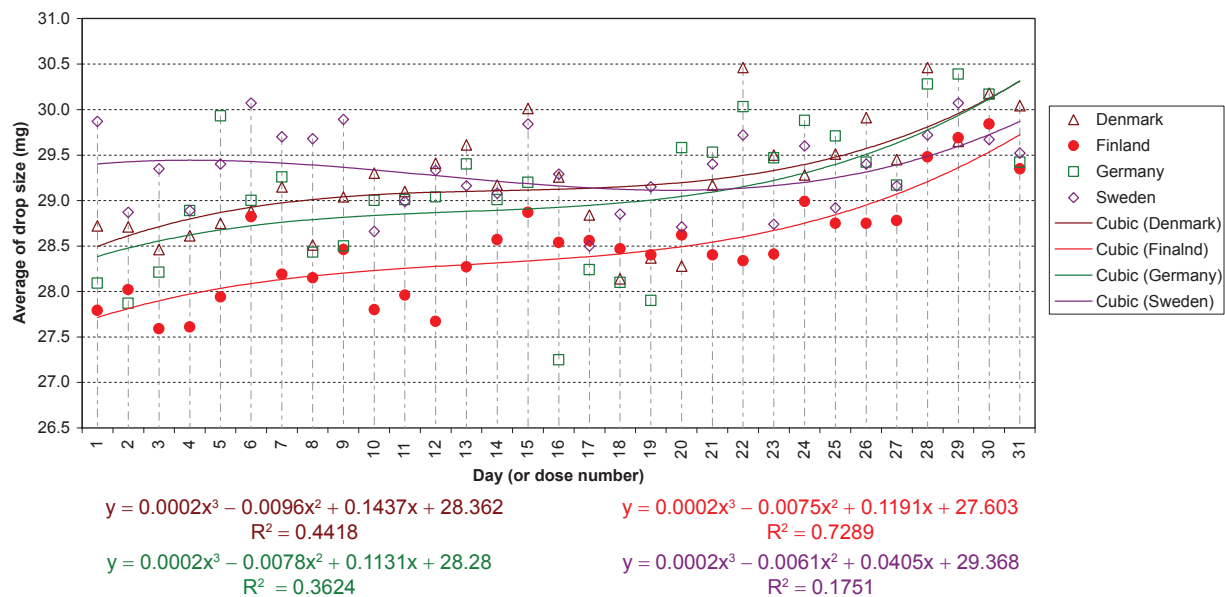


Figure 4 Bimatoprost 0.03% + timolol: daily average of drop size by country and trend fitting.

holds 7 to 9 μL of tears^{30,31} and contains a maximum fluid content of about 30 μL .³⁰ Hence, an instillation volume of 20 μL is usually considered adequate.³² In fact, the average drop-size in all countries studied always exceeded 20 μL , but only the first 20 μL would remain in the eye. Some of the remainder would be partially absorbed, with possible systemic effects, with the remainder coursing down the cheek and leading to possible skin effects. Nonetheless, a sufficient delivery of drug into the eye is assured. However, from bioavailability and toxicological points of view volumes <20 μL should be instilled.^{33–35} Moreover, smaller drop-sizes minimize waste and increase the number of drops available from bottles filled to a standard volume. Amongst monotherapy products TP bottles delivered the smallest drop sizes, as did TP/T amongst fixed combinations. Drop-size is determined by various

factors, eg, design and physical characteristics of the dropper tip and bottle, physico-chemical properties of the solution, and the manner in which the patient dispenses drops.³⁶

The methods we used to count drops were highly standardized in order to minimize the biases when comparing drop counts between brands. Therefore, it probably does not truly reflect the clinical reality of glaucoma patients and counts realized according to daily practice might be associated with higher variability. However, we think that the probability of getting contradictory results in daily practice might be low, when brand bottles look very similar. Drop counts collected with a medical device at the patient home would be required to confirm our findings.

All sampled eye-drop bottles provided sufficient drops for 28 to 31 days of treatment, as required by the Summaries of

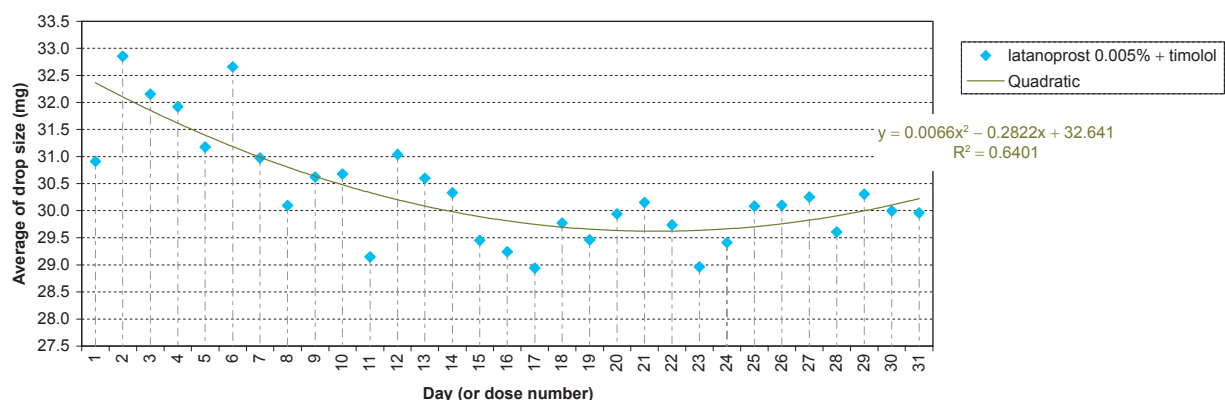


Figure 5 Latanoprost 0.005% + timolol: daily average of drop size and trend fitting.

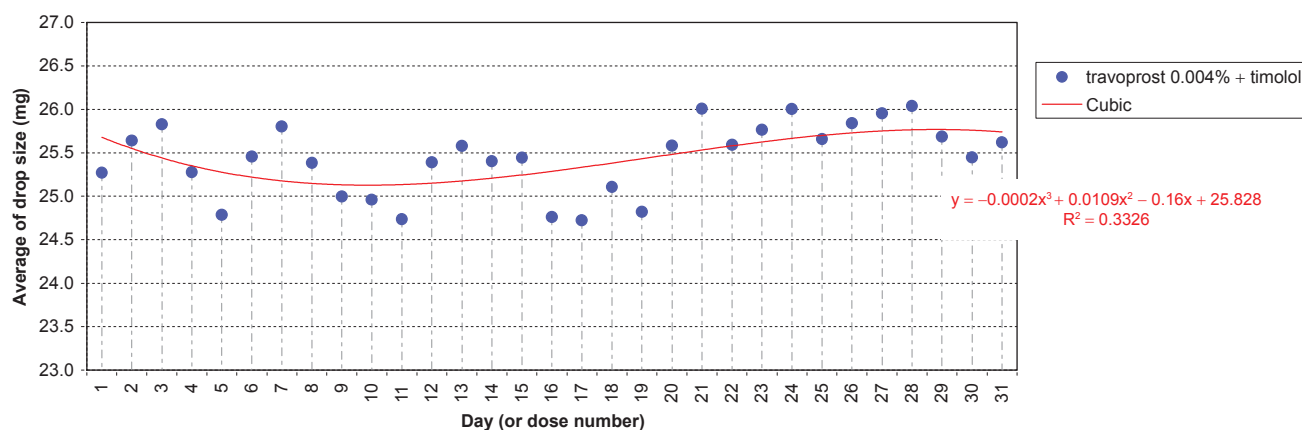


Figure 6 Travoprost 0.004% + timolol: daily average of drop size and trend fitting.

Product Characteristics. Extra drops were an assurance that the bottles could be used up to at least 28 or 31 days. Among monotherapy products, TP and BP provided greater surety than LP in all 4 countries. For fixed combination products, TP/T provided the greatest reserve in all 4 countries. Extra drops are important as older and some younger patients find it difficult to instill glaucoma drops and sometimes may miss entirely.^{37–39} In such situations TP and TP/T bottles provided

the greatest reserve of drops, despite containing less fluid than their competitors.

The fact that for BP and BP/T we found different drop-counts between countries raises the question of cost generalizations between countries and suggests that purchasers might well conduct counts before reaching decisions. Also, parallel imports might not be neutral in terms of the number of drops provided.

Table I Daily drop-size (mg) by country of each drug

Drug	Drug	Country	N	Mean	(SD)	[Range]
PGA	bimatoprost 0.03%	Denmark	310	27.74	(0.943)	[23.1–31.0]
		Finland	310	28.28	(1.211)	[25.9–34.4]
		Germany	310	28.31	(0.929)	[25.9–31.2]
		Sweden	310	28.20	(0.842)	[23.1–30.8]
	latanoprost 0.005%	Denmark	310	29.99	(3.158)	[21.9–48.0]
		Finland	310	29.75	(3.373)	[20.0–48.9]
		Germany	310	29.86	(2.931)	[22.9–49.1]
		Sweden	310	29.70	(3.002)	[22.5–49.0]
	travoprost 0.004%	Denmark	310	25.87	(1.415)	[20.6–32.6]
		Finland	248	25.04	(1.756)	[17.6–28.6]
		Germany	310	26.06	(2.168)	[15.5–33.9]
		Sweden	310	24.58	(1.857)	[19.4–32.1]
PGA/timolol	bimatoprost 0.03% + timolol	Denmark	310	29.22	(1.100)	[25.3–33.2]
		Finland	310	28.49	(1.017)	[25.2–31.4]
		Germany	310	29.08	(1.308)	[22.9–35.4]
		Sweden	310	29.33	(0.995)	[25.3–32.8]
	latanoprost 0.005% + timolol	Denmark	310	30.18	(2.52)	[12.6–50.8]
		Finland	310	30.54	(2.692)	[20.6–46.1]
		Germany	310	30.42	(2.803)	[21.8–46.5]
		Sweden	310	30.22	(3.326)	[20.2–53.9]
	travoprost 0.004% + timolol	Denmark	310	25.79	(1.313)	[21.8–29.4]
		Finland	310	25.54	(1.567)	[18.9–28.9]
		Germany	310	25.85	(1.329)	[20.6–30.2]
		Sweden	310	24.57	(1.694)	[18.3–28.7]

Abbreviations: N, number of weighted drops; PGA, prostaglandin analogue; SD, standard deviation.

Table 2 Prostaglandin analogue monotherapy bottle contents and costs (euros) for Denmark

	Bimatoprost 0.03% (BP)	Latanoprost 0.005% (LP)	Travoprost 0.004% (TP)
Total fill (g)	3.22 ± 0.09	3.01 ± 0.02	2.63 ± 0.01
[Range]	[3.09–3.31]	[2.99–3.04]	[2.63–2.65]
Number of drops	104 ± 2	79 ± 2	94 ± 5
[Range]	[102–107]	[75–80]	[90–101]
No. days treatment per month	31/28	31/28	31/28
% drops remaining after monthly treatment (31/28 days)	41%/46%	21%/29%	34%/41%
Product public price	20.95	24.36	20.94
Annual cost (31 days)	247	287	247
Daily cost (31 days)	0.676	0.786	0.675
Annual cost (28 days)	273	318	273
Daily cost (28 days)	0.748	0.870	0.748

Of course, pharmaceutical savings are not sufficient when considering treatment costs and must be set in the context of effectiveness. In this respect, a recent meta-analysis by Denis et al¹⁹ showed that monotherapy with 2 recent PGAs (TP and BP) were more effective than LP in controlling IOP. According to data in the UK GPRD, the probability of no treatment switch with TP as first-line treatment was 69.5% after 1 year.⁴⁰ On applying the IRR (1.17), measured by Denis et al¹⁹ the probability of no treatment switches with LP as first-line treatment was 59.4%, about 10% more than with TP. Therefore, costs generated by more frequent treatment switches⁴¹ must be added to the higher price of LP. Consequently, in the present 4 European countries, TP would better control IOP at a lower treatment cost.

A similar conclusion may be drawn for second-line fixed combination treatments. According to Denis et al⁴² the probability of a treatment switch with TP/T instillations

is less than for LP/T. Consequently, patients treated with the first-line/second-line sequence TP/TP/T would experience fewer treatment failures than those treated with the LP/LP/T sequence. At 60 months TP used as the first-line prostaglandin followed by TP/T as the second-line treatment would avoid one third-line prescription in every 11 incident cases. Since, in the present 4 countries, TP and TP/T drug costs were less than those of LP and LP/T, respectively, the former drug sequence would provide a better IOP control at a lower treatment cost. A full cost-effectiveness analysis needs to be conducted to confirm these hypotheses.

Our survey suffers from several limitations. First, we purchased only a maximum of 5 bottles in each country from a single selected pharmacy, hence national extrapolation is questionable. Second, we assumed that our procedure mimicked the patients' mode of instillation. Our standardized

Table 3 Prostaglandin analogue monotherapy bottle contents and costs (euros) for Finland

	Bimatoprost 0.03% (BP)	Latanoprost 0.005% (LP)	Travoprost 0.004% (TP)
Total fill (g)	3.31 ± 0.08	3.00 ± 0.02	2.74 ± 0.01
[Range]	[3.249–3.43]	[2.97–3.02]	[2.73–2.74]
Number of drops	103 ± 4	79 ± 3	104 ± 11
[Range]	[98–109]	[74–82]	[93–116]
No. days treatment per month	31/28	31/28	31/28
% drops remaining after monthly treatment (31/28 days)	40%/45%	21%/29%	41%/46%
Product public price	24.97	24.97	24.11
Annual cost (31 days)	294	294	284
Daily cost (31 days)	0.805	0.805	0.778
Annual cost (28 days)	326	326	314
Daily cost (28 days)	0.892	0.892	0.861

Table 4 Prostaglandin analogue monotherapy bottle contents and costs (euros) for Germany

	Bimatoprost 0.03% (BP)	Latanoprost 0.005% (LP)	Travoprost 0.004% (TP)
Total fill (g)	3.22 ± 0.09	3.01 ± 0.02	2.68 ± 0.01
[Range]	[3.09–3.31]	[2.99–3.04]	[2.66–2.69]
Drop-count	103 ± 3	79 ± 4	92 ± 4
[Range]	[98–106]	[73–82]	[89–99]
No. days treatment per month	31/28	31/28	31/28
% drops remaining after monthly treatment (31/28 days)	40%/45%	22%/29%	33%/39%
Product public price	30.61	31.61	29.88
Annual cost (31 days)	360	372	352
Daily cost (31 days)	0.987	1.020	0.964
Annual cost (28 days)	399	412	390
Daily cost (28 days)	1.093	1.129	1.067

Table 5 Prostaglandin analogue monotherapy bottle contents and costs (euros) for Sweden

	Bimatoprost 0.03% (BP)	Latanoprost 0.005% (LP)	Travoprost 0.004% (TP)
Total fill (g)	3.22 ± 0.05	3.00 ± 0.03	2.82 ± 0.15
[Range]	[3.18–3.28]	[2.96–3.03]	[2.71–2.99]
Number of drops	103 ± 2	79 ± 2	115 ± 10
[Range]	[100–105]	[77–81]	[102–128]
No. days treatment per month	31/28	31/28	31/28
% drops remaining after monthly treatment (31/28 days)	40%/45%	21%/29%	46%/51%
Product public price	21.77	21.77	20.93
Annual cost (31 days)	256	256	246
Daily cost (31 days)	0.702	0.702	0.675
Annual cost (28 days)	284	284	273
Daily cost (28 days)	0.778	0.778	0.748

Table 6 Prostaglandin analogue/timolol fixed combination bottle contents and costs (euros) for Denmark

	Bimatoprost 0.03%/timolol BP/T	Latanoprost 0.005%/timolol LP/T	Travoprost 0.004%/timolol TP/T
Total fill (g)	3.28 ± 0.09	3.03 ± 0.05	2.87 ± 0.01
[Range]	[3.20–3.41]	[2.98–3.07]	[2.86–2.88]
Number of drops	102 ± 3	82 ± 1	104 ± 5
[Range]	[99–106]	[81–83]	[99–112]
No. days treatment per month	31/28	31/28	31/28
% drops remaining after monthly treatment (31/28 days)	39%/45%	24%/32%	41%/46%
Product public price	30.46	29.29	27.64
Annual cost (31 days)	359	345	325
Daily cost (31 days)	0.982	0.945	0.892
Annual cost (28 days)	397	382	360
Daily cost (28 days)	1.088	1.046	0.987

Table 7 Prostaglandin analogue/timolol fixed combination bottle contents and costs (euros) for Finland

	Bimatoprost 0.03%/timolol BP/T	Latanoprost 0.005%/timolol LP/T	Travoprost 0.004%/timolol TP/T
Total fill (g)	3.36 ± 0.04	3.01 ± 0.01	2.83 ± 0.01
[Range]	[3.32–3.42]	[3.00–3.03]	[2.82–2.84]
Number of drops	107 ± 2	79 ± 1	107 ± 10
[Range]	[104–110]	[78–80]	[97–124]
No. days treatment per month	31/28	31/28	31/28
% drops remaining after monthly treatment (31/28 days)	42%/47%	22%/29%	42%/47%
Product public price	30.73	30.73	29.85
Annual cost (31 days)	362	362	351
Daily cost (31 days)	0.991	0.991	0.963
Annual cost (28 days)	401	401	389
Daily cost (28 days)	1.098	1.098	1.066

Table 8 Prostaglandin analogue timolol fixed combination bottle contents and costs (euros) for Germany

	Bimatoprost 0.03%/timolol BP/T	Latanoprost 0.005%/timolol LP/T	Travoprost 0.004%/timolol TP/T
Total fill (g)	3.49 ± 0.06	3.03 ± 0.02	2.85 ± 0.02
[Range]	[3.43–3.58]	[3.01–3.05]	[2.82–2.86]
Number of drops	105 ± 3	80 ± 1	108 ± 6
[Range]	[100–108]	[78–82]	[100–116]
No. days treatment per month	31/28	31/28	31/28
% drops remaining after monthly treatment (31/28 days)	41%/47%	24%/30%	42%/48%
Product public price	33.18	34.12	31.17
Annual cost (31 days)	391	402	367
Daily cost (31 days)	1.070	1.101	1.005
Annual cost (28 days)	433	445	406
Daily cost (28 days)	1.185	1.219	1.113

Table 9 Prostaglandin analogue/timolol fixed combination bottle contents and costs (euros) for Sweden

	Bimatoprost 0.03%/timolol BP/T	Latanoprost 0.005%/timolol LP/T	Travoprost 0.004%/timolol TP/T
Total fill (g)	3.29 ± 0.04	3.03 ± 0.03	2.83 ± 0.02
[Range]	[3.22–3.34]	[2.99–3.06]	[2.81–2.85]
Number of drops	102 ± 3	80 ± 1	115 ± 9
[Range]	[98–104]	[79–81]	[102–125]
No. days treatment per month	31/28	31/28	31/28
% drops remaining after monthly treatment (31/28 days)	39%/45%	23%/30%	46%/51%
Product public price	25.50	28.96	25.50
Annual cost (31 days)	300	341	300
Daily cost (31 days)	0.823	0.934	0.823
Annual cost (28 days)	332	378	332
Daily cost (28 days)	0.911	1.034	0.911

methodology, however, allowed us to obtain unbiased drop-counts from all bottles. Nonetheless, we recognize that real life instillation practices vary widely and that the drop-size ranges we used are probably under-estimated. Third, the evaluation was not 'blinded', ie, the investigator knew the treatment in each bottle. However, our measurements were objective and our procedures standardized, reproducible and validated. Fourth, we used only direct drug costs when claiming for lower cost, other costs were not taken into account. Hence, our survey is preliminary and a full evaluation is under investigation. On the other hand, from a societal point of view, costs are known to increase with accumulating treatment failures.⁴¹ Hence, the cost differences reported in this paper represent a conservative estimate of the true differences. Fifth, no sensitivity analysis was performed for potential wasted drops, ie, missed instillations and monthly extra drops used in real life. These associated costs, however, may be extrapolated directly from the tables. Lastly, we did not account for patient compliance which is known to be rather poor in glaucoma treatment.^{43,44} This could affect the number of days within a bottle, especially if patients do not account for the expiratory date.

Conclusions

In Denmark, Finland, Germany and Sweden, eye-drop bottles of travoprost 0.004% ± timolol incurred the lowest annual treatment costs, while providing sufficient surplus to compensate for potential fluid wastage from missed instillations, when compared to bimatoprost 0.03% ± timolol and latanoprost 0.005% ± timolol.

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