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Persistence of glaucoma medical therapy in the Glasgow Glaucoma Database

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Persistence of Glaucoma Medical Therapy in the Glasgow Glaucoma Database

Abstract

Aims: To report the persistence of glaucoma medical therapy in a database of 1006 patients with ocular hypertension (OHT), normal tension glaucoma (NTG) and primary open angle glaucoma (POAG) attending the Glaucoma Clinic at Glasgow Royal Infirmary, Glasgow, U.K.

Method: Analyses have been carried out using specially written queries to generate reports relating to initial treatment choice and persistence for individual drugs. Queries were investigated in the database time period from 16th February 1982 to 11th February 2009. When investigating drug persistence, the results from the database were split into two distinct time periods from 1997 to 2001 and from 2002 to 2009 to reflect the available treatment options used.

Results: The number of patients with each diagnosis was as follows: POAG 608; OHT 246; NTG 152. The Kaplan-Meier estimate for mean persistence from 1997 to 2001 (time to treatment discontinuation) of latanoprost was 58.8 ± 1.95 months, timolol was 41.8 ± 3.94 months, brimonidine was 24.1 ± 3.05 months, and betaxolol was 22.9 ± 2.04 months. The Kaplan-Meier estimate for mean persistence from 2002 to 2009 of latanoprost (time to treatment discontinuation) was 52.0 ± 2.26 months, bimatoprost was 25.8 ± 2.89 months, and travoprost was 23.0 ± 1.27 months. The Kaplan-Meier estimate for mean persistence of latanoprost (time to treatment change) was 37.5 ± 2.47 months, travoprost was 30.2 ± 2.70 months, and bimatoprost was 17.5 ± 2.88 months.

Conclusion: The introduction of the first prostaglandin analogue, latanoprost dramatically improved treatment persistence for glaucoma patients. In the current prostaglandin-rich treatment environment, our data does not show any significant difference between prostaglandins with respect to treatment persistence.

Key words: Glaucoma, Database, Persistence

Introduction

Glaucoma is estimated to affect about 67 million people throughout the world,(1) with a prevalence of 2% of the adult population in developed countries (2-4). Medical therapy has been the mainstay of treatment for several years and previous studies have demonstrated that the lowering of intraocular pressure (IOP) decreases the risk of visual field loss (5, 6).

There are several terms used in the literature to describe the interaction between the physician and patient with regard to medical therapy for glaucoma. In order to maintain the maximum benefit from treatment, patients must take medications as directed and this is known as compliance. Perhaps more appropriately, an agreement between both patients and physician regarding treatment decisions is important and this is known as concordance. Once initiated on treatment, patients must also continue on medications over the long term and this is known as persistence. This is of particular importance in patients with glaucoma in whom disease may develop

insidiously, and previous studies of compliance and persistence among glaucoma patients have shown these to be poor.(7-10)

We have previously described, in this journal, a large and unique computerised database established at the glaucoma clinic at Glasgow Royal Infirmary, with data now spanning 27 years (11). We now present our findings on treatment persistence in patients on glaucoma medical therapy.

Subjects and methods

The Glasgow Glaucoma Database

The database was designed using Microsoft Access with the intention of collecting information on all patients who had undergone, or were undergoing, medical treatment for ocular hypertension (OHT), normal tension glaucoma (NTG), or primary open angle glaucoma (POAG). In 1999 the database was populated with retrospective data abstracted from medical records dating from as early as 1981, according to the algorithm in Figure 1a. Information collected for each patient at start of treatment included the following: patient identification number; date of birth; sex; diagnosis; starting treatment and date commenced. If a subsequent visit resulted in no alteration of treatment, the date of the visit was simply logged. If an alteration did occur, this was documented in the database along with detailed reasons for the change. Since 1999, the database has been updated prospectively for all new and existing patients at every clinic visit. It currently contains complete treatment histories on 1006 patients, representing over 7000 patient treatment years. Data are saved

securely on a central server and may be accessed simultaneously from multiple clinic based computers. Analyses have been carried out using specially written queries to generate reports relating to initial treatment choice and persistence for individual drugs.

Patient Selection

Queries were investigated in the database time period from 16th February 1982 to 11th February 2009. When investigating drug persistence, the results from the database were split into two distinct time periods from 1997 to 2001 and from 2002 to 2009. Only monotherapies that were first prescribed before or at each period onset and administered to more than 5% of patients during that period were included in the analyses. Our definition of initial treatment was the first visit at which the patient was administered glaucoma medication. Furthermore, the analysis population was restricted to patients that received identical treatment to both eyes at their first visit. We assumed that new patients in the clinic were treatment-naive at the first visit recorded in the database. First visit records that were blank were ignored and subsequent medications were not analysed.

Prescribing policies

We had an unrestricted hospital formulary. The treatment hierarchies historically used in our practise are shown in figure 1b. In the mid 1990s several novel topical intraocular pressure (IOP) lowering agents were introduced. The initial treatment protocol that was implemented in our clinic in 1997 attempted to arrange the newer

agents in a hierarchy, with brimonidine selected as the favoured second line agent following beta blockers. Initial audit using the database, however, quickly revealed an unacceptable increase in the discontinuation rate due to adverse effects in the years that followed. It was clear that brimonidine and dorzolamide were particularly implicated and these findings informed the introduction of a new protocol in 2000. The average interval between treatment change periods was 3 months.

Defining time to failure

End of initial treatment persistence was defined in two ways:

- Time to initial treatment discontinuation.
- Time to initial treatment change.

Initial treatment discontinuation occurred once initial treatment in either eye was discontinued or surgery in either eye was performed. Surgery, discontinuation or the first record of a new treatment addition in either eye indicated a treatment change event. Patients that did not change/discontinue initial treatment on/before 11/02/09 or were recorded as dead, lost to follow up, or moved away were considered censored observations.

Statistical analysis

Relative persistence was assessed using Cox proportional hazards models (12). This approach allows the adjustment of relative treatment estimates by the potentially important co-variates: treatment, sex, age, diagnosis, IOP, and comorbidities

(including diabetes and cardiovascular disease). Covariates were included based on the likelihood of their association with persistence. By accounting for the potential influence of these covariates, we could make more reliable and accurate estimates of relative treatment persistence. The Cox proportional hazards model assumes that the hazards of discontinuation and change were proportional between treatments over time. Kaplan-Meier survival curves and Kaplan-Meier mean estimates were calculated for each medication analysed. The survival curves revealed no significant violation of the assumption of proportionality between treatments.

Results

The mean age of the database population was 66.5 years, ranging from 18 to 93 years. Female patients made up the majority of patients comprising 58% of the total. The number of patients with each diagnosis was as follows: POAG 608; OHT 246; NTG 152. The intraocular pressure (IOP) range was 11 to 59 with a mean of 23.4.

Figure 2a shows the initial treatments by the year that they were started, and figure 2b shows all treatment prescriptions by year. The most frequently started drug administered to at least 1% of the database population was latanoprost in 302 patients, followed by betaxolol in 211 patients, timolol in 151 patients, travoprost in 77 patients, brimonidine in 56 patients, bimatoprost in 33 patients, and lastly dorzolamide which was initiated in 22 patients.

Persistence for medications from 1997-2001

Cox proportional hazard ratios for time to treatment discontinuation for medications most frequently used in the period 1997-2001 are shown in table 1a:

Medications	Hazard ratio (95% confidence interval)
Betaxolol vs. latanoprost	4.35 (3.26, 5.81)
Brimonidine vs. latanoprost	3.74 (2.43, 5.75)
Timolol vs. latanoprost	2.31 (1.57, 3.42)
Betaxolol vs. timolol	1.88 (1.28, 2.76)

Table 1a: Cox proportional hazard ratios for time to treatment discontinuation for medications most frequently used in the period 1997-2001

The Kaplan-Meier survival curve for time to initial treatment discontinuation is shown in figure 3a. The Kaplan-Meier estimate for mean persistence of latanoprost was 58.8 $\pm$ 1.95 months, timolol was 41.8 $\pm$ 3.94 months, brimonidine was 24.1 $\pm$ 3.05 months, and betaxolol was 22.9 $\pm$ 2.04 months.

Cox proportional hazard ratios for time to initial treatment change are shown in table 1b.

Medications	Hazard ratio (95% confidence interval)
Betaxolol vs. latanoprost	2.59 (2.02, 3.32)
Brimonidine vs. latanoprost	2.55 (1.76, 3.69)
Betaxolol vs. timolol	1.74 (1.21, 2.50)
Brimonidine vs. timolol	1.71 (1.10, 2.66)
Timolol vs. latanoprost	1.49 (1.05, 2.11)

Table 1b: Cox proportional hazard ratios for time to initial treatment change in the period 1997-2001.

The Kaplan Meier-survival curve for time to initial treatment change is shown in figure 3b. The Kaplan-Meier estimate for mean persistence of latanoprost was 43.2 $\pm$ 2.28 months, timolol was 32.0 $\pm$ 3.60 months, brimonidine was 16.8 $\pm$ 2.64 months, and betaxolol was 15.8 $\pm$ 1.68 months.

It appeared that patients receiving latanoprost as an initial treatment were the least likely to discontinue their treatment or to have their treatment regimen altered followed by timolol.

Persistence for medications from 2002-2009

Cox proportional hazard ratios for time to treatment discontinuation and time to initial treatment change for prostaglandin analogues used in the period 2002-2009 are shown in table 2.

Medication	Hazard ratio for time to treatment discontinuation (95% confidence interval)	Hazard ratio for time to initial treatment change (95% confidence interval)
Bimatoprost vs. latanoprost	1.06 (0.52, 2.16)	1.18 (0.71, 1.97)
Travoprost vs. latanoprost	0.94 (0.57, 1.57)	0.75 (0.51, 1.12)
Travoprost vs. bimatoprost	0.89 (0.41, 1.97)	0.64 (0.36, 1.15)

Table 2: Cox proportional hazard ratios for time to treatment discontinuation and time to initial treatment change for prostaglandin analogues used in the period 2002-2009.

The Kaplan-Meier survival curve for time to initial treatment discontinuation is shown in figure 3c. The Kaplan-Meier estimate for mean persistence of latanoprost was 52.0 $\pm$ 2.26 months, bimatoprost was 25.8 $\pm$ 2.89 months, and travoprost was 23.0 $\pm$ 1.27 months.

The Kaplan Meier-survival curve for time to initial treatment change is shown in figure 3d. The Kaplan-Meier estimate for mean persistence of latanoprost was 37.5 $\pm$

2.47 months, travoprost was 30.2 ± 2.70 months, and bimatoprost was 17.5 ± 2.88 months.

There did not appear to be an unequivocal difference between the three prostaglandin analogues when comparing either time to discontinuation or time to initial treatment change.

Discussion

Assessment of patients in a 'real world' setting, as with our database, allows more accurate conclusions to be drawn compared with the strictly controlled regimes in a clinical trial. We believe that our database following up patients over a 27 year period is unique in the United Kingdom.

The analysis from 1997 – 2001, demonstrates clearly that patients on latanoprost had superior persistency compared to the beta blockers and the alpha agonist brimonidine. Patients on latanoprost were less likely to either discontinue use or switch to a subsequent therapy than other classes of glaucoma medications. Although definitions of persistency may differ slightly between studies, these findings are similar to those found in large, retrospective studies in the literature (13-16). This maybe due to much lower rates of adverse effects with latanoprost than other medications as we have reported in a previous study (11). Latanoprost continues to be the most prescribed drug in our clinic as can be seen in figure 2b.

Our analysis from 2002 to 2009 comparing persistency between prostaglandin analogues failed to show a clear advantage of one medication over another. These findings therefore agree with the results of Wilensky et al who found similar persistency rates between latanoprost, travoprost and bimatoprost, in their retrospective study (17). However, two other studies in America have shown different results, with both finding that latanoprost had a superior persistency than either travoprost or bimatoprost (18, 19).

There are several possible reasons to explain this difference in findings. Both American papers were retrospective studies of pharmacy and medical claims data that used proxy measures for persistency such as identifying index drug refills. Such methods may be subject to potential confounding errors and bias. Conversely all of our patients in the database were assessed in the clinic by surgeons, and the persistency of each drug was recorded directly.

It is also important to consider that in the USA, medication costs both to patients and health insurance companies, are potential sources of bias in the reporting of drug persistency rates in the literature. This is less of a problem in the U.K. National Health Service where medications remain free at the point of use for patients.

Our patients on prostaglandin analogues have been followed up continuously for up to 7 years, whereas both of the American studies only examined pharmacy and medical claims data for patients for approximately one year (18, 19). Caution must always be used when extrapolating the results from short term studies to long term clinical outcomes. Hypersensitivity reactions to brimonidine, for example, were

underestimated by early short term studies (20, 21). A previous long term study from our database highlighted the true, higher incidence of this problem with brimonidine (22). It is therefore possible that the shorter study period for these papers overestimated the persistency rates of latanoprost.

A potential criticism of this study is the smaller number of patients compared with the much larger populations from the American studies, but we feel that the long length of prospective follow up in our population collectively representing over 7000 treatment years, balances this and gives our study sufficient statistical power.

In conclusion, our study has found that the introduction of the first prostaglandin analogue, latanoprost, as initial monotherapy, dramatically improved treatment persistence for glaucoma patients in the time period from 1997- 2001. In the current prostaglandin-rich treatment environment from 2002 - 2009, our data do not show any significant difference between prostaglandins with respect to treatment persistence, when used as initial monotherapy. Greater numbers of patients, and longer periods of follow up are required to give meaningful information on the relative treatment persistence for the newer prostaglandin analogues.

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Figure Legends

Figure 1a: Glasgow Royal Infirmary glaucoma database patient information algorithm.

Figure 1b: The treatment hierarchies used in 1997 and 2000.

Figure 2a: Initial treatments by year.

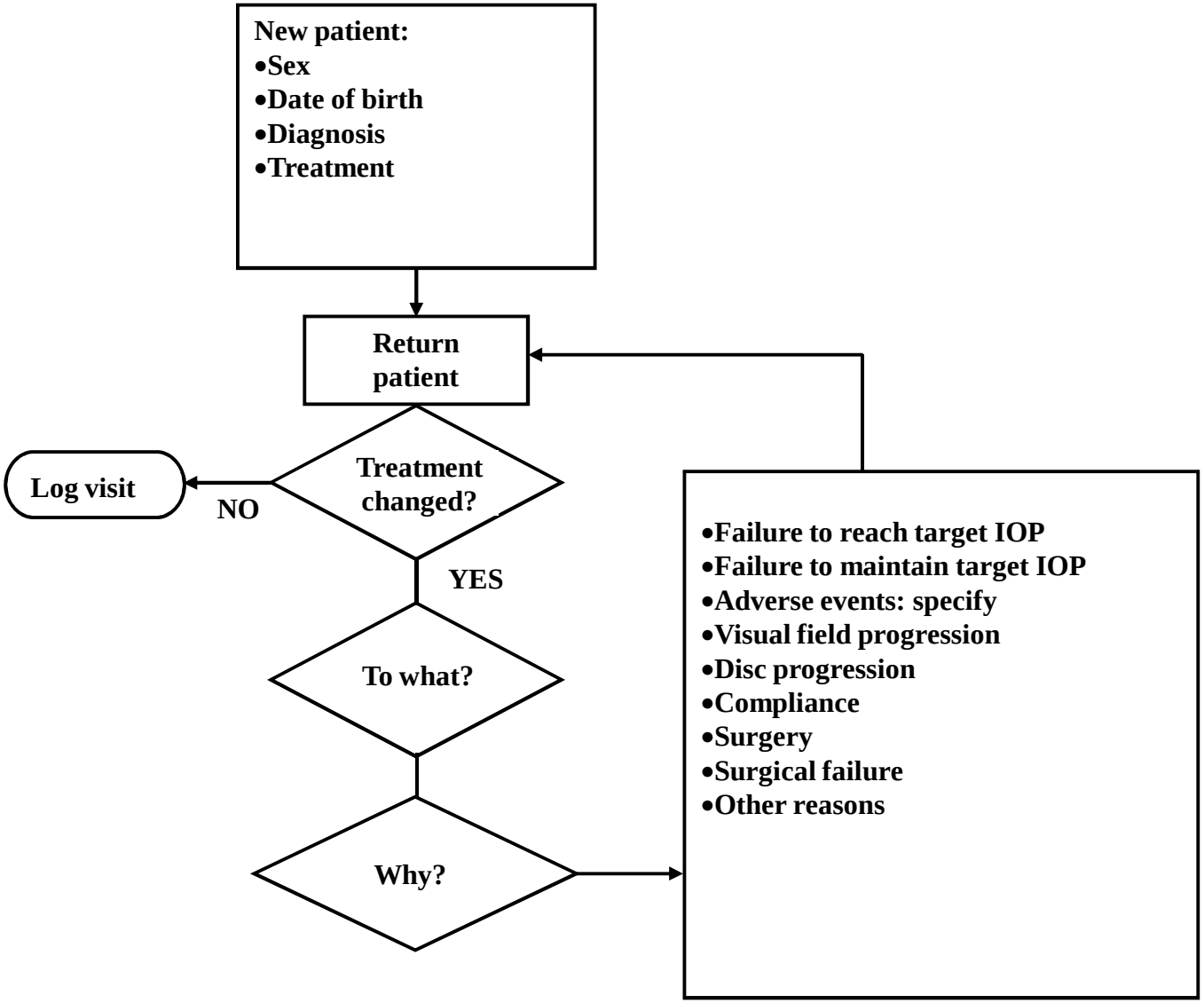
Figure 2b: All treatments administered once by year.

Figure 3a: Kaplan-Meier survival function for time to interval treatment discontinuation for patients receiving initial treatment on or after 1st January 1997.

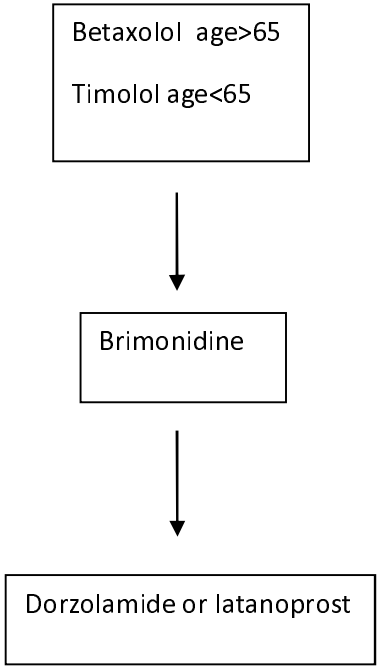
Figure 3b: Kaplan-Meier survival function for time to interval treatment change for patients receiving initial treatment on or after 1st January 1997.

Figure3c: Kaplan-Meier survival function for time to interval treatment discontinuation for patients receiving initial treatment on or after 1st January 2002.

Figure 3d: Kaplan-Meier survival function for time to interval treatment change for patients receiving initial treatment on or after 1st January 2002.


New patient:
•Sex
•Date of birth
•Diagnosis
•Treatment
Return patient
Treatment changed?
Log visit
NO
YES
To what?
Why?
•Failure to reach target IOP
•Failure to maintain target IOP
•Adverse events: specify
•Visual field progression
•Disc progression
•Compliance
•Surgery
•Surgical failure
•Other reasons

The treatment protocol in 1997



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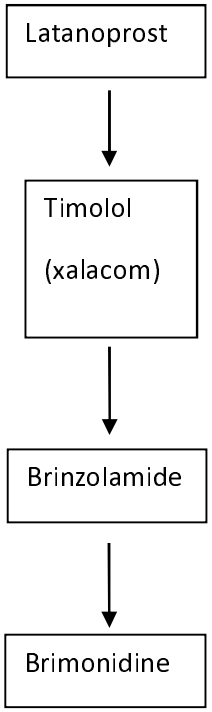

Figure 2a: Initial Treatments by Year

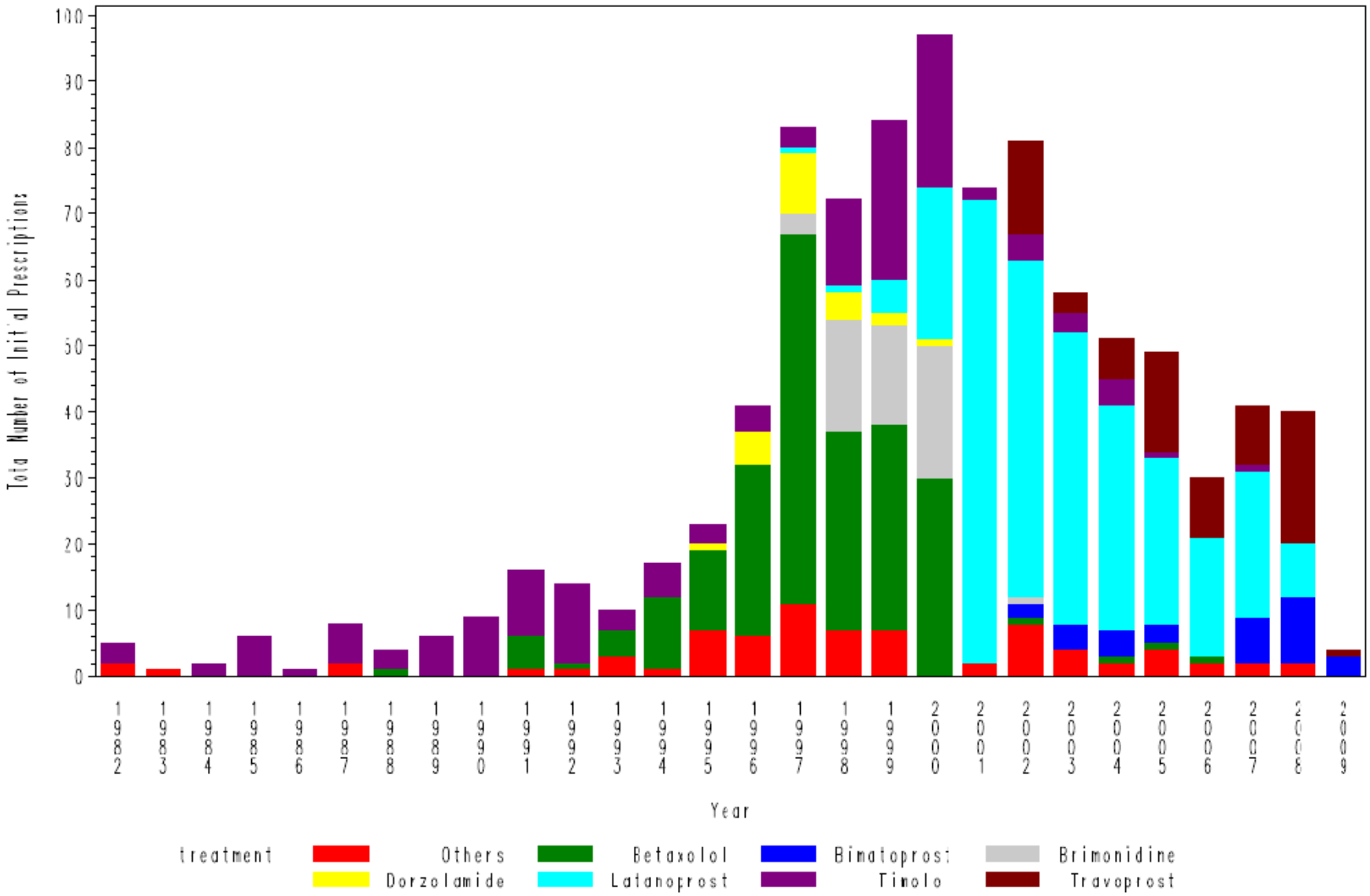

Figure 2b: All Treatments Administered At Least Once By Year

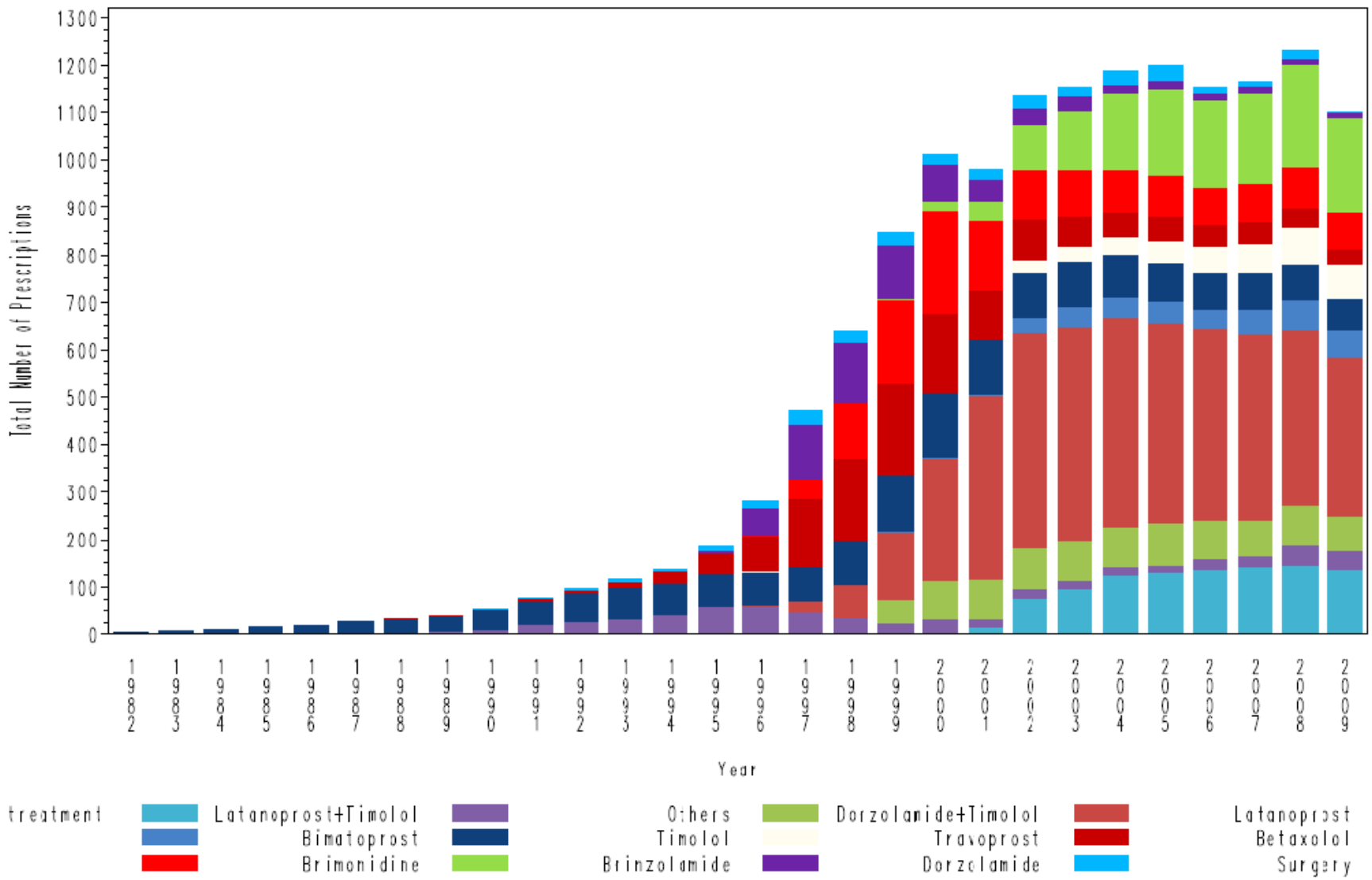

Figure 3a: Kaplan-Meier Survivor Function for Time to Interval Treatment Discontinuation for Patients Receiving Initial Treatment on or After 1 Jan 1997

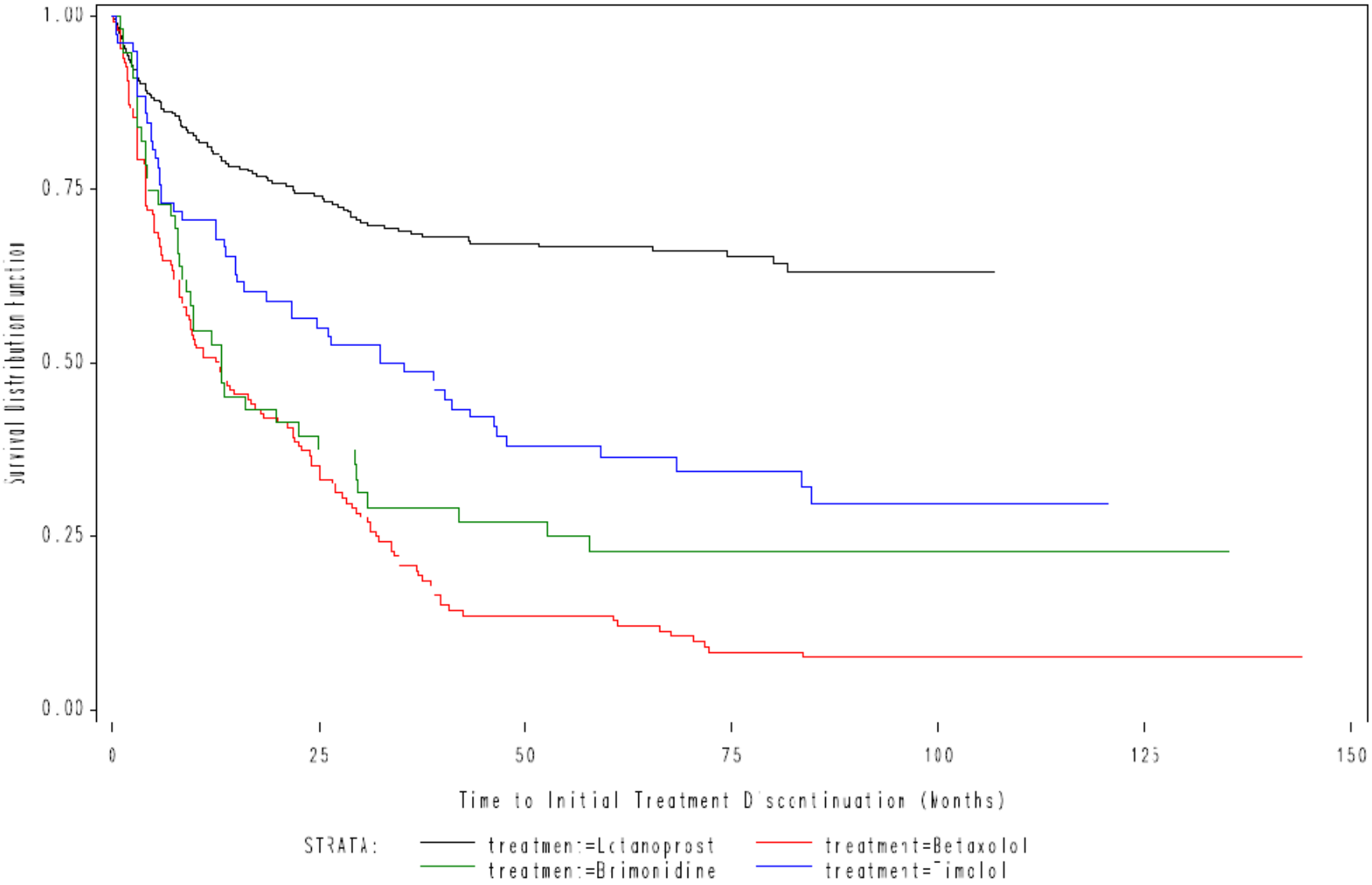

Figure 3b: Kaplan-Meier Survivor Function for Time to Interval Treatment Change for Patients Receiving Initial Treatment on or After 1 Jan 1997

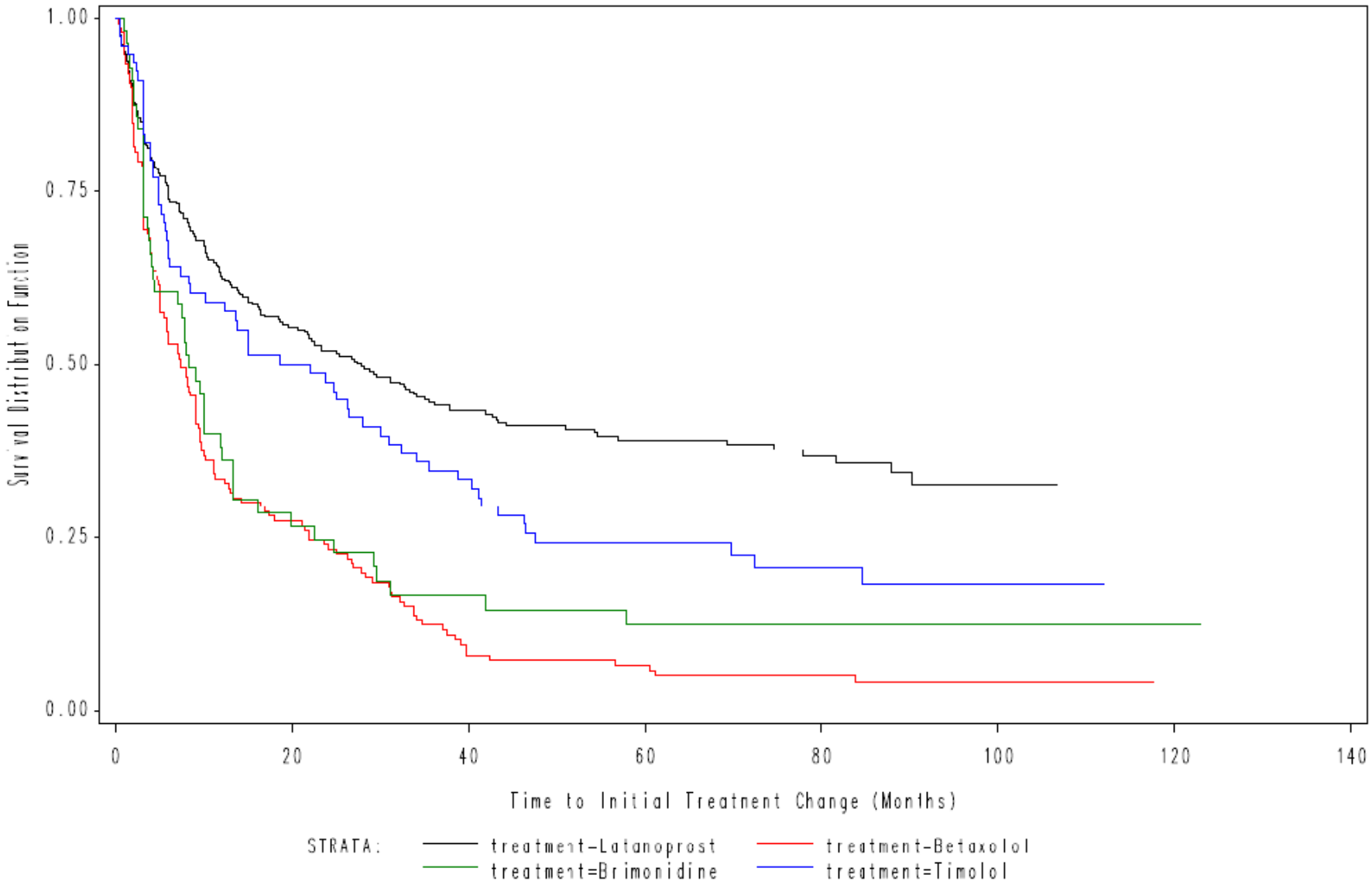

Figure 3c: Kaplan-Meier Survivor Function for Time to Interval Treatment Discontinuation for Patients Receiving Initial Treatment on or After 1 Jan 2002

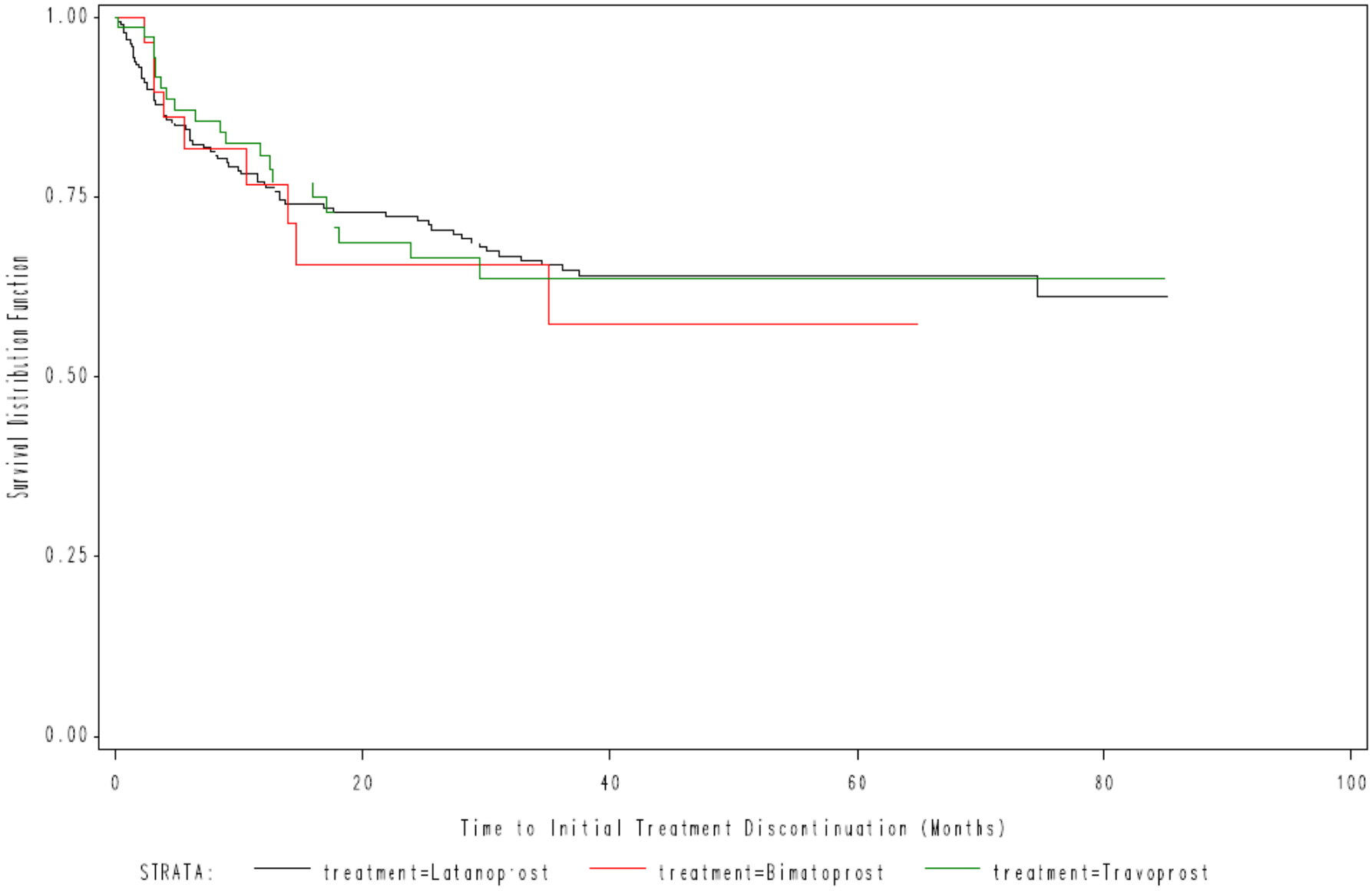
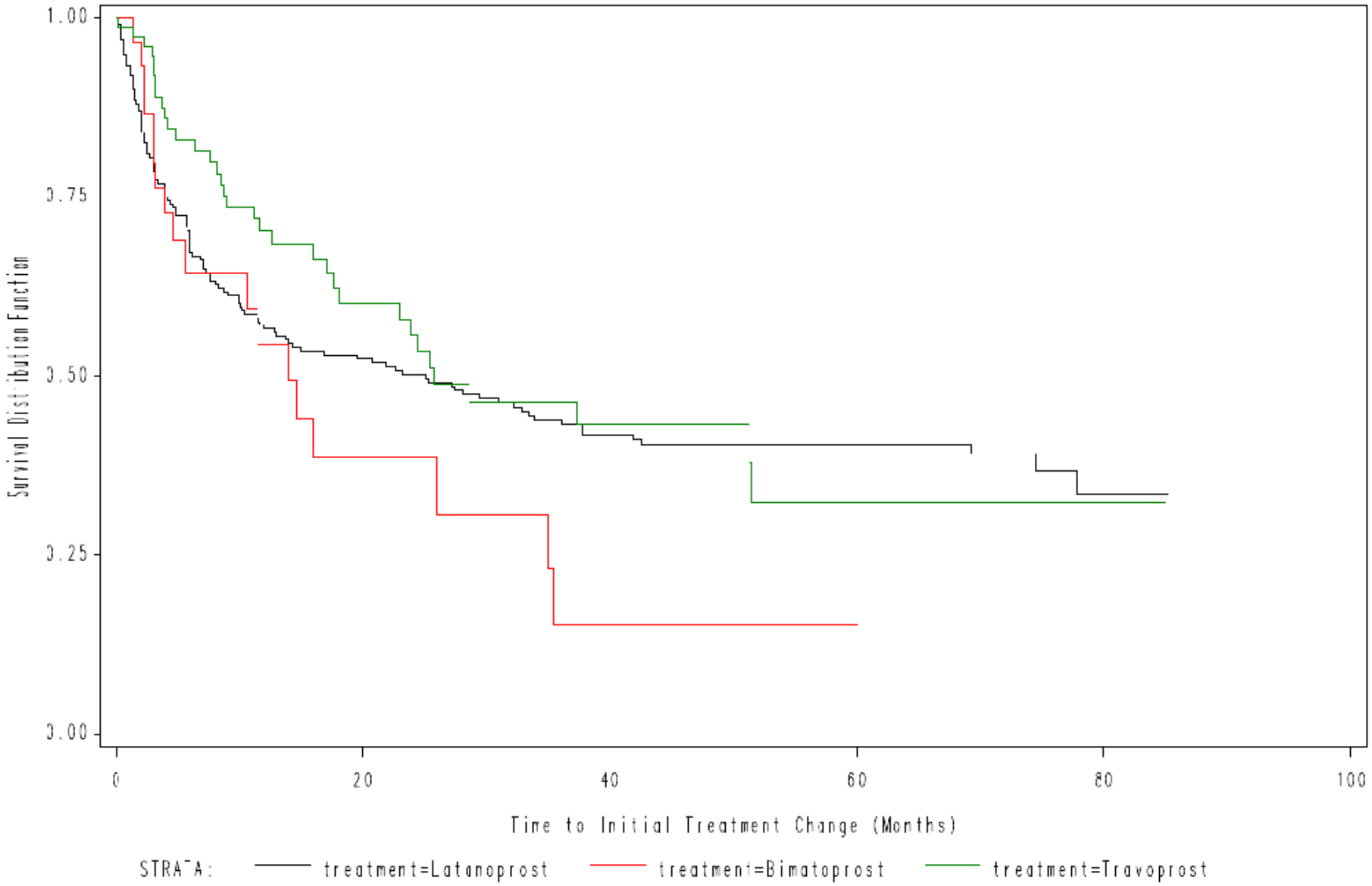
Figure 3d: Kaplan-Meier Survivor Function for Time to Interval Treatment Change for Patients Receiving Initial Treatment on or After 1 Jan 2002