

Version 2.0

# PharmaCoach and Medication Persistence

An observational study to assess the overall effectiveness of PharmaCoach on medication dispensing persistence.

Disclosure: this study has been partly financed by 2comply bv, the owner of the PharmaCoach program.

**PHARMO INSTITUTE**

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## Background

### Introduction

Medication compliance is one of the most challenging problems of pharmaceutical care. Patients that do not follow correctly medical advice, have a substantial risk to minimize the effectiveness of the prescribed drug therapy. It has been estimated that even in developed Western countries, approximately 50% of patients with chronic diseases do not follow treatment recommendations properly (compliance) or do not use medications long enough to be effective (persistence)[1, 2]. Consequently, patients have less effect of medications than expected, suffer unnecessary from preventable morbidity and adverse drug effects which in turn contributes also to the economic burden of those conditions. Moreover, reimbursement of dispensed drugs that cannot work because their continuation is stopped, is among the most ineffective investments in pharmaceutical care. It has been estimated that 50% of all yearly installed chronic treatments is ineffective due to early discontinuation, which amounts up to billions of Euro's wasted reimbursement costs of drugs in the Netherlands alone. In fact, we can see medication non-compliance as an investment-loss to improve health. Improving compliance and persistence is henceforward an effective strategy to improve the (cost) effectiveness of drug use in society without having to invest in new drug treatments.

The past years, many different strategies and devices have been developed and implemented in medical care in order to help patients to improve their medication compliance. These compliance intervention tools (CIT) range from patient counseling techniques, SMS services to high-tech electronic warning devices. PharmaCoach is a CIT developed by the 2Comply company which has been implemented the past years in an increasing number of pharmacies in the Netherlands. The PharmaCoach program is a pharmacy-linked web-based, multi-intervention program that coaches patients to comply with the direction of use of their drugs. Patients dispensed drugs with the intention of long-term treatment are invited to visit the PharmaCoach website. At the site patients can review their medications, information is offered to inform patients why drug should be taken long-term, the patient is counseled to motivate long-term use, and if drugs are suddenly discontinued, the physician and pharmacy is informed of this

discontinuation. In case the discontinuation is rational, e.g., a 75 years old patient with terminal cancer discontinues lipid lowering drugs, the PharmaCoach ® intervention is stopped ([www.2comply.nl](http://www.2comply.nl)). Medication non-compliance and non-persistence are complex problems in which person's characteristics interacts with believe systems, trust in medications and the prevailing disease (severity). Clinical observations have showed that patients refill too late, irregularly or even unexpectedly discontinue the intended long-term pharmacotherapy. The 2Comply has asked the PHARMO Institute to validate the effect of PharmaCoach to improve medication persistence in daily practice. In this report the results of several studies that address this question are summarized.

### Study objectives

The questions asked purport to three different, but related objectives:

1. Does PharmaCoach improves medication persistence, and
2. if so, to what extent, and
3. which patients may profit most from the PharmaCoach program

To answer these questions several studies have been performed. A first feasibility study has been performed among 27 pharmacies that also contribute data to the PHARMO Institute. This database has been described elsewhere ([www.pharmo.com](http://www.pharmo.com)). The study had the intention to explore and measure the effect of PharmaCoach and to explore potential biases and confounding factors. The results of this study have already been reported and have been used to design and perform a second study. The results of this second study are reported in this report.

The results of the feasibility study showed a very large effect of PharmaCoach on the dispensing compliance rates compared to controls, those who not (yet) participated in de PharmaCoach program. Improvement rates were observed ranging from 20% to 200%, on average 68%.

However, the participation rate of the PharmaCoach program in these 27 pharmacies was very low. Some pharmacies contributed only a single patient to a particular drug group. Furthermore, inclusion criteria are not defined other than to offer PharmaCoach to those patients that use 'chronic medications'. It is well-known from literature that the timing and frequency of visiting the pharmacy is related to dispensing compliance. In extreme: patients that comply, visit the pharmacy per definition regularly; those who don't, even don't show up at all. Compliant

patients are therefore more likely to be invited selected as the first to be selected for the PharmaCoach intervention. Other selection processes might be present among those invited. Also because of the low participation (inclusion) rate, it is likely that invited PharmaCoach participants are more compliant than random selected controls, consequently overestimating the effect of the PharmaCoach application. In the feasibility study, there were no means to correct or to study the effect of potential selection bias. Consequently, the risk of overestimation the effect of PharmaCoach was real but undetermined in size. We therefore started a second study in which we included only pharmacies with the highest participation rate of the PharmaCoach in order to be able to detect and study the impact of potential selection bias. Seven pharmacies were subsequently added to the PHARMO network.

## Material and methods

### Design second observational study

As discussed we performed a second study among 7 newly recruited, anonymised Mediq pharmacies with the highest participation rates of the PharmaCoach application. Data were retrospectively collected, coded and included as part of the PHARMO network. Data were obtained from the PharmaCoach database and linked with the PHARMO network to identify patients anonymously, their invitation date to participate in the PharmaCoach program, drug dispensing, dispensing dates and duration of use. The minimum length of follow-up after invitation was 6 months. The end of the inclusion period was defined as February 28th, 2010. The design of the study was a retrospective follow-up study. The follow-up was defined as time since invitation date until end of the study period.

Here we defined medication dispensing persistence as the decline in probability of exposure during a defined period of time. Suppose we follow 100 patients during a period of one year, full persistence is achieved if all 100 patients have enough supply of the drug to be exposed each day from  $t=0$  until the end of the follow-up period. In practice, however, we expect that an undefined number of patients will discontinue therapy for whatever reason and hence, at the end of the follow-up period not 100 but  $100-x$  patient have enough supply to be exposed. The prevalence is an estimate of persistence. The prevalence difference between the intervention

group (study participants) and non-intervention group (control) at a defined point in time is then an measurement for the effect of PharmaCoach.

### Patient selection

Two different cohorts of patients were identified. The inclusion in both these cohorts was limited to those dispensed drugs belonging to one of the drug groups listed in Table 1. The selection of drug groups was based on the assumption that these drug groups need to be used chronically. These drugs groups are flagged as trigger to initiate the invitation to participate with the PharmaCoach program. The first cohort included all patients as users of the selected drug groups who had a history of drug dispensing at least one year prior to the PharmaCoach invitation date. The medication history, one year before the intervention date was used as proxy of the propensity to discontinue therapy after  $t=0$  and was used as an estimate of selection bias. The second cohort, was recruited from the remaining patients (short-term users) as those without a (long) history of drug use were past prevalence behavior could not be a major reason to bias recruitment.

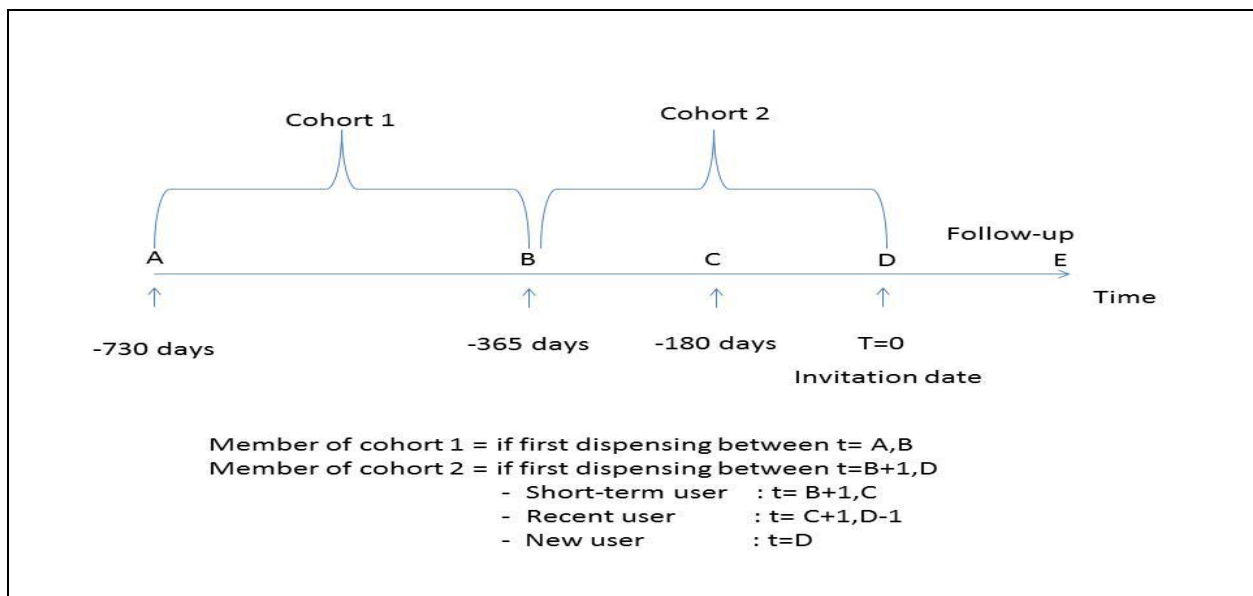


FIGURE 1: RECRUITMENT DIAGRAM FOR COHORT 1 AND 2. ( END OF RECRUITMENT FEB. 28<sup>TH</sup>, 2010 [E])

Ad Cohort 1. Study participants were identified as patients with an invitation date before Februari 28<sup>th</sup>, 2010 with a follow-up period of at least 6 month. Patients were recruited as study participant with a dispensing date (t=0) in the same month as the invitation date and who already had been dispensed at least once a prescription of the same drug group in the second year before the invitation. Inclusion periods vary over pharmacies and within pharmacies and over drug groups. Within each pharmacy and drug group, controls were selected randomly from those patients with at least 1 dispensing within the inclusion period of the study participants. The age of the controls at one or more dispensings within the inclusion period, had to be within the age range of all invited patients per pharmacy (age band 5 years). Next, for each control a dispensing date was randomly selected as start of follow-up (t=0) from all dispensing dates within the inclusion period. Controls have at least one dispensing in the second year before t=0, not (yet) invited to PharmaCoach. All study participants and controls therefore complied with the same inclusion criteria and had a history of drug of at least one year prior to t=0. Each day before and after t=0, the prevalence of use in the study and control group was estimated as the point prevalence of exposure. The denominator included the study participants or controls invited or randomly selected at t=0. The period of 1 year before t=0 (B-D, figure 1) was used to study selection bias, i.e. whether study participants or controls were a priori less or more likely ‘good’ compliers.

TABLE 1: SELECTED DRUG GROUPS

Drug group	ATC code
Anti-lipaemics	C10
Anti-depressants	N06A
Anti-hypertensivs	C02, C03, C07, C08, C09
Oral antidiabetics	A10B
Glaucoma medication	S01E
Inhalational corticosteroids	R03BA
Anti-Osteoporosis drugs	M05A, G03C, A12A, A12CD, A11CC
Anti-Parkinsonian drugs	N04
Anti-psychotics	N05A
Thrombolytics	B01AC

Ad Cohort 2. Study participants and controls were comparable in selection criteria as described for cohort 1, except that the first dispensing within the group is at most 365 days before t=0.

These patient are stratified with respect to their history of use of drug groups into three cohorts, representing new starters, recent starters and short-term users as illustrated in figure 1. Short-term users were those patients that started drug use of the index drug group 365 to 180 days before the index date. Recent starters were defined as those who started the drug 1 and 180 days before the invitation (index) date, whereas new users were defined as those patients that for the first time started use at t=0. Study participants and controls were grouped in the defined drug groups in one of the three mutual exclusive patient groups as short-term, recent or new user.

### Statistical analyses

For each patient the prevalence of drug use is assessed each day before and after t=0. Here, in both cohorts we allowed patients to return into the study base if they restart use after an undefined time period of discontinuation of therapy. In Cohort 1, the prevalence was also measured each day before inclusion for -1 to -365 days before. These prevalence rates were plotted for study participants and controls for the different drug groups and anonymised pharmacies. A logistic model was used to control for differences in factors related to dispensing persistence that also might have impact on the effectiveness of PharmaCoach :

$$glm(formula = Resp \sim Rx + Drug + Sex + Age5 + T2T0 + SelBias + Effect^P, \\ family = binomial("logit"))$$

where,

Rx	=	code for the pharmacy
Drug	=	ATC code for the index drug groups (e.g.. anti-hypertensives)
Sex	=	gender (men, women)
Age5	=	5 years age band of the patient (e.g., 40-44 years of age)
T2T0	=	timing in 30-day periods relative to t=0 over [-365,365]
Selbias	=	study or control subject, overall difference in compliance between study and control subjects
Effectp	=	indicator for t>0 and study participant, the effect of PharmaCoach
corrected		for difference in compliance between study and control
subjects before		t=0.

The logistic model was used to study which factors are significant related to differences in dispensing persistence. In cohort I, an estimate of the overall differences in prevalences of study participants and controls was included (Selbias) and a term describing the differences in

prevalence between study participants and controls after t=0 (EffectP). In the absence of selection bias, the estimate for the overall difference on the log(OR) scale in prevalence (Selbias) should be zero. All analyses and estimation of prevalence odds ratios (POR) were performed using the R statistical package, version 2.11.

## Results

### Cohort I

#### General and univariate results

In the seven selected pharmacies, the invitation rate of the PharmaCoach intervention within drug groups was in the range of 3-30%. Overall, study participants accounted for 9.1% of all patients that matched the inclusion criteria of our study. The results of the inclusion process, the persistence and percentage differences prevalences rates among study participants and controls are presented in Table 2.

TABLE 2: DIFFERENCES IN DISPENSING PERSISTENCE BETWEEN PARTICIPANTS AND CONTROLS BY DRUG GROUP

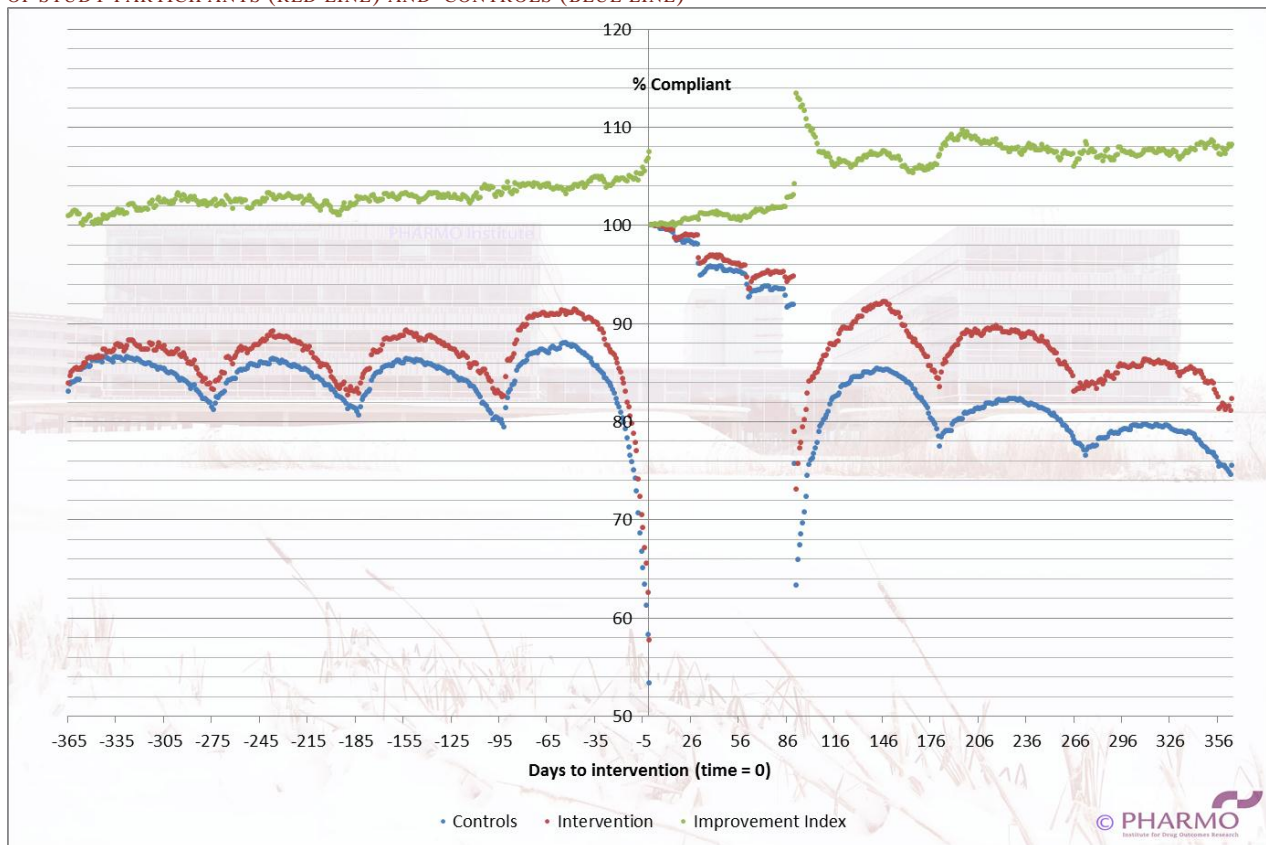
Drug Group (bias)	Selected Participants (Yes) And controls (No)			Dispensing persistence after one year (%)		
	Participants	Controls	%	Participants	Controls	%Difference
Anti-depressisants (0)	179	2107	7.8	69	64	7.8
Anti-lipaemics (0)	957	10428	8.4	88	80	10
Anti-hypertensives (0)	570	5656	9.2	80	76	5.3
Anti-diabetics (0)	161	1657	8.9	88	76	15.8
Glaucoma medications (0)	33	247	11.8	65	72	-9.7
Inhalationalcorticosteroids (+)	40	361	10	47	47	0
Anti-osteoporotic meds. (+)	51	686	6.9	58	59	-1.7
Anti-Parkinsonian meds. (?)	12	87	12.1	100	72	37
Anti-psychotics (0)	32	359	8.2	82	71	15.5
Anti-thrombolytics (0)	299	3438	8	83	75	10.7
<b>Total</b>			9.1	76	69.3	9.1

The invitation rates are on average 8-10 times higher than in the first study (see report 1) and ranged between 12.1 % for users of anti-parkinsonian drugs to 6.9% for anti-osteoporotic drugs. The largest numbers invited study participants were observed among users of anti-lipaemics

(statins), anti-hypertensives and thrombolytics (low dose aspirin). The largest differences in prevalence (dispensing persistence) after one year between study participants and controls were observed for patients using anti-diabetics (+15.8%) and those using anti-psychotics (+15.5%). It should be noted these patients included patients that were put on therapy at least one year ago.

In Figure one, the prevalence of use, averaged over all drug groups for study participants and controls, are presented. The past prevalence for both groups was, as expected from their long-term use history, high and ranged between 85 and 90% and suggest that study participants were a priori more dispensing compliant than controls.

FIGURE 2: PREVALENCE OF USE SUMMARIZED OVER ALL DRUG GROUPS, AND PERCENTAGE DIFFERENCE (GREEN LINE) OF STUDY PARTICIPANTS (RED LINE) AND CONTROLS (BLUE LINE)



Erratum: compliant in graphs should be prevalence.

After 365 days a clear difference in the prevalence (dispensing persistence) is observed for the study participants compared to controls. The graphs for the individual drug groups are present in the appendix 1 (watch: different color definitions). Here, we observed that study participants and controls already had a slightly different prevalence of drug use before start of the follow-up

period, indicating that study participants had a slight increased tendency to stay persistent compared to controls. The shape of the curve, clearly shows a repeating pattern that patients refill their medications on average every 90 days whereas the sharp declines explain that a substantial percentage of patients visits the pharmacy too late for refill medication.

Although for the total group of drug users, higher a higher prevalence was observed among study participants compared to controls, no differences in prevalence were observed among patients using inhalational corticosteroids and anti-osteoporotic medications. For anti-parkinsonian drugs the number of study participants was too low and the presence of bias therefore undefined. We also studied differences in presence of likelihood of over representation of patients with a tendency for better persistence among the different pharmacies (appendix 2, pharmacies are anonymized). Here, differences could be observed in the presence of selection bias. There was tendency that the lower the participation rate, the larger the selection bias. However, numbers were too small to produce meaningful statistics.

### **Adjusted, multivariate analyses**

Ad cohort 1. Adjusted for all the other factors listed in Table 3, and thus also for a priori differences in exposure prevalence of the individual drug groups, the PharmaCoach application is associated with a 38% (30-47%) improvement of compliance compared to controls (prevalence odd ratio: 1.38, 95%CI: 1.30-1.47). As hypothesized and observed in the compliance graphs listed (see appendices), study participants were a priori more likely to become persistent than controls. The selection bias could be quantified as an independent predictor for compliance, prevalence odds ratio: 1.26 (95CI : 1.21-1.32). The results of the multivariate analyses also clearly showed (Table 3) that medication dispensing persistence is independently associated with several other risk factors. Relative to users of antidepressants, users of anti-hypertensives are 2.1 times more persistent, whereas users of inhalational corticosteroids are 3 times less persistent. We also observed, independently from other factors, different a priori medication persistence per pharmacy. In pharmacy 4, 5 and 6, the medication persistence, adjusted for all other co-variables, are much lower compared to pharmacies 1,2,3 and 7. Compliance is also associated with gender and age. Men and younger patients are more likely to be persistent than women and older patients.

TABLE 3: FACTORS INDEPENDENDLY ASSOCIATED WITH DISPENSING COMPLIANCE

Factor	Odds Ratio	Low CI95%	High CI95%
Effect of PharmaCoach	1.38	1.30	1.47
Selection bias	1.26	1.21	1.32
Antidepressants	1.0 (Ref.)		
Anti-hypertensives	2.15	2.07	2.21
Anti-lipaemics	1.56	1.52	1.61
Oral antidiabetics	1.81	1.74	1.89
Glaucoma medication	1.20	1.11	1.29
Inhalation corticosteroids	0.33	0.19	0.57
Anti-osteoporosis drugs	0.62	0.39	0.97
Anti-parkinsonian drugs	2.40	2.05	2.82
Antipsychotics	1.60	0.82	3.11
Thrombolytics	1.74	1.69	1.80
Pharmacy 1	1.0 (Ref.)		
Pharmacy 2	0.90	0.8785	0.93
Pharmacy 3	1.05	0.7468	1.46
Pharmacy 4	0.52	0.5088	0.54
Pharmacy 5	0.65	0.4811	0.88
Pharmacy 6	0.68	0.6647	0.71
Pharmacy 7	1.02	0.9833	1.05
Gender (Women)	0.93	0.92	0.95
Age (5 years)	1.01	1.01	1.01
Days relative to t=0*	1.0 (ref)		
-330 Prior	1.17	1.11	1.22
-270	0.89	0.85	0.93
-210	1.03	0.98	1.08
-150	1.19	1.13	1.25
120 Posterior	0.95	0.90	0.99
180	0.70	0.67	0.74
240	0.85	0.81	0.89
300	0.71	0.67	0.74
360	0.56	0.54	0.59

Lastly and obviously, the longer the follow-up time, the lower the prevalence odds ratios, showing on average a loss of persistence, measured over all studied drug groups of approximately 50% after one year. Ad Cohort 2. In cohort 2 (a,b,c), patients are stratified according to their past use of drugs into new, recent and short-term users. Because of sample size considerations resulting from this stratification, only enough data were available for study participants and controls who were dispensed anti-lipemics, anti-hypertensives or thrombolytics. As show in Table 4, for all three individual drugs groups, a trend was observed that the effectiveness of PharmaCoach shows improving compliance rates with recency of use.

TABLE 4: PREVALENCE AFTER 1 YEAR FOR DIFFERENT CARDIOVASCULAR DRUGS

Drug group		Persistence (%) Participants	Persistence (%) Controls	Improvement (unadjusted)
<b>Anti-lipemics</b>				
Short-term	36/543	76.3	69.9	9%
Recent	72/673	80	63.1	27%
New	71/825	68.6	54.1	27%
<b>Anti-hypertensives</b>				
Short-term	96/834	81.4	71	15%
Recent	103/1032	80.4	62.2	29%
New	73/1366	70.8	34.4	106%
<b>Thrombolytics</b>				
Short-term	42/305	82.4	60.9	35%
Recent	41/474	60.9	58.7	4%
New	39/718	65.5	38.2	71%
<b>Averaged Overall effect of PharmaCoach</b>				
Short-term	Na	80.0	67.3	19%
Recent	Na	73.8	61.3	20%
New	Na	68.3	42.2	62%

. For all drug groups the largest effects were observed for new users, ranging from 27% difference in prevalence for the anti-lipemics (statins) to 109% for new users of anti-

hypertensives (109%). Most of these differences in prevalence (medication persistence) between study participants and controls were modified by other factors such as age, gender and pharmacy. As shown in Table 4, the unadjusted compliance rates improved with recency of use, ranging on average from 19 to 62% for short-term to new users.

The results of the logistic regression analyses for cohort 2, revealed that the same factors as studied in cohort 1 (data on file), are independent risk factor for compliance. These factors included age, gender, type of drug group, duration of follow-up, type of pharmacy and differences in past prevalence of the drugs, i.c. short-term use, recent use and new use. Corrected for all these risk factors the effect of PharmaCoach on the overall compliance yielded a prevalence odds ratio of 2.4 (95%CI: 2.1-2.7), ranging from 2.1 (95%CI: 1.6-2.6) among short-term users to 2.9 (95%CI: 1.7-5.0) for new users.

## Discussion

The results of this observational study all show that the PharmaCoach program had a statistical significant, overall positive effect on the dispensing compliance rates of the selected drugs used to treat chronic conditions. This effect was independent of age, gender, type of drug groups, pharmacy and duration of follow-up and observed for long-term-users as well as new users. The magnitude of improvement of the compliance rates ranged from 38% in long-term users of the total casemix of studied drug groups to over 100% for patients who started recently with the drug used for prevention of chronic cardiovascular complications.

The studies we performed had several limitations that might have influenced our risk estimates. Firstly, controls were selected the time they were not yet invited to participate in the PharmaCoach project. We allowed these patients to participate during their follow-up period to prevent over-recruitment of those never eligible for PharmaCoach. Re-analyses of our data showed that approximately 10% of the patient indeed participated during the follow-up, thereby slightly overestimating the prevalence in controls and hence underestimating the effect of PharmaCoach. Secondly, with the random introduction of PharmaCoach, it is to expected that long-term users are overrepresented or that PharmaCoach is first applied by patients with a higher tendency to comply a priori. The over-recruitment results in selection bias overestimating the prevalence among study participants and hence overestimating the effect of PharmaCoach. In cohort 1, we observed and quantified this effect which was reasonably large. Independent from other factors, the bias itself contributed for 25% of the effect in Cohort 1. However, after correction the effect of PharmaCoach was still statistical significantly increased. Thirdly, in cohort 2 we could not correct for the aforementioned selection bias as we had and could not obtain information from patients that allowed us to identify those study participant with a higher tendency to become compliant. These patients recently started and hence had no prior information that could predict compliance. However, the largest effects of PharmaCoach were observed among new users, who have no history and hence it is not obvious that pharmacists can know whether new users are more likely to become good compliers. Fourthly, by the selection procedures of study participants and controls, patients that used combinations of the selected drugs groups, e.g., anti-lipaemics and anti-hypertensives have been entered twice in the study base. This could have as a consequences that patient were invited for Drug A and later in time

for drug B (new use). Henceforward, if patient become more compliant and motivated to comply with drug A due to the PharmaCoach intervention, they probably would be more likely to become compliant at the start of invitation for drug B. This bias could result in an overestimation of the PharmaCoach effect. However, mono-users of the selected drugs groups are quite scarce and estimating the effect exclusively for these patients was impossible due to limited sample size. Fifthly, study participants were included if they were invited to use the PharmaCoach program. However, we did not know whether they indeed used the PharmaCoach intervention properly or at all. The loggings of the patients show that approximately 70% logged several times to the PharmaCoach website indicating that they actively participated in the program. Because 30% did not participate, the effect of PharmaCoach could have been underestimated. Several biases are probably present in our study that either under- or overestimated the overall effect of the PharmaCoach program. Most of these biases were related to the a priori tendency of patients to be 'bad' or 'good' compliers. However, in the several subgroups of long-term, short-term, recent and new users and after adjustment large and statistical significant effects of study participants compared to controls were consistently observed. Although we can not excluded residual confounding, we have no evidence the overall positive effect of PharmaCoach program on improving dispensing compliance is explained by these biases .

The magnitude of the effect of PharmaCoach is difficult to quantify because many interrelated factors will have effect on the overall effectiveness of the program. This effect is most likely guided by the baseline compliance dispensing rates. These rates may vary among pharmacies, age, gender, type of drug group and history of drug dispensing. From a population perspective the absolute gain in improving the prevalence is limited for those who already have high prevalence rates. In other words, as we observed in cohort 1, including already long-term treated patients with high prevalence rates, absolute improvements are achieved of approximately of 30-50%. However, for those patients with a prevalence of already 80%, the maximum to improve prevalence is 20%. The absolute improvement of 10% then relates to a relative improvement of 50% or a prevalence odds ratio of 2. For new users, in cohort 2, the prevalence rate on average improved from 42.2% among controls to 68.3%, a difference of 26.1%. Given a maximum dispensing compliance of 100% and a maximum to increased prevalence of 100% -42.2% =57.8, the relative improvement is also approximately 2 (57.8%/26.1%). In both situations the absolute gain is different but the relative gain is

comparable. Moreover, among new users, the effect of PharmaCoach is large but still not perfect because  $100\% - 68.3\% = 31.8\%$ , approximately one-third of all new users of the selected cardiovascular drugs is still not dispensing compliant. Furthermore, for some drug groups in study 1, like for example the inhalational corticosteroids (ICS), no effect of PharmaCoach could be observed. The absence of any effect could be explained by the fact that there is still an ongoing debate whether treatment with ICS should be intermittent or long-term in daily practice.

The PharmaCoach program's objective is to motivate patients to use their drugs according to the direction of long term use. In this study, we only measured if patients filled and re-filled their dispensing accordingly. We could not validate whether patients indeed used the dispensed drugs at all. However, the first problem to fix among non-compliers is that they at least should have access to the drugs. In many studies, where relationships between dispensing compliance and outcomes have been studied, also in the absence of knowledge whether patient used their drugs at all, it has been shown that those patients with increased dispensing compliance do have increased rates to achieve treatment goals and less risk to develop complications [3-10]. Subsequently, it can be deduced that improving dispensing compliance will result in major reductions of disease complications as well as adverse drug reactions resulting in saving lives and reductions of hospitalizations and primary care.

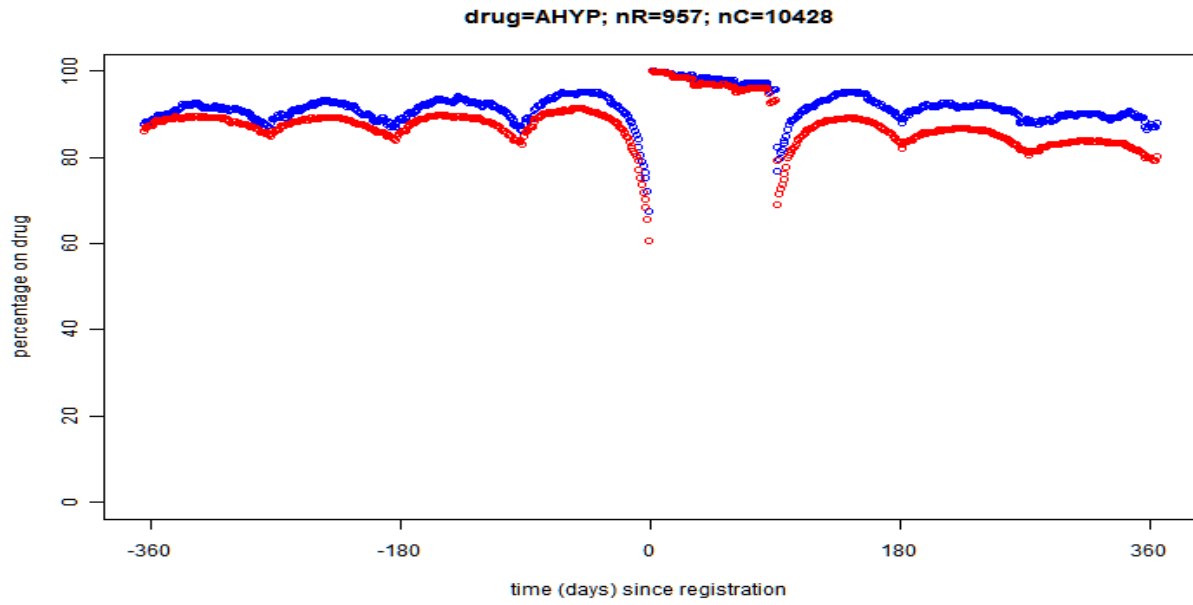
## Conclusion

Given the limitations of observational studies, we found that PharmaCoach is an effective tool to assist patients to improve medication dispensing persistence. The positive effect is observed and statistical significant ( $p < 0.05$ ) for all type of users. In patients with already high baseline medication dispensing persistence (long-term users) of approximately 80%, still a 9.1% improvement was observed. Among patients that recently started drugs to be used life-long, we found PharmaCoach to be highly effective to improve dispensing persistence rates with a mean of 62%.

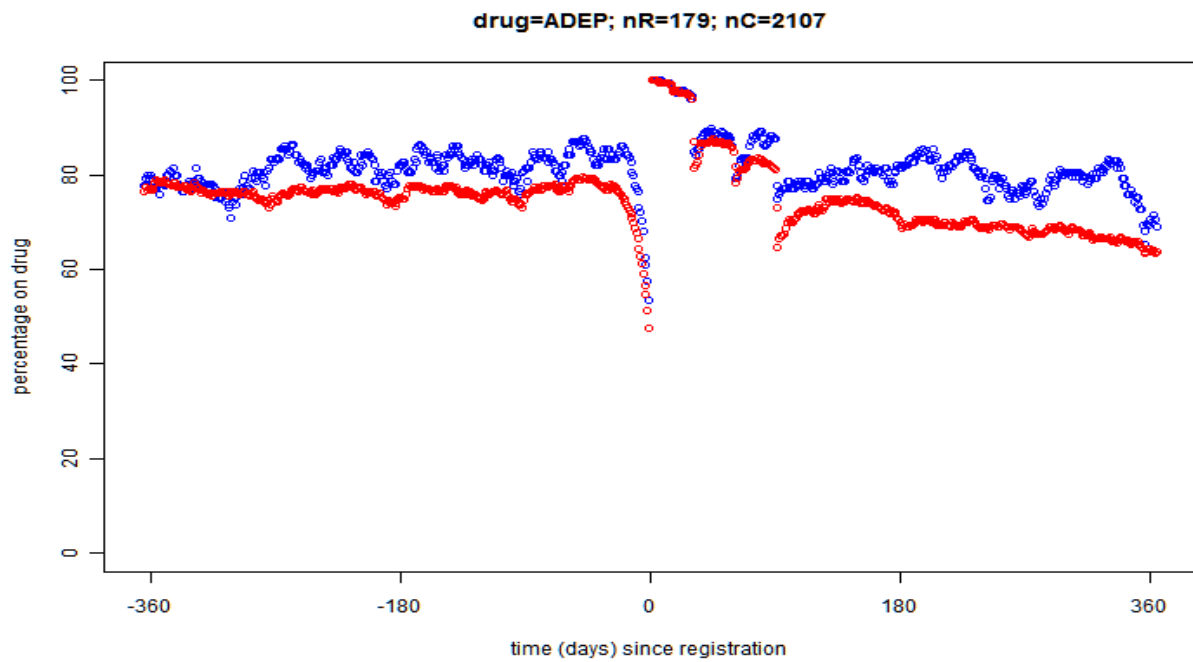
## Appendix 1: Persistence graphs by drug group (Cohort I)

Blue lines are intervention groups, red lines are controls. Cave different from major report.

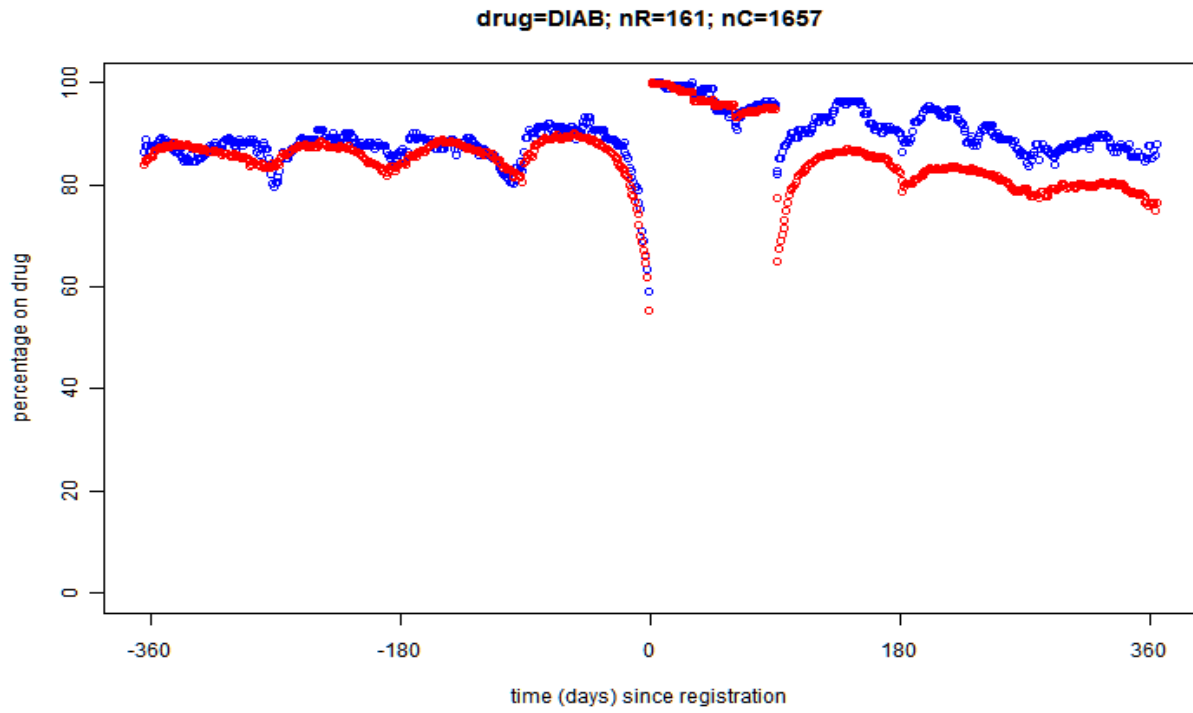
Anti-hypertensives



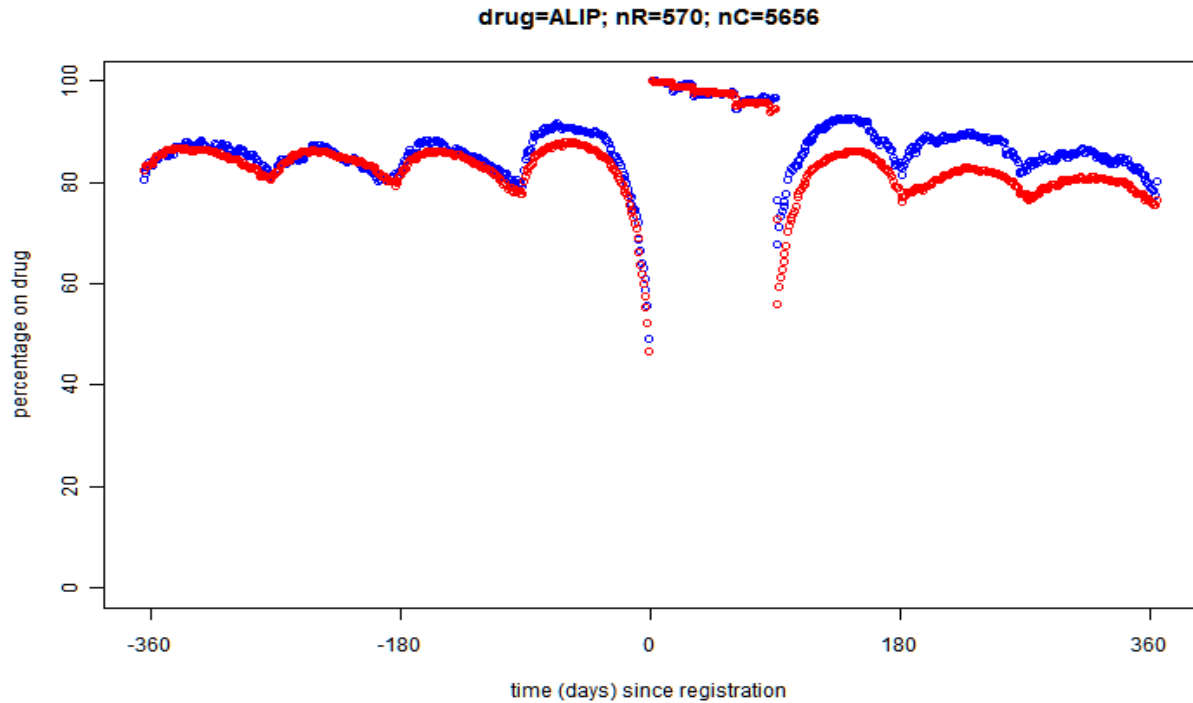
Antidepressants



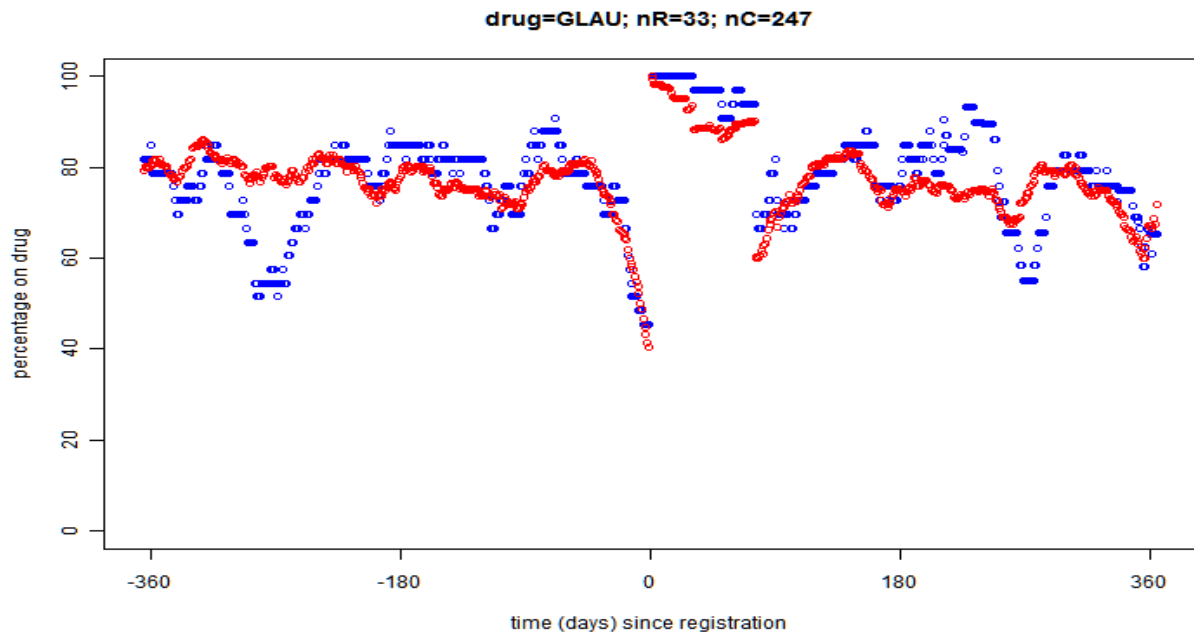
## Anti-diabetics



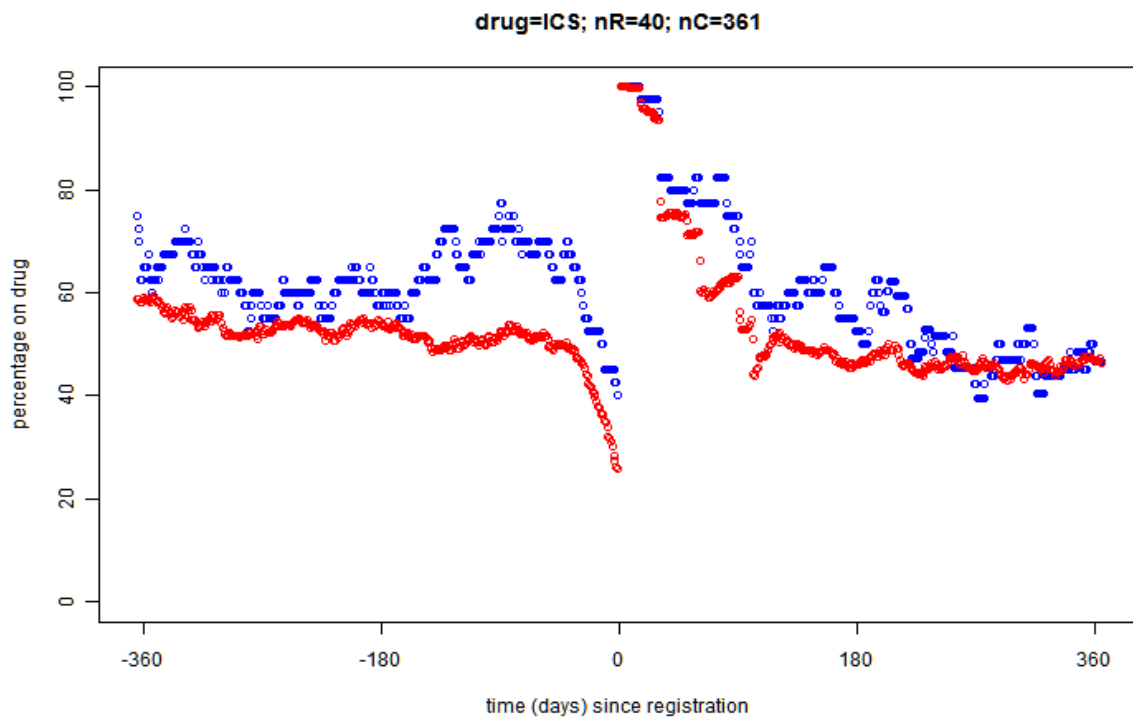
## Lipidlowering drugs



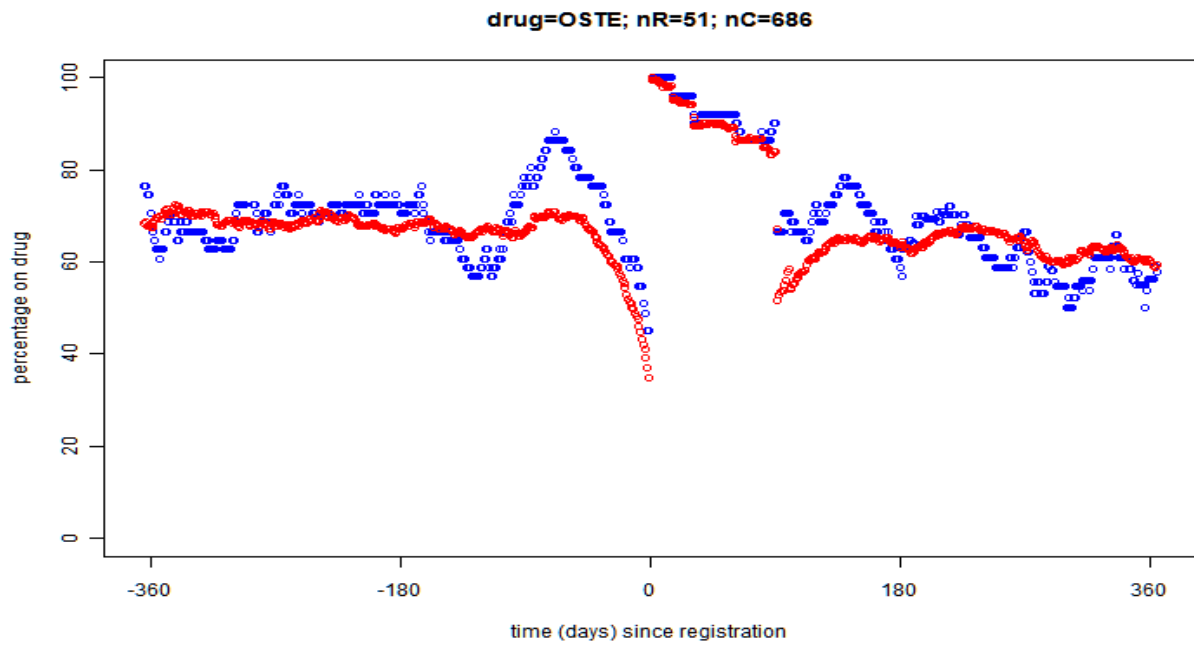
Glaucoma meds.



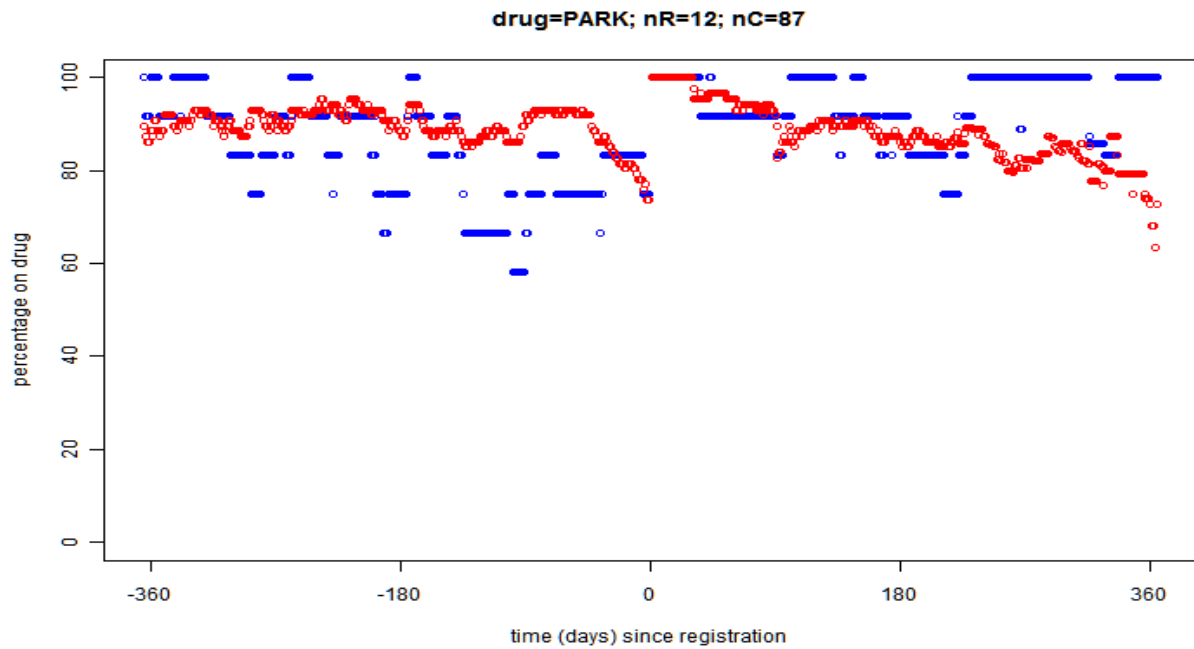
Inhalational corticosteroids



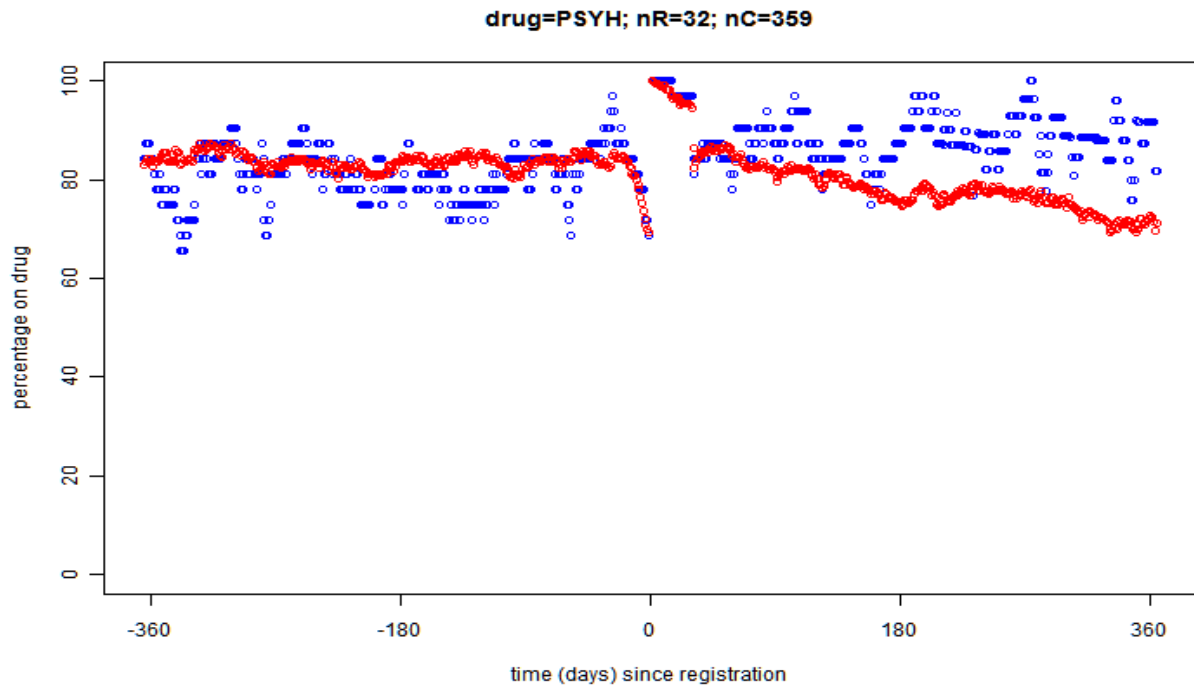
## Anti-osteoporotic drugs



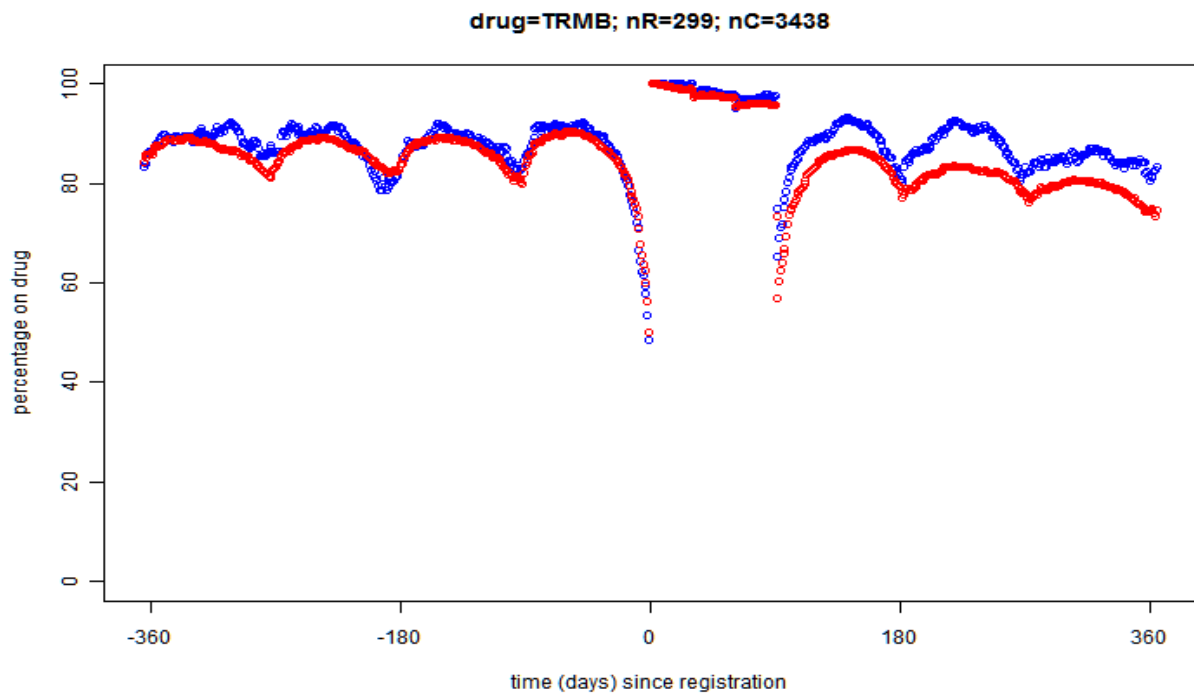
## Anti-parkinsonian drugs



## Antipsychotics

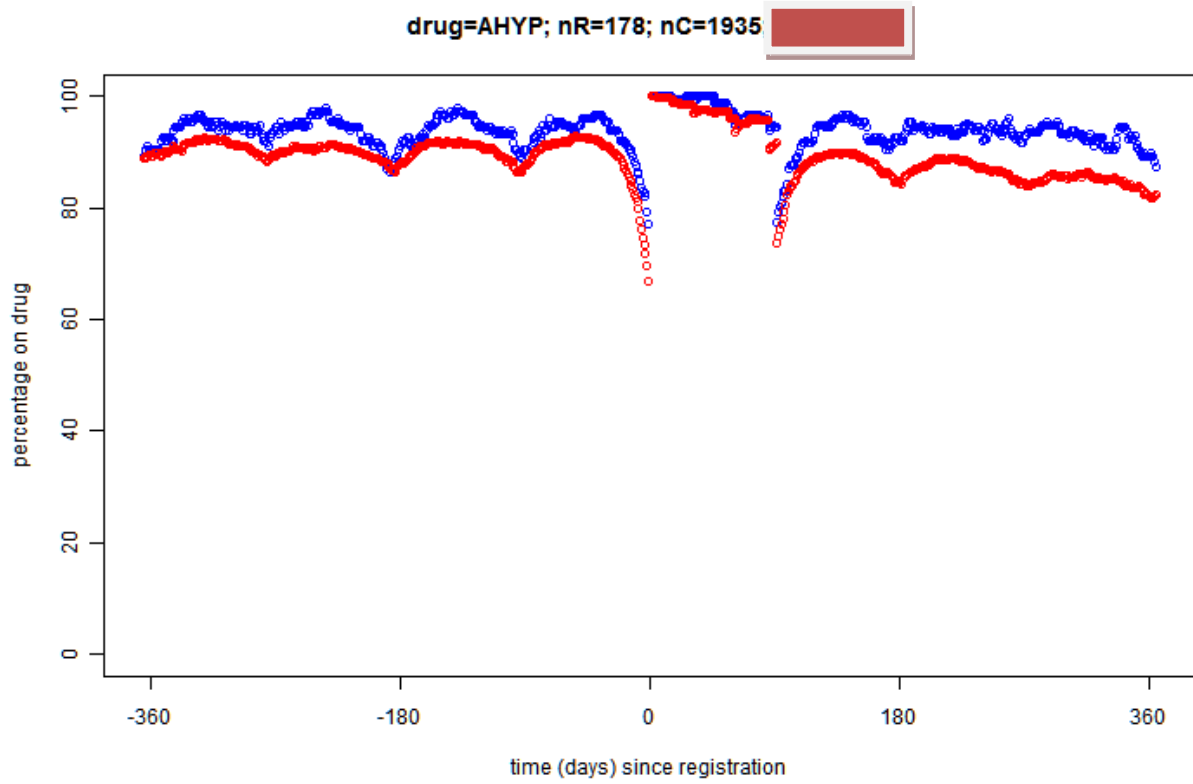
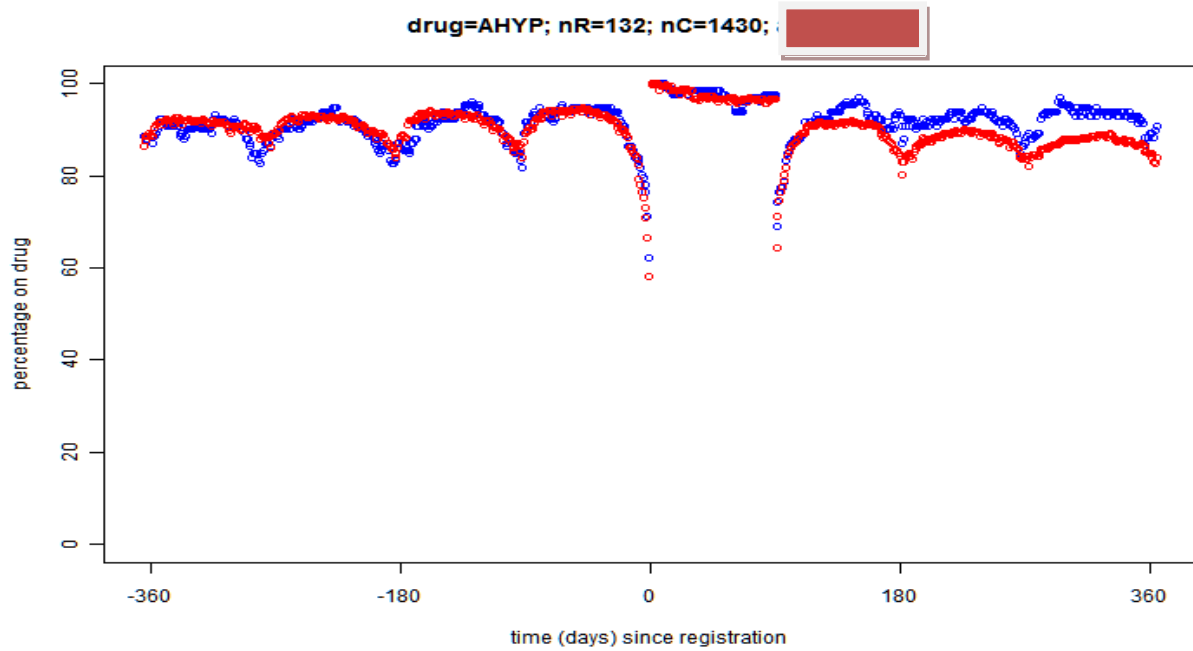


## Antitrombotics

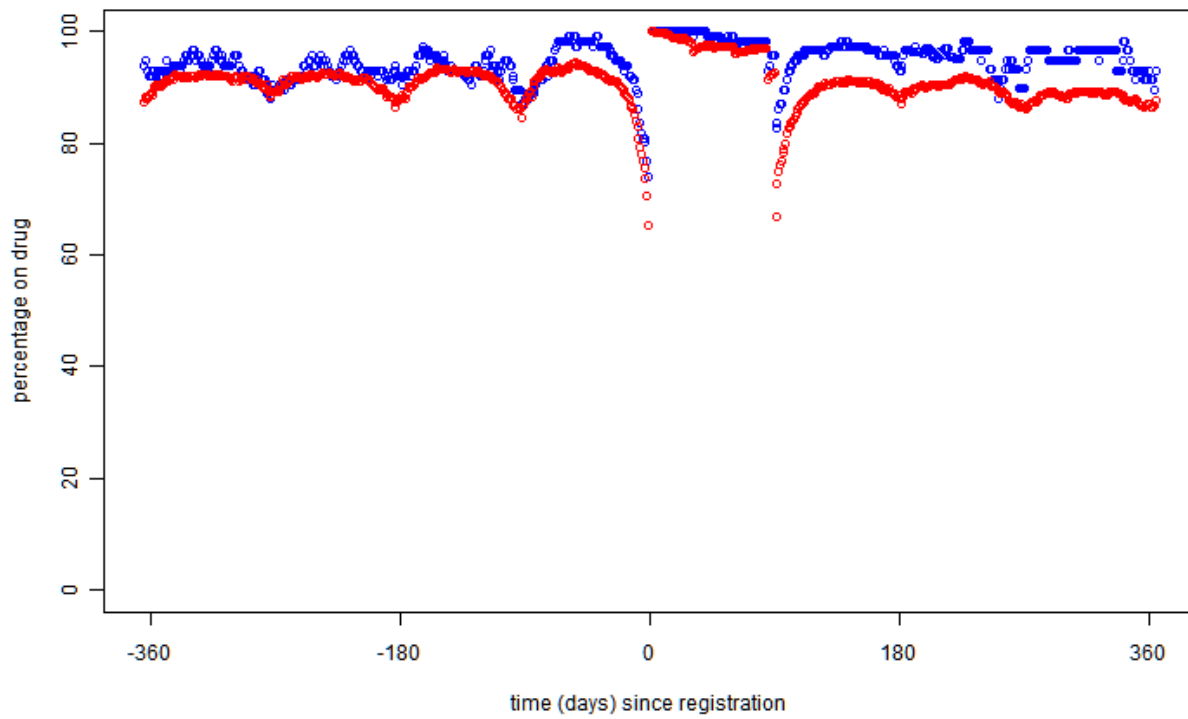


## Appendix 2: Selection bias per pharmacy

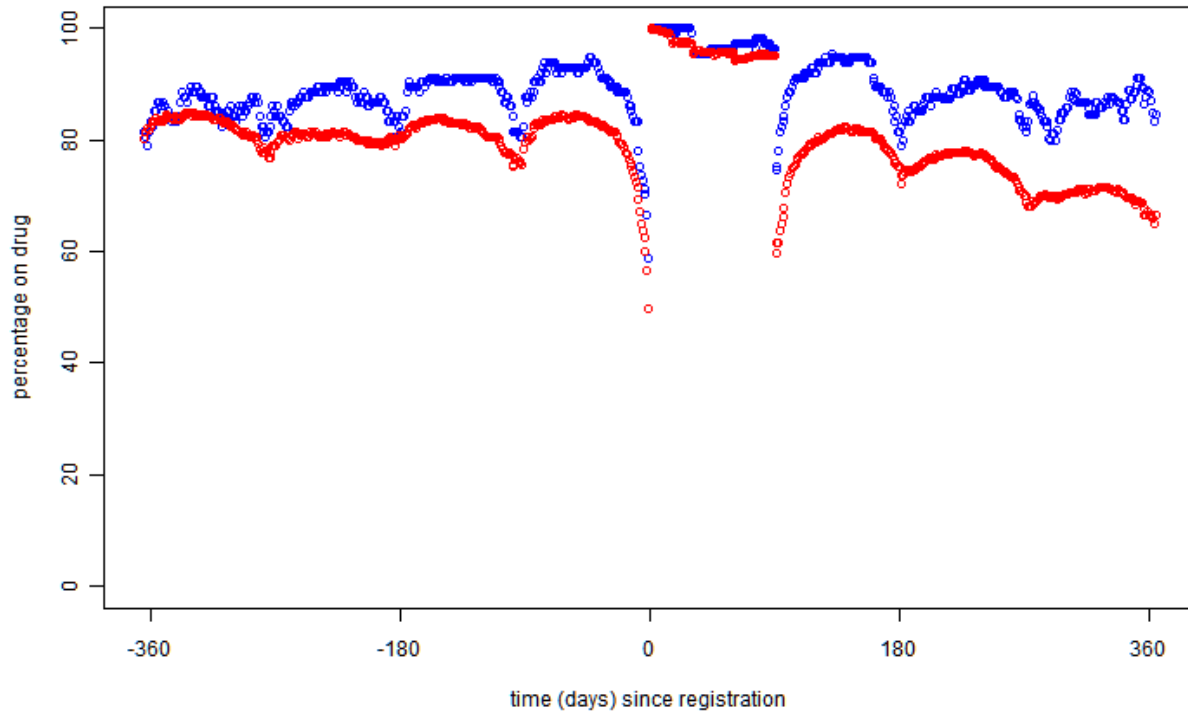
Cohort 1 (example: antihypertensives) red are controls  
)

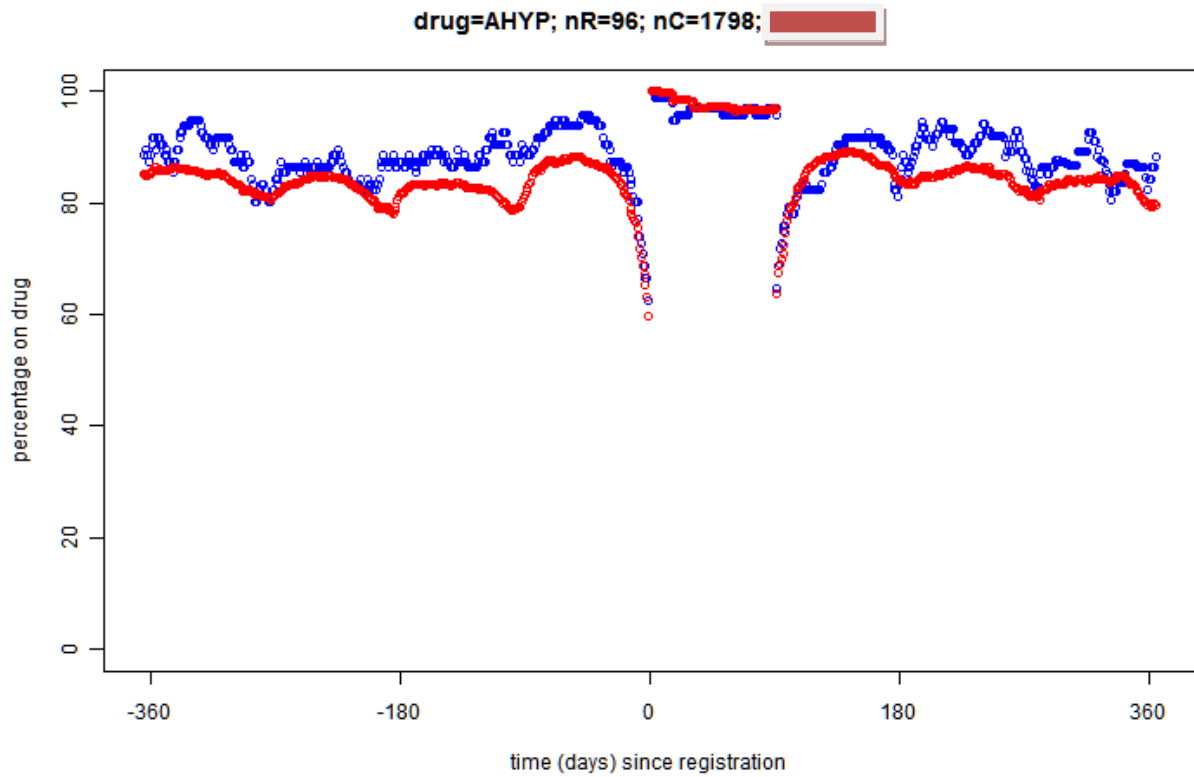
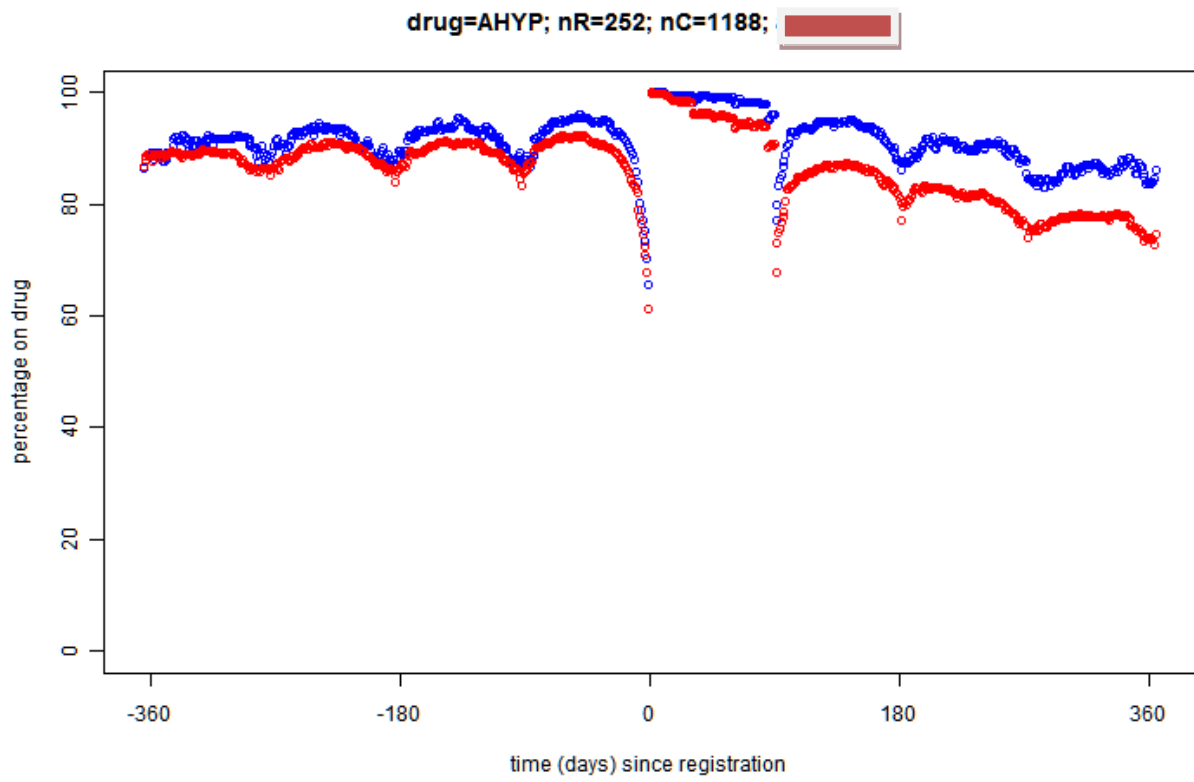


drug=AHYP; nR=116; nC=1333; [redacted]

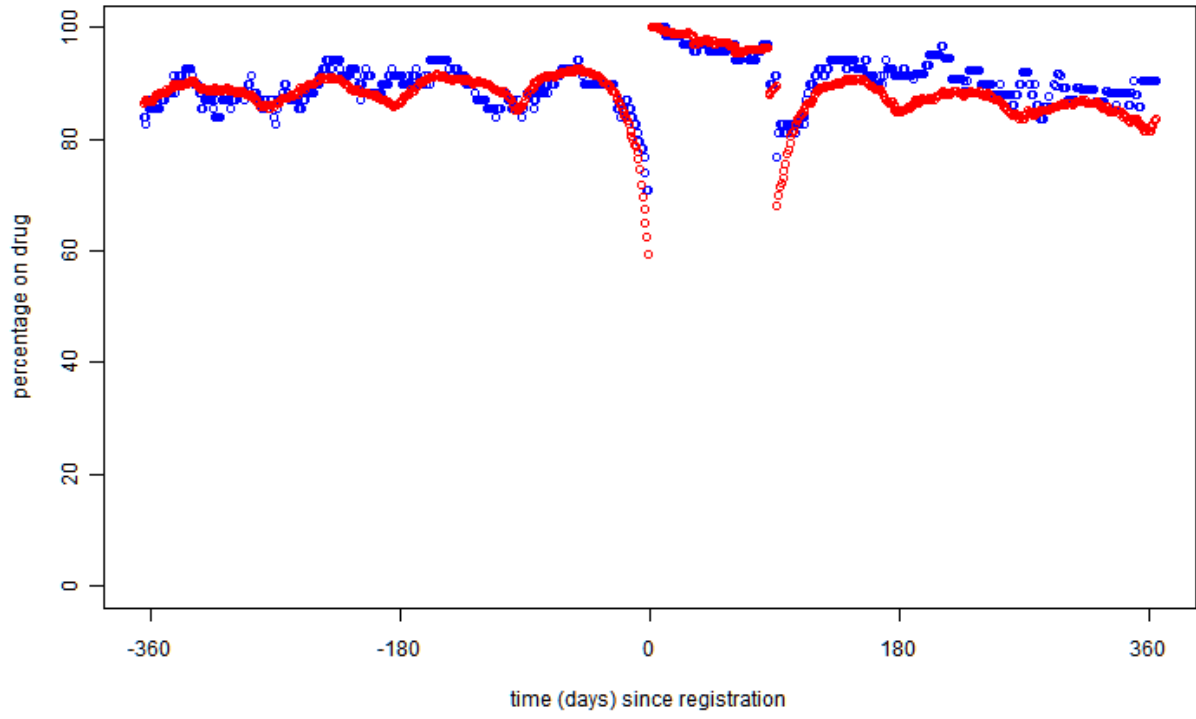


drug=AHYP; nR=114; nC=1110; [redacted]





drug=AHYP; nR=69; nC=1634;

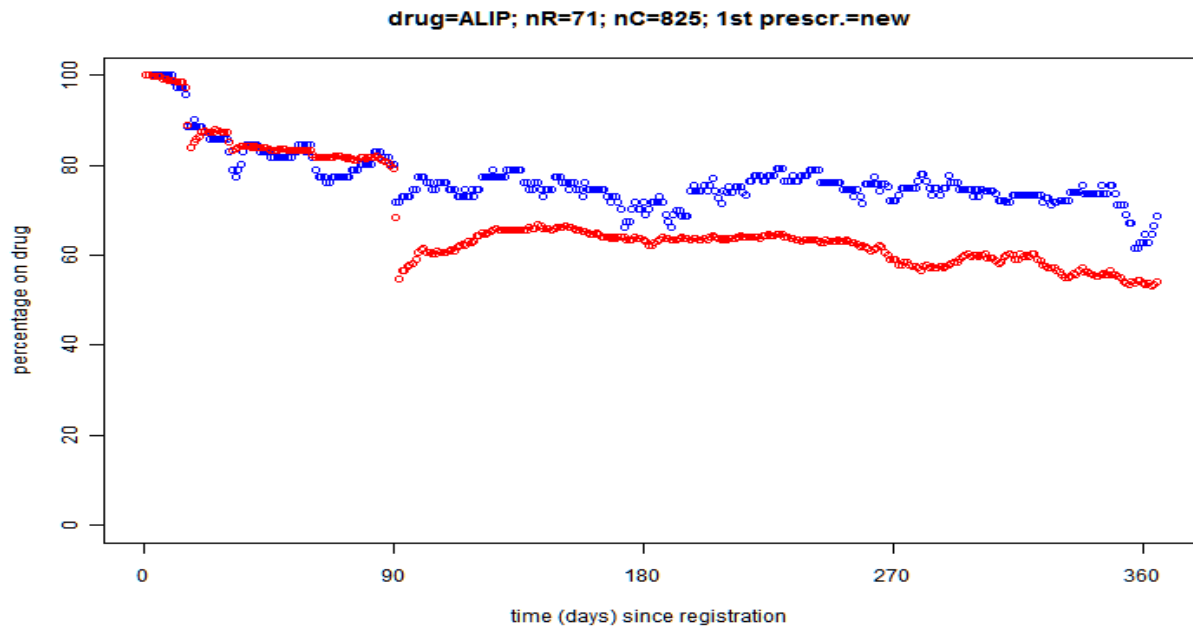


## Appendix 3: Dispensing compliance graphs (Coh

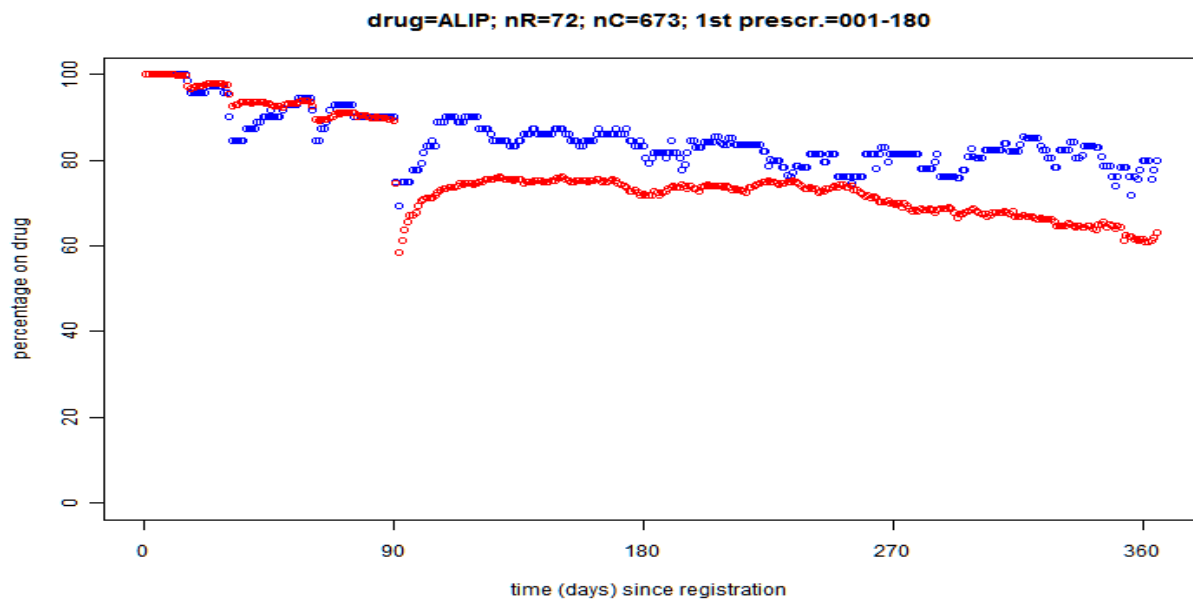
Red = control  
Blue = PharmaCoach

Anti-lipaemics

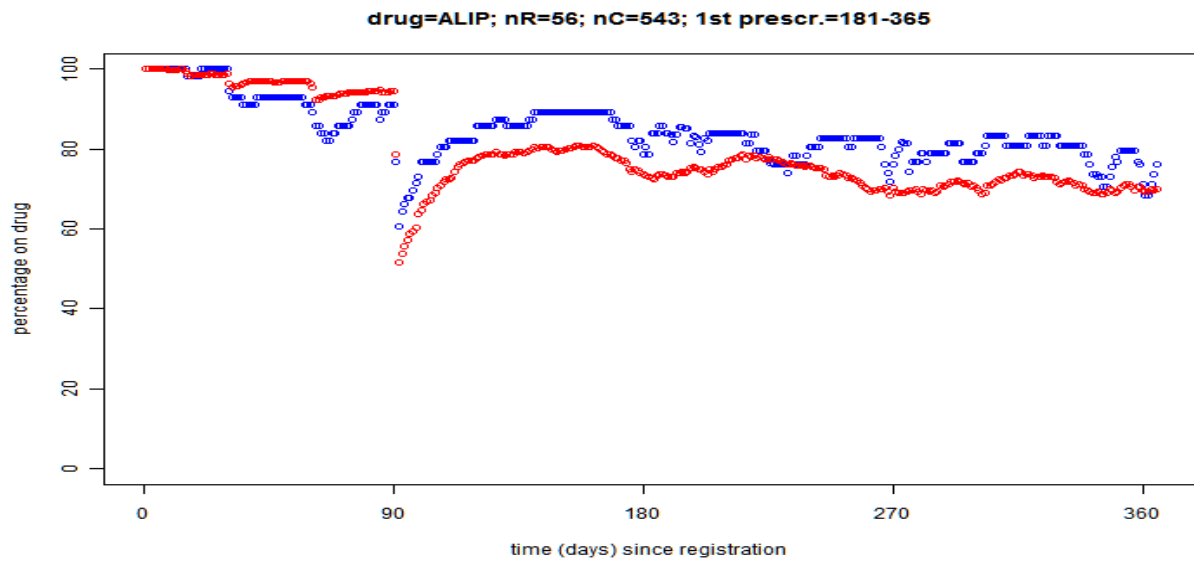
New users



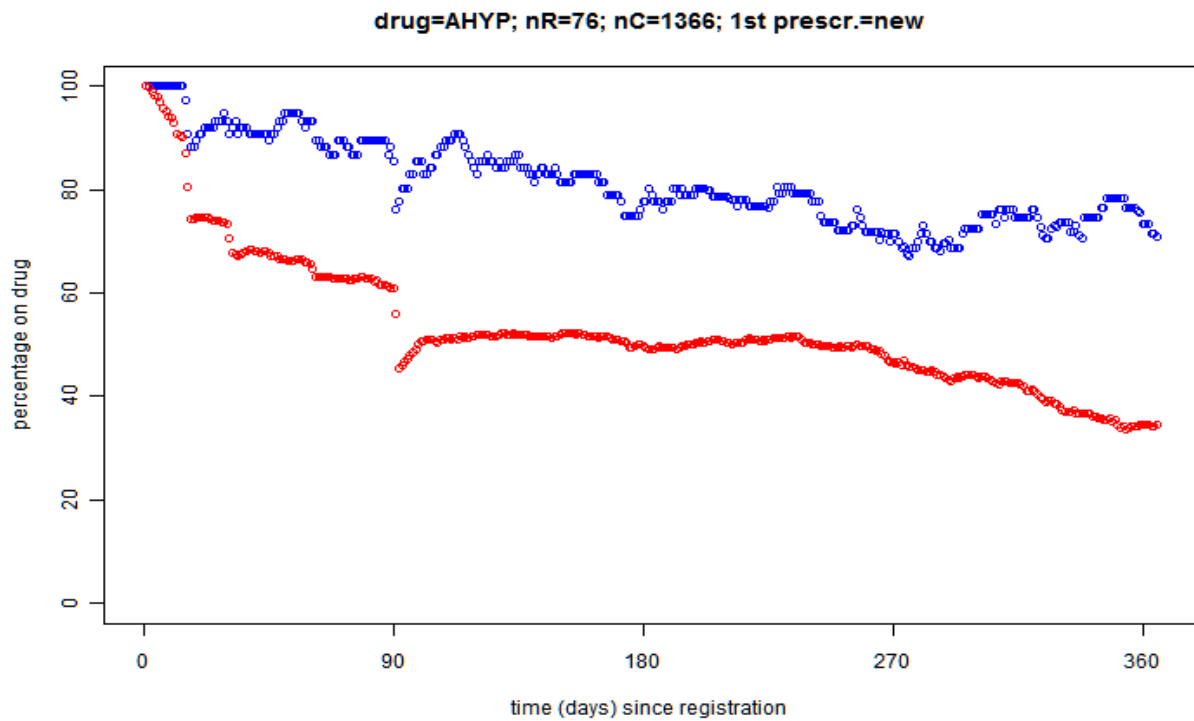
Recent use



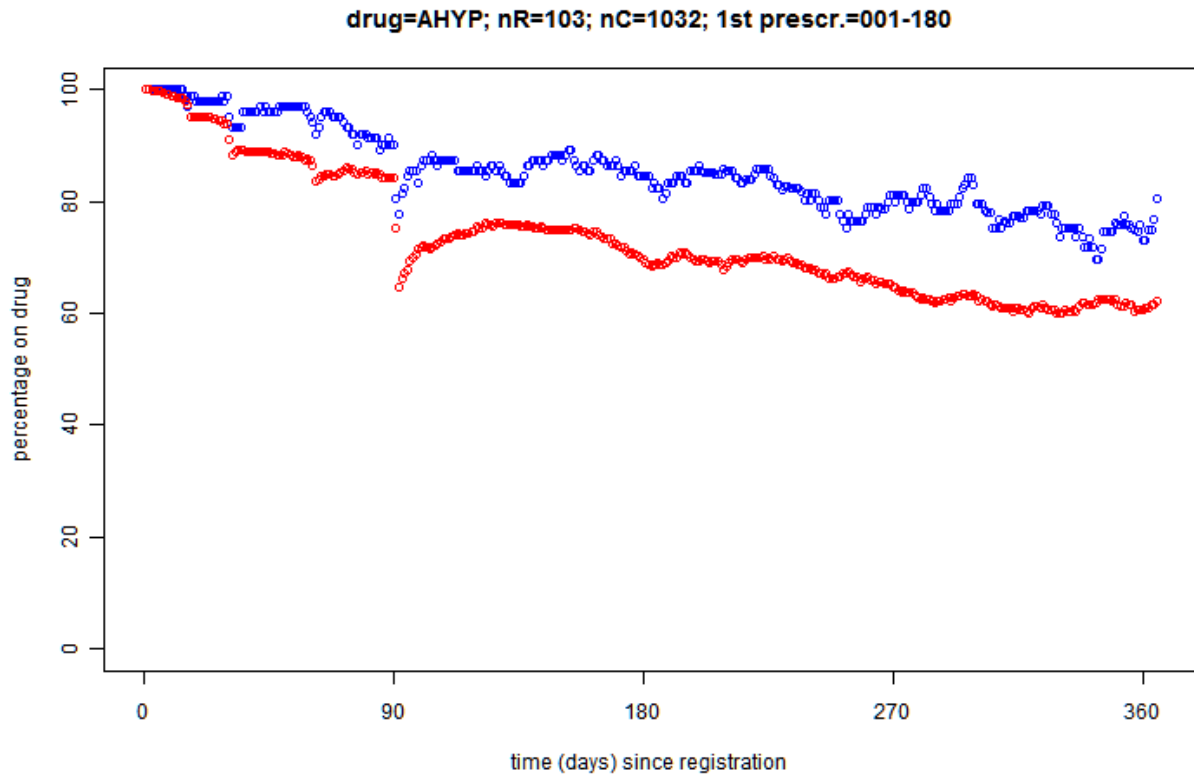
## Long term use



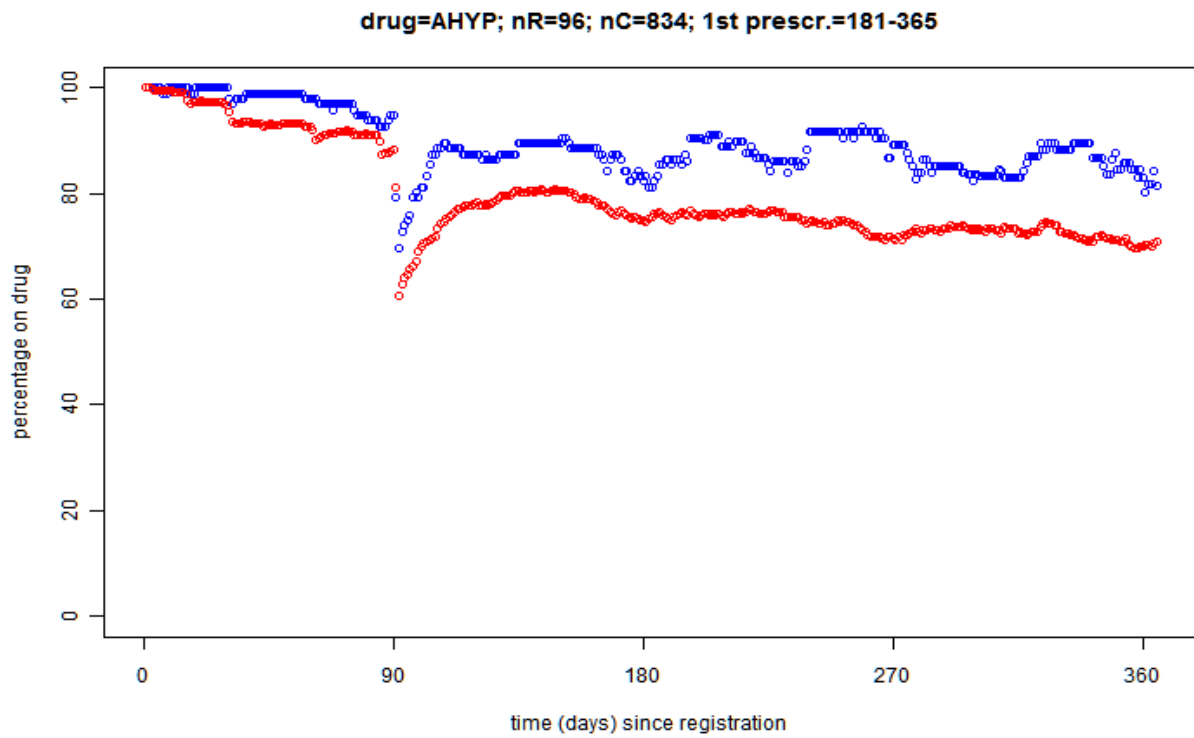
## Anti-hypertensives New users



### Recent users

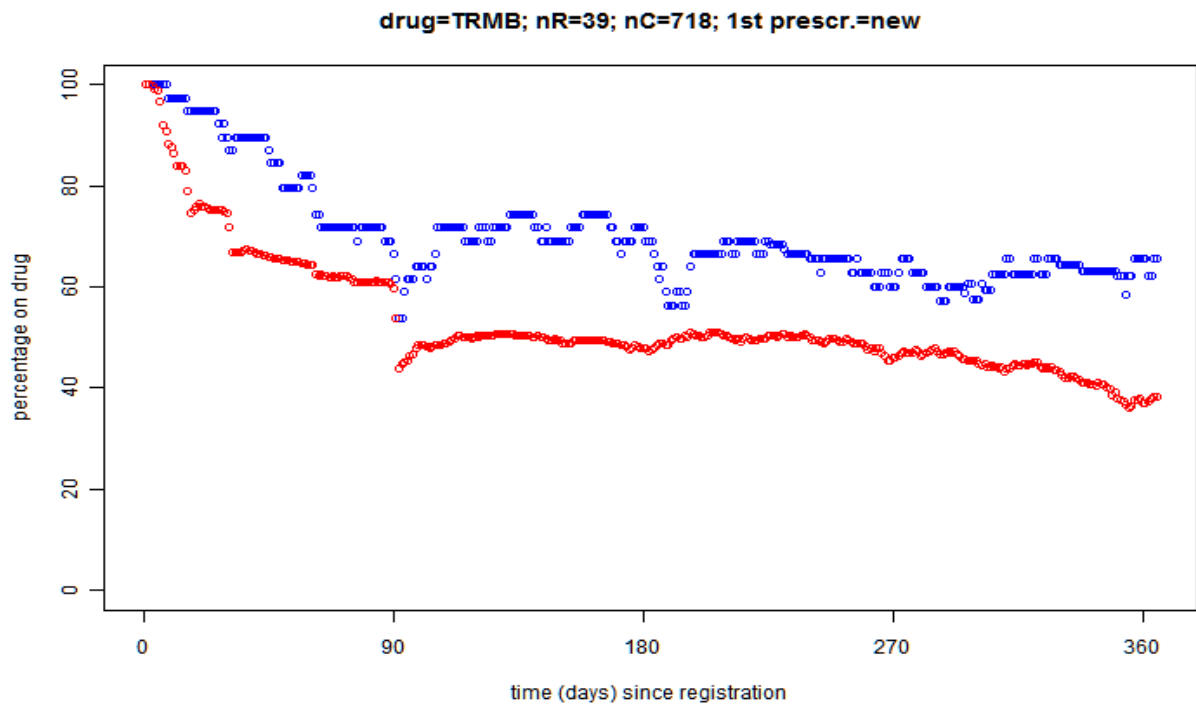


### Longterm users

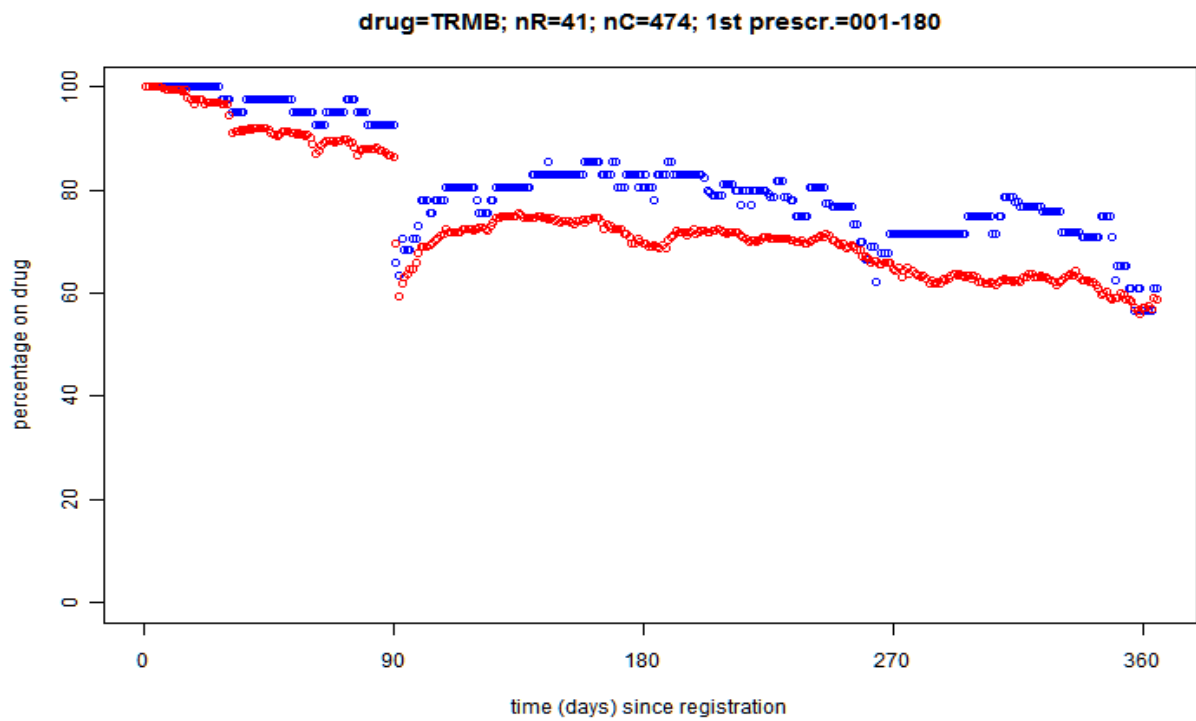


# Thrombolytics

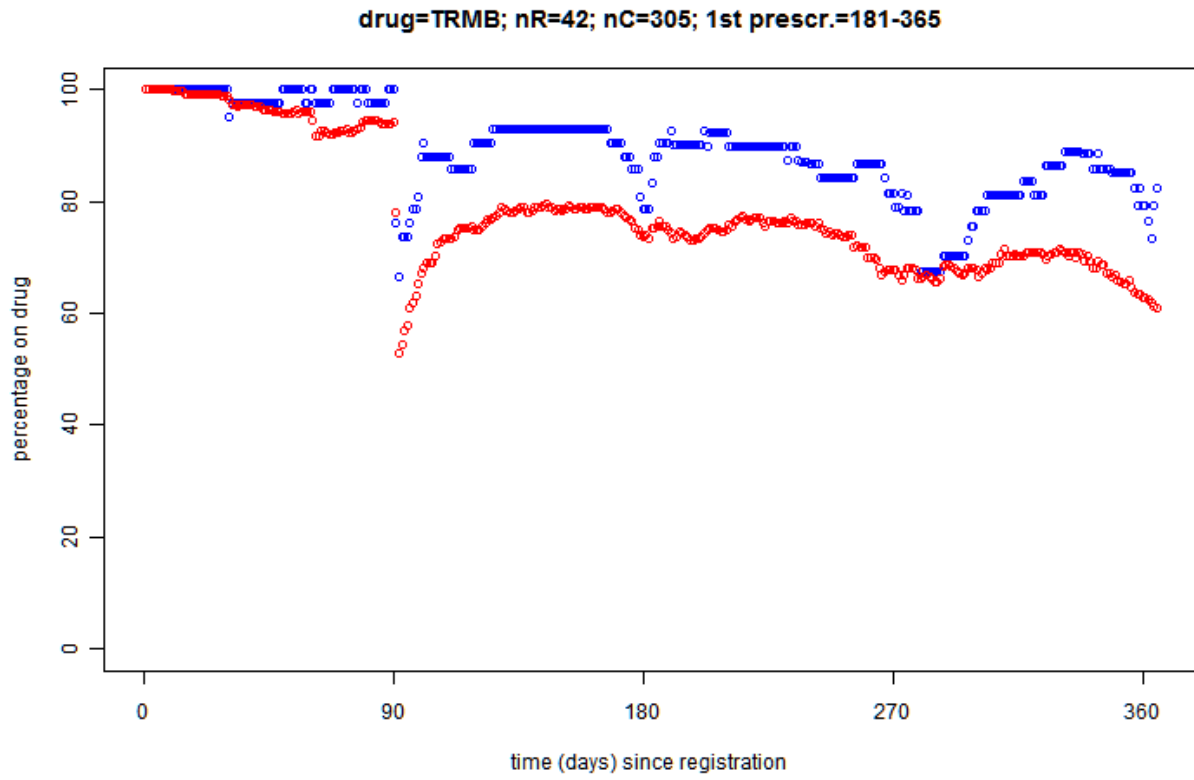
## New users



## Recent users



Longterm users



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