ORIGINAL PAPER

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Impact of prolonged antihypertensive duration of action on predicted clinical outcomes in imperfectly adherent patients: comparison of aliskiren, irbesartan and ramipril

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SUMMARY

Background: Most patients miss occasional doses of antihypertensives. The use of 'forgiving' drugs (i.e. drugs with duration of action longer than the 24-h dosing interval) may allow an adequate blood pressure (BP) reduction to be maintained despite missed doses. **Aim:** To quantify the effects of adherence level and duration of action on estimated mean systolic BP (SBP) reduction and cardiovascular disease (CVD) risk. **Method:** For 1250 patients, we simulated 256-day dosing histories with realistically distributed drug holidays based on a study of electronically monitored dosing records. Adherence was set to the desired level by altering the proportion of doses missed. Mean office SBP-lowering effect (aliskiren 300 mg, −14.1 mmHg; irbesartan 300 mg, −13.3; ramipril 10 mg, −10.1 mmHg) and the rate of SBP increase after stopping treatment (off-rate; aliskiren, 1.0 mmHg/day; irbesartan, 3.6 mmHg/day; ramipril, 4.0 mmHg/day) were taken from the results of a randomised, double-blind trial. SBP was averaged over time and patient to estimate mean reductions in SBP and 10-year CVD risk (Framingham risk equation, baseline absolute 10-year CVD risk: 27%). **Results:** Predicted reductions in SBP and CVD risk with aliskiren were larger and less affected by imperfect adherence than the reductions with irbesartan or ramipril. For aliskiren, reducing adherence from 90% to 60% led to a predicted rise in SBP of 1.0 mmHg and three additional CVD events per 1000 treated patients; larger predicted differences were observed for irbesartan (2.5 mmHg; 7.5 events/1000 treated patients) and ramipril (2.2 mmHg; 6.7 events/1000 treated patients). **Conclusion:** To offset the effects of imperfect adherence, a common challenge with antihypertensives, for better BP management it may be prudent to prescribe 'forgiving' drugs.

What's known

- Most patients with hypertension miss occasional doses of their prescribed antihypertensive medication. We previously developed a method to investigate the effects of different levels of adherence and drug off-rate (i.e. how quickly the BP-lowering effect is lost after doses are missed) on predicted mean SBP reduction and CVD risk.
- This study applied data from a randomised clinical trial to this method to compare the predicted effects of different levels of adherence on the clinical effectiveness of the direct renin inhibitor, aliskiren, the angiotensin receptor blocker, irbesartan and the angiotensin-converting enzyme (ACE) inhibitor, ramipril.

What's new

- Aliskiren 300 mg, which has a low off-rate (i.e. prolonged BP-lowering effect beyond the 24-h dosing interval), provided reductions in predicted SBP and CVD risk that were less affected by poor adherence than the reductions provided by irbesartan 300 mg or ramipril 10 mg (drugs with higher off-rates).
- Thus, reducing adherence to irbesartan or ramipril from 90% (typical of randomised controlled trials) to 60% (poor adherence) was predicted to lead to double the loss of average SBP increases and additional CVD events compared with the same reduction in adherence to aliskiren.
- Clinicians must make every effort to counsel and encourage each of their patients to adhere to their prescribed medication, a common challenge with antihypertensives. However, to offset the effects of imperfect adherence, for better BP management it may be prudent to prescribe 'forgiving' drugs.

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Disclosures
Y. Brede and A. Lowy are employees of Novartis Pharma AG, Basel, Switzerland, and are therefore eligible for Novartis stock and stock options. M. Burnier has received research grants from, and has been a speaker for, Novartis Pharma AG and AARDEX Ltd.

Introduction

The achievement of adequate blood pressure (BP) reduction in patients with hypertension remains a challenge despite the wide availability of antihypertensive agents with proven BP-lowering efficacy in clinical trials (1). The clinical effectiveness of these drugs, i.e. the BP reductions achieved with their use in clinical practice (2), may be influenced by many factors that are absent from clinical trials. The extent to which patients with hypertension adhere to their treatment regimen (i.e. the extent to which they take their medication as prescribed) is thought to be one of the main determinants of whether adequate BP

reduction is achieved (3). Imperfect adherence is common; according to a study of electronically monitored dosing records from 4783 patients with hypertension in clinical trials, approximately 10% of patients miss a scheduled dose of their antihypertensive medication on any given day (4). Adherence in clinical practice is almost certainly worse than this; one well-designed study found that adherence to combination therapy with benazepril and amlodipine was 75% (5), but values as low as 25% have been reported for some patients (6).

The imperfect adherence with antihypertensive medication observed in clinical practice is important because the consequent loss of BP reduction may increase the risk of cardiovascular disease (CVD) events (7,8). The effects on BP of imperfect adherence may be ameliorated by using drugs that have a slow loss of BP-lowering effect during treatment interruptions (i.e. a low off-rate) and a long duration of action. As missing occasional doses of drugs with low off-rates does not markedly impair BP reduction, these are often referred to as 'forgiving' drugs (9,10). Such drugs include, for example, the calcium channel blocker amlodipine (11) and the direct renin inhibitor (DRI) aliskiren (12). However, the impact of adherence and off-rate on clinical effectiveness has not been evaluated quantitatively. Quantifying the differences in BP-lowering effect in clinical practice compared with controlled clinical trials at the level of individual drugs is important, as these differences will have an impact on the level of CVD risk reduction that can be achieved and hence healthcare costs.

We developed a method to quantify the chain of factors linking adherence levels, and the impact of drug off-rate, with outcomes (13). Using BP data from a randomised, clinical trial, we applied this method to predict the effects of adherence level on mean systolic BP (SBP) reduction and CVD risk with three drugs with notably different off-rates: the DRI aliskiren, the angiotensin receptor blocker (ARB) irbesartan and the angiotensin-converting enzyme (ACE) inhibitor ramipril.

Methods

Underlying principles

We developed a method to quantify the effects of occasionally missing prescribed doses, and the influence of the off-rate during these treatment interruptions, on clinical outcomes. This method is described in detail elsewhere (13). Briefly, for 1250 patients, we simulated 256-day dosing histories with realistically distributed drug holidays (periods of non-adherence) based on a study of electronically monitored dosing records for patients in hypertension clinical trials (4). SBP reduction was determined on each day of the 256-day period for a range of adherence levels, based on the following properties of the antihypertensive agent in question: mean office SBP-lowering effect assuming continuous use (mmHg), rate of loss of antihypertensive effect when treatment is stopped (off-rate; mmHg/day) and rate of onset of antihypertensive effect when treatment is initiated or restarted (on-rate; mmHg/day). SBP was averaged over time and patients to estimate the mean SBP reductions that would theoretically be achieved. The Framingham risk equation (FRE) was then used to predict the effects on CVD risk of loss of SBP reduction owing to missed doses.

Inputs and outputs

Mean office SBP-lowering effects and off-rates were taken from the results of a 9-week, randomised, double-blind trial of aliskiren 300 mg, irbesartan 300 mg and ramipril 10 mg [Palatini et al. (12,14)]. In that study, patients were randomised to receive double-blind, once-daily aliskiren, irbesartan or ramipril. After at least 6 weeks of continuous active treatment, patients received a simulated single missed dose (single-blind placebo instead of active treatment). Off-rate was taken as the difference between the BP reduction after a missed dose compared with an active dose, as measured by ambulatory BP monitoring. The mean office SBP-lowering effect was evaluated as the mean change from baseline in sitting SBP at week 9 (Table 1). On-rates could not be determined from the Palatini study and were instead fixed at 5 mmHg/day for all three antihypertensives. This optimistic estimate was chosen to reflect the rapid drop in SBP that is achieved when antihypertensive treatment is initiated. Various adherence levels from 50% to 100% were evaluated. Adherence levels of 90% [typical of randomised controlled trials (4)], 75% [estimated typical adherence in clinical practice (5)] and 60% (poor adherence) were examined in more detail.

Table 1 Mean office SBP-lowering effect and off-rate for aliskiren, irbesartan and ramipril [12,14]

Antihypertensive agent	Mean office SBP-lowering effect (mmHg)	Off-rate† (mmHg/day)
Aliskiren 300 mg	−14.1	1.0
Irbesartan 300 mg	−13.3	3.6
Ramipril 10 mg	−10.1	4.0

†Rate of loss of antihypertensive effect when treatment is stopped. SBP, systolic blood pressure.

The SBP reductions were used to estimate 10-year CVD risk, as determined by the FRE for CVD (15). Patient baseline characteristics for the FRE were derived mostly from published patient survey data (Table 2). Baseline absolute 10-year CVD risk was 27.0% in this patient population. The changes in absolute CVD risk were determined, as were the number of CVD events per 1000 treated patients and the number needed to treat (NNT) to avoid one CVD event.

Sensitivity analysis

A one-way sensitivity analysis was performed to test the robustness of the findings. In this sensitivity analysis, the on-rate was set at 10 mmHg/day. All other inputs were kept the same.

Results

Antihypertensive characteristics of aliskiren, irbesartan and ramipril

The BP-lowering characteristics of aliskiren, irbesartan and ramipril were taken from a randomised controlled trial of the effects of a simulated missed dose on BP [Palatini et al. (12,14)]. Aliskiren had the lowest off-rate (1.0 mmHg/day) and the greatest mean office SBP-lowering effect (−14.1 mmHg; Table 1). By contrast, ramipril had the highest off-rate (4.0 mmHg/day) and provided the smallest mean office SBP reduction (−10.1 mmHg).

Table 2 Inputs for the Framingham risk equation for CVD

Patient characteristics	Mean	Source
Age, years	65.20	NHANES [32]
Female, %	52.86	NHANES [32]
Race, % Black	25.55	NHANES [32]
SBP, mmHg*	155.95	NHANES [33]
BMI, kg/m^2	29.65	NHANES [34]
Smokers, %	27.53	NHANES [35]
Patients with diabetes	16.96	NHANES [36]
Duration of diabetes	11.72	NHANES [36]
HDL, mmol/l	1.47	NHANES [37]
Total cholesterol, mmol/l	5.41	NHANES [38]
Patients with LVH, %	2.73	Anderson et al. [39]
Patients with atrial fibrillation, %	2.06	Go et al. [40]
HbA1c, %	5.92	NHANES [41]

*Only patients with SBP between 140 and 200 mmHg are included. CVD, cardiovascular disease; BMI, body mass index; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure.

Predicted effect of adherence level on average SBP reduction

Predicted average reductions in SBP with aliskiren 300 mg were less affected by imperfect adherence than those with irbesartan 300 mg or ramipril 10 mg (Figure 1). For irbesartan, reducing adherence from 90% to 60% led to a predicted rise in SBP of 2.5 mmHg (i.e. the predicted average SBP reduction decreased from 12.3 to 9.8 mmHg). Similarly, reducing adherence to ramipril from 90% to 60% led to a predicted rise in SBP of 2.2 mmHg (i.e. the predicted average SBP reduction decreased from 9.3 to 7.1 mmHg). When adherence to aliskiren was reduced from 90% to 60% the predicted rise in SBP was 1.0 mmHg (i.e. the predicted average SBP reduction decreased marginally, from 13.7 to 12.7 mmHg).

Predicted effect of adherence level on CVD risk

Imperfect adherence had less effect on the predicted reductions in CVD risk with aliskiren 300 mg than with irbesartan 300 mg or ramipril 10 mg (Figure 2). When adherence was reduced from 90% to 60%, the predicted absolute reduction in CVD risk with irbesartan was reduced from 3.7% to 2.9%, and an additional 7.5 events were predicted per 1000 irbesartan-treated patients. The NNT to avoid one CVD event increased by seven patients, from 27.4 to 34.4. Similarly, reducing adherence to ramipril from 90% to 60% was predicted to decrease the absolute CVD risk reduction from 3.7% to 2.9%, and lead to an additional 6.7 events per 1000 treated patients. The NNT to avoid one CVD event increased from 36.1

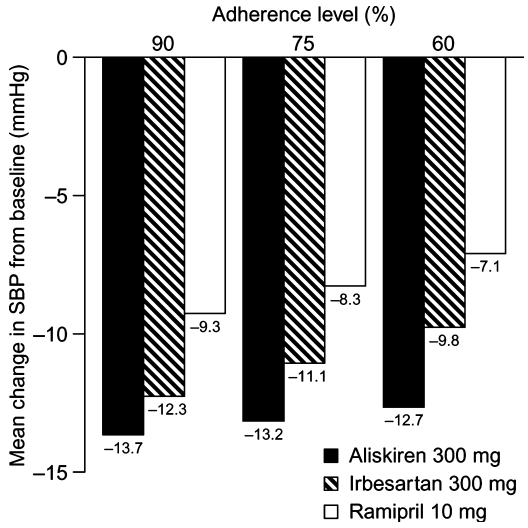

Figure 1 Predicted mean SBP reductions with aliskiren 300 mg, irbesartan 300 mg or ramipril 10 mg for different levels of adherence

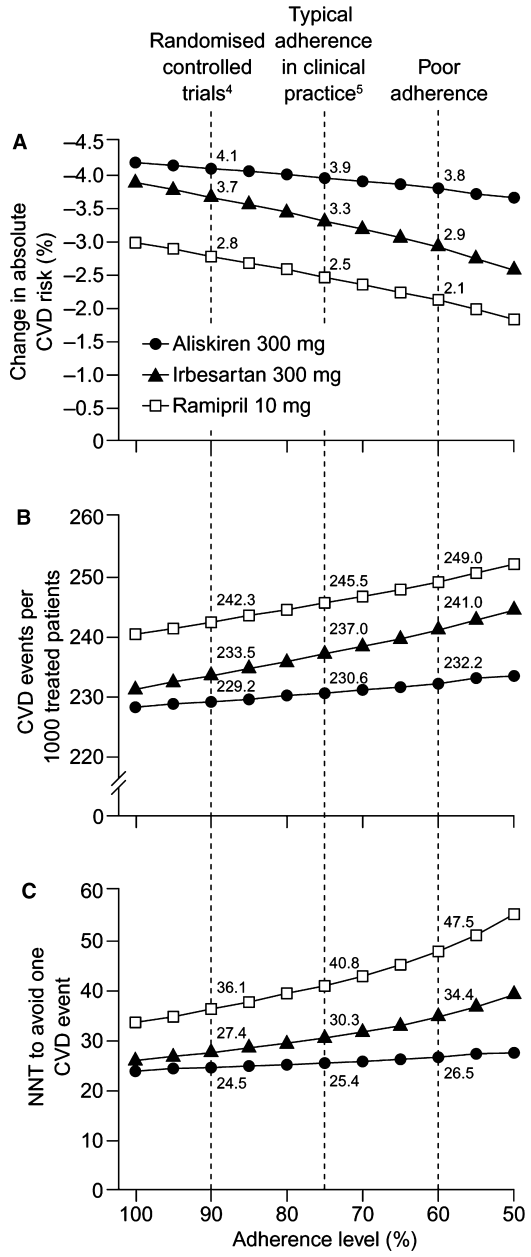

Figure 2 Predicted (A) reduction in absolute CVD risk, (B) CVD events per 1000 treated patients and (C) NNT to avoid one CVD event for aliskiren 300 mg, irbesartan 300 mg or ramipril 10 mg at different adherence levels

to 47.5 patients. With aliskiren, reducing adherence from 90% to 60% was predicted to decrease the absolute CVD risk reduction by 0.3%, from 4.1% to 3.8%, and only an additional 3.0 events were predicted per 1000 treated patients. The NNT to avoid one CVD event increased by two patients, from 24.5 to 26.5.

Sensitivity analysis

A one-way sensitivity analysis, in which the on-rate was set to a very optimistic 10 mmHg/day, showed that the findings were robust with respect to changes in this key input parameter (Table 3). For irbesartan and ramipril, reducing adherence from 90% to 60% in this scenario led to a rise in SBP of 2.0 and 1.9 mmHg, respectively, and 6.2 and 5.6 additional CVD events per 1000 treated patients respectively. Consistent with the overall analyses, smaller differences were observed for aliskiren (0.9 mmHg rise in SBP and an additional 2.9 events per 1000 treated patients).

Discussion

Imperfect adherence to antihypertensives is prevalent – indeed, one study of electronically monitored dosing records found that approximately 10% of patients in clinical trials miss a dose of their antihypertensive medication on any given day (4). In clinical practice, adherence is generally rather poorer; an adherence level of 75% is typical, but values as low as 25% have been reported in some patient groups (5,6). It is intuitive that missing occasional doses of an antihypertensive that has a fast loss of BP-lowering effect during treatment interruptions (i.e. a high off-rate) will have a greater impact on BP reduction and CVD risk than missing doses of an antihypertensive that has a lower off-rate, but this has not been evaluated quantitatively. A prospective, randomised, controlled trial to evaluate the clinical consequences of multiple missed doses in terms of cardiovascular events is not feasible because of the ethical questions this would raise. We therefore developed a method to quantify the chain of factors linking adherence levels with clinical outcomes, which showed that for drugs with medium-to-high off-rates (~5–15 mmHg/day), the levels of occasional non-adherence observed in practice had a clinically relevant impact on predicted BP reductions and CVD risk (13). The present study applies this method to compare the relative effect of imperfect adherence to the DRI aliskiren, the ARB irbesartan and the ACE inhibitor ramipril, based on BP characteristics taken from a randomised, controlled clinical trial [Palatini et al. (12,14)].

The Palatini study (12,14) was used to derive inputs for the mean BP-lowering effect of aliskiren, irbesartan and ramipril, and the off-rate for each drug. In the study, patients received continuous, double-blind aliskiren, irbesartan or ramipril for at least 6 weeks, and then received a simulated single missed dose (single-blind placebo instead of active treatment). The off-rate was determined as the difference between the ambulatory SBP reduction after an active dose and after the simulated missed dose. The mean office SBP-lowering effect was the mean sitting

Table 3 Sensitivity analyses using an on-rate* of 10 mmHg/day

Parameter	% adherence	Aliskiren 300 mg	Irbesartan 300 mg	Ramipril 10 mg
Average SBP reduction, mmHg	90	13.7	9.4	12.3
	75	13.3	8.4	11.3
	60	12.8	7.5	10.3
Reduction in absolute CVD risk, %	90	4.1	2.8	3.7
	75	3.9	2.5	3.4
	60	3.8	2.2	3.1
Events per 1000 patients treated	90	229.2	242.2	233.3
	75	230.5	245.0	236.4
	60	232.1	247.8	239.5
NNT to avoid one CVD event	90	24.5	35.9	27.2
	75	25.3	39.9	29.7
	60	26.3	45.0	32.8

*Rate of onset of antihypertensive effect when treatment is initiated. CVD, cardiovascular disease; NNT, number needed to treat; SBP, systolic blood pressure.

SBP at week 9. By applying these drug characteristics to our model, we found that imperfect adherence typical of that seen in clinical practice was predicted to have less effect on SBP reduction with the DRI aliskiren (300 mg; off-rate, 1.0 mmHg/day) than with the ARB irbesartan (300 mg; off-rate, 3.6 mmHg/day) or the ACE inhibitor ramipril (10 mg; off-rate, 4.0 mmHg/day). Consequently, the effects on CVD risk reduction of imperfect adherence with aliskiren were predicted to be less than for imperfect adherence with irbesartan or ramipril. Reducing adherence to irbesartan or ramipril from 90% [typical of randomised controlled trials (4)] to 60% (poor adherence) led to approximately double the average SBP increases predicted with the same reduction in adherence to aliskiren.

Many studies have shown that non-adherence and non-persistence with antihypertensive therapy may have both clinical and economic implications. For example, a retrospective cohort study found that the risk of hospitalisation in 7981 patients with hypertension was significantly higher when the medication possession ratio (MPR) was <60% than when the MPR was ≥80% (risk of hospitalisation, 24% vs. 19%) (16). Another retrospective cohort study of patients with hypertension in the Régie de l'Assurance Maladie du Québec and Med-Echo databases showed that amongst hospitalised patients with hypertension over a 3-year period, an MPR <80% was associated with additional costs of approximately $3574 per patient compared with an MPR ≥80% (17). However, these studies probably overestimate the true impact of non-adherence and non-persistence, because they cannot distinguish between true causal effects and healthy user bias (i.e. the tendency for people exhibiting one specific healthy behaviour to be healthier in other ways and thus less prone to adverse outcomes for reasons that are not linked causally to the behaviour of interest). Moreover, studies based on MPR alone cannot distinguish between non-adherence and non-persistence (permanent discontinuation of treatment). It is important to note that our method excluded effects of non-persistence, because clinical outcomes were predicted based on the characteristics of patients from the study of Vrijens et al. (4), who were fully persistent with treatment, but who missed occasional doses. Non-persistence with antihypertensives is certainly a major problem; approximately 50% of patients discontinue treatment permanently during the first year of treatment (4,18,19). However, the various strategies that have been employed to improve persistence have generally met with limited success (20). The importance of our study is that it estimates the potential value of utilising treatment strategies that reduce the impact of occasional non-adherence on BP reduction and CVD risk.

The limitations of our method are described in detail elsewhere (13), but the following key limitations should be noted. First, a search of the literature failed to identify any additional studies beyond the Palatini study with the data required to enable modelling of off- and on-rates with aliskiren, irbesartan or ramipril. In the absence of data in the literature regarding on-rates for antihypertensives, an optimistic on-rate of 5 mmHg/day was assumed for all three drugs in the present analysis, to give cautious estimates of the effects of changes in adherence level. A sensitivity analysis showed that changing the on-rate from 5 to 10 mmHg/day did not alter the

key findings. Second, the method assumes that the antihypertensive off- and on-rates are linear and constant over time. Although the use of non-linearly changing rates is more likely to reflect what would happen for most antihypertensive drugs, off-rate data beyond the first day after a missed dose were unavailable from the Palatini study modelled in the present analysis. Importantly, our assumption of linear off- and on-rates provides a reasonable approximation over 1–2 days of missed doses, which is the duration of the majority of drug holidays (4). There were also no data available regarding changes in off-rate during long-term treatment, hence the treatment data from the 9-week Palatini study were by necessity applied throughout. This is a limitation because it does not take into account the effects upon off- and on-rates of homeostatic adaptations to long-term antihypertensive treatment. Finally, our method assumed that adherence levels were independent of drug class. This assumption is an oversimplification as, for example, adherence to ARB is higher than adherence to ACE inhibitors (21–23), which probably reflects the superior tolerability of the ARB (24–27). The tolerability of aliskiren in short-term clinical trials has been shown to be similar to that of ARB (28–31), but no studies have been published on long-term adherence and persistence with aliskiren in clinical practice.

In conclusion, in this analysis, to quantify the impact of non-adherence and different off-rates on clinical outcomes, reductions in SBP and CVD risk with aliskiren 300 mg were predicted to be less affected by imperfect adherence than the reductions with irbesartan 300 mg or ramipril 10 mg. To offset the potential effects on clinical outcomes of imperfect adherence, a common challenge in patients treated with antihypertensives, it may be wise to prescribe 'forgiving' drugs, i.e. drugs that have low off-rates.

Acknowledgement

The study was supported by Novartis Pharma AG, Basel, Switzerland. The authors take full responsibility for the content of the paper and thank Drs Richard White and Jenny Handford (Oxford PharmaGenesis™ Ltd., Oxford, UK) for medical writing support, editorial assistance and collation and incorporation of comments from all authors; this work was funded by Novartis Pharma AG, Basel, Switzerland.

Author contributions

AL is the guarantor, he designed the method used in the manuscript and he was the lead author of the writing committee. MB and YB contributed to the interpretation of the analysis and were members of the writing committee. All authors had full access to all the data and can take responsibility for the integrity of the data and the accuracy of the data analysis, and approved the final version of the manuscript for publication.

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Paper received October 2010, accepted December 2010