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ORIGINAL RESEARCH ARTICLE

In Silico Comparison Between Metoprolol Succinate and Bisoprolol on 24-Hour Systolic Blood Pressures

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Abstract

Objective To compare the effects of bisoprolol and metoprolol CR/ZOK (metoprolol succinate controlled release) on systolic blood pressure (bp_{sys}) over a 24-h period in an in silico model.

Methods On the basis of the observed data from ambulatory blood pressure measurements (ABPM), a model with an appropriate distribution and correlation structure was derived for simulation of 24-h bp_{sys} patterns during treatment with commonly studied doses, assumed to be equipotent, of bisoprolol and metoprolol CR/ZOK. Input into the simulations was aligned with the available data on the diurnal efficacy and pharmacology profiles of these substances. The validity of the model was tested in a bootstrap model.

Results The simulation model reproduced the observed data with high congruence ($p = 1.0$). The mean 24-h bp_{sys} values did not significantly differ between the two simulated groups (estimated overall change in bp_{sys} [Δbp_{sys}] for metoprolol versus bisoprolol = 2.7 mmHg [95 % confidence interval −0.3 to 5.7 mmHg]; $p = 0.08$). There were clear diurnal differences, with bisoprolol being more effective earlier and metoprolol CR/ZOK being more effective later in the 24-h day. A validity test with 100 repeated samples gave an overall mean group difference of 1.4 ± 3.59 mmHg ($p = 0.63$ relative to simulation).

Conclusion In a robust model for the simulation of 24-h ABPM, comparisons between bisoprolol and metoprolol CR/ZOK indicate a comparable overall blood pressure-lowering effect but different diurnal patterns, consistent with the pharmacokinetics of the two drugs. This difference may be of clinical relevance, given the recognized diurnal pattern of cardiovascular events.

Key Points

To provide maximal efficacy in preventing cardiovascular events, β-blockers should be present at sufficient strength over the entire 24-h day.

This modeling study showed that bisoprolol and metoprolol succinate provide comparable overall blood pressure-lowering activity.

However, there are differences between the two drugs in the diurnal pattern of their antihypertensive effects, with metoprolol succinate providing greater efficacy toward the end of the 24-h day.

1 Introduction

Cardiovascular (CV) events, such as acute coronary syndromes, stroke, and sudden cardiac death, show time-varying incidence ranging over the 24-h day and according to the season of the year. The reasons for this variation are not fully understood, but it is known that the adrenergic neurohormonal system is one important factor [1, 2]. Consequently, it is believed that the prophylactic effect

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exerted by β-blocking drugs on the incidence of CV events can be explained by these drugs' anti-adrenergic effects [3, 4]. It also follows that to be maximally effective, the β-receptor blocking effect should be present at sufficient strength over the entire 24-h day.

In recognition of the advantages of improved compliance and the need for day-long efficacy, major β-blocker drugs have been developed for once-daily intake. Modification to prolong the elimination of a drug is one approach to make once-daily administration feasible. Another means toward this is to extend the time of absorption. Bisoprolol fumarate attains once-daily dosing because of slow receptor dissociation, while metoprolol CR/ZOK (metoprolol succinate) exemplifies the controlled-release path for once-daily dosing [5, 6].

Metoprolol CR/ZOK and bisoprolol are both (with various national limitations) approved for control of hypertension, ischaemic heart disease, heart failure, and reduction of the risk of CV events associated with these conditions [7, 8]. However, because of their differing pharmacokinetic profiles, there may be diurnal differences in cardioprotective effects between the two drugs. To further explore this possibility, an in silico model of 24-h blood pressures was developed, making use of published data.

2 Methodology

2.1 Data Extraction

Data on the pharmacokinetic and blood pressure effects of bisoprolol were obtained as summary data from the published literature [6, 9–18]. Corresponding published information on metoprolol CR/ZOK was available on the individual subject level [5, 19]. Ambulatory blood pressure measurement (ABPM) values for untreated hypertensive patients were also obtained on the individual level.

The Ovid Medline and Embase databases were queried for publications in the English language with abstracts on metoprolol and bisoprolol, using both substance names and product labels. Papers with abstracts informing on blood pressure, ABPM, or pharmacokinetics were further studied, and those providing 24-h data in numerical formats were used. No publication with results based on admitted patients was included.

All data from clinical trials were obtained from studies that had obtained ethics approval.

2.2 Simulation

In an initial step, hourly systolic blood pressure (bp_{sys}) values for 266 untreated hypertensive subjects (aged 55 ± 9.4 years; 103 of whom were female) were derived as the means of three measurements per hour for a 24-h day (from 1000 hours to 1000 hours).

As a second step, corresponding mean hourly bp_{sys} values were calculated and adjusted to the plasma concentration curves for bisoprolol (as published) and metoprolol CR/ZOK, on the basis of a steady-state situation, with dosing being simultaneous with the start of the blood pressure recording.

Thirdly, two sets of random data for bisoprolol and metoprolol CR/ZOK, respectively, were generated, representing hourly bp_{sys} values in 266 subjects, and aligned to the calculated mean hourly values. This operation was based on bp_{sys} values following a normal distribution (truncated to >75 to <210 mmHg), constant variance over the 24 time points, and expected individual bp_{sys} value as the means of the preceding individual value and the group average values for the current time point.

2.2.1 *Simulation Model*

A linear mixed model of repeated measurements with an autoregressive correlation structure with moving averages was used to obtain predicted values and covariance from the ABPM data on the 266 untreated patients. These values were then used to simulate individual data from a bivariate normal distribution. Using the same regression model and covariance, simulated individual 24-h ABPM bp_{sys} values were built from the data created for the bisoprolol and metoprolol CR/ZOK data sets, respectively. Published information on variance of bp_{sys} is generally based on office or summary recordings, and is smaller than the observations of individual time points in ABPM [13]. For this reason, and on the basis of the available ABPM source data, the standard deviation (SD) of the simulated values was expanded by ≈4 mmHg.

2.3 Statistics

Summary results are presented as means ± SDs. Estimates are given with 95 % confidence intervals, and a *p*-value of <0.05 is taken as statistically significant. A linear mixed model was employed to test differences between groups in bp_{sys} by time point. All statistical operations were done with R 2.15.1 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

3 Results

Demographic data and baseline average 24-h bp_{sys} values were congruent between the observed and published data. The distribution of individual observed hourly bp_{sys} values appeared to be random (Fig. 1a).

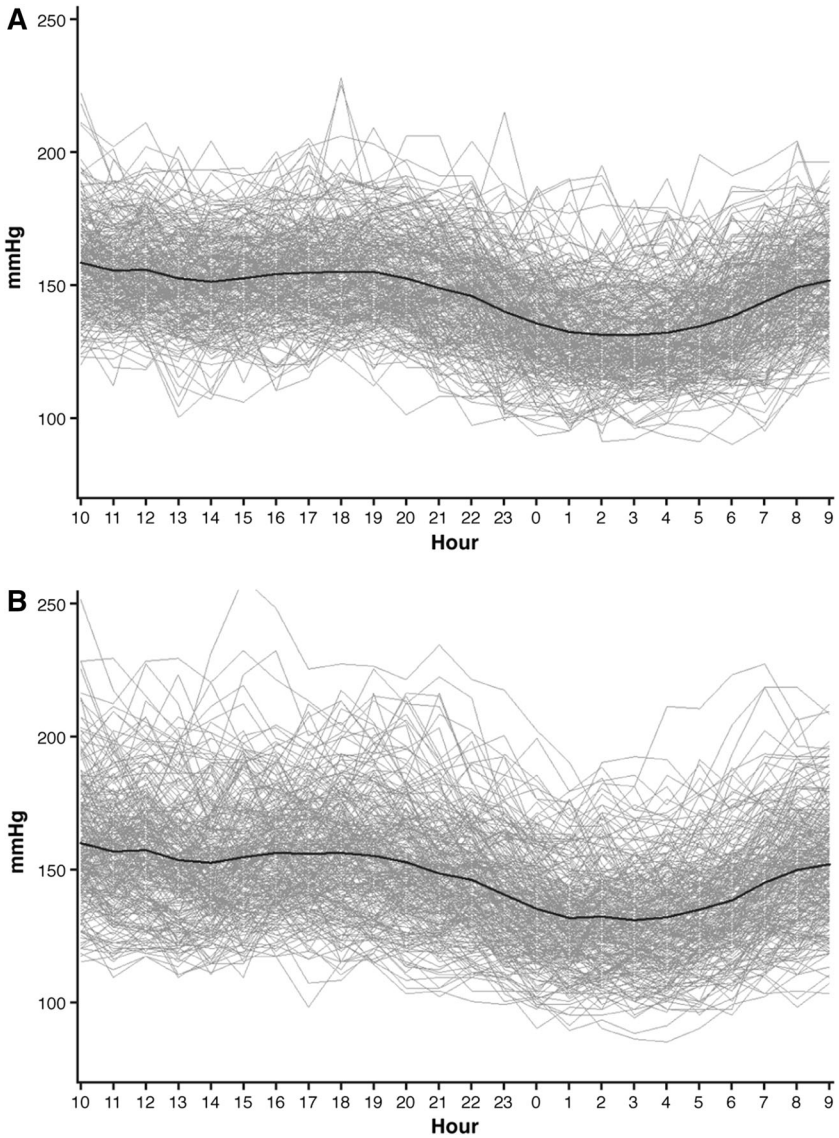

Fig. 1 Mean and individual observed and simulated baseline systolic blood pressure (bp_{sys}) values. **a** Observed untreated bp_{sys} by subject and time of day (hours). **b** Simulation of untreated bp_{sys} by subject and time of day (hours)

Validity testing of the model through repeated sampling showed consistency over 100 random samples of 64 crossed cases, with normally distributed p values for the overall difference ($p = 0.6$) in the drug group effect, as well as for the drug group by time point variable.

Distribution of hourly observed and simulated blood pressures are presented in Table 1. The mean $bp_{sys} \pm$ SD values for the observed data were 146.2 ± 19.37 mmHg, with an intra-individual SD of ±14.57. The mean ± inter- and intra-individual SDs for the simulated baseline bp_{sys} values were 146.6 ± 22.86 and ± 15.03 mmHg, respectively.

Figures 1 and 2 give a graphical display of the mean and individual bp_{sys} values for the observed baseline, simulated baseline, and simulation of the two drug groups. The broader distribution seen for bp_{sys} obtained in the simulation is also seen in the wider SDs.

Estimates of the change in bp_{sys} (Δbp_{sys}) for bisoprolol, and for metoprolol CR/ZOK versus bisoprolol, are presented in Table 2 and Fig. 2. The mean 24-h bp_{sys} values were 128 ± 18.7 and 128 ± 18.0 mmHg ($p > 0.1$) for the simulated bisoprolol and metoprolol data, respectively. The estimated overall difference between the two groups, when controlled for the time effect, was 2.7 mmHg (95 % confidence interval −0.3 to 5.7 mmHg).

The data for bisoprolol display a bimodal pattern, and those for metoprolol CR/ZOK display a unimodal one (Fig. 2). Plasma concentration curves for the two drugs are presented in Fig. 3. Temporal differences in blood pressure-lowering effects are seen, with bisoprolol being more effective around its maximum plasma concentration, and metoprolol CR/ZOK being more effective during the latter two thirds of the 24-h day (Fig. 4, lower part, showing metoprolol Δbp_{sys} relative to bisoprolol Δbp_{sys}).

Table 1 Observed and simulated systolic blood pressure (bp_{sys}) values, expressed as means ± standard deviations

Time of day (hours)	Observed (mmHg)	Simulation (mmHg)		
	Baseline	Baseline	Bisoprolol	Metoprolol
10	158.2 ± 16.97	159.6 ± 22.32	133.4 ± 19.11	136.1 ± 18.04
11	155.2 ± 15.80	156.4 ± 21.72	129.3 ± 18.33	134.0 ± 19.24
12	155.6 ± 16.27	157.0 ± 21.93	128.7 ± 17.67	135.3 ± 18.27
13	152.3 ± 16.96	153.2 ± 22.07	127.2 ± 17.78	131.1 ± 16.87
14	151.1 ± 16.24	152.2 ± 21.82	124.5 ± 16.09	131.0 ± 17.90
15	152.3 ± 16.15	154.3 ± 22.53	128.8 ± 18.44	130.2 ± 16.64
16	154.0 ± 16.60	155.9 ± 20.54	128.5 ± 18.2	128.4 ± 17.33
17	154.5 ± 17.10	155.6 ± 20.78	129.0 ± 19.08	130.6 ± 18.12
18	154.9 ± 17.46	155.8 ± 21.81	131.0 ± 19.78	126.6 ± 18.23
19	154.8 ± 16.76	154.9 ± 22.25	129.9 ± 18.00	127.3 ± 17.44
20	152.4 ± 16.98	152.3 ± 22.34	128.6 ± 18.61	128.1 ± 15.61
21	148.8 ± 17.79	148.1 ± 21.73	126.4 ± 18.57	126.5 ± 16.10
22	145.9 ± 18.14	145.7 ± 20.16	124.7 ± 17.50	125.0 ± 16.61
23	139.8 ± 18.20	140.1 ± 19.93	124.0 ± 17.82	123.7 ± 16.79
00	135.4 ± 17.62	134.8 ± 19.19	123.9 ± 17.02	120.5 ± 17.01
01	132.1 ± 17.41	131.3 ± 18.35	126.3 ± 19.52	121.4 ± 17.23
02	131.2 ± 17.05	131.8 ± 19.23	126.4 ± 20.20	119.0 ± 15.77
03	131.0 ± 16.99	130.5 ± 18.45	125.4 ± 18.76	120.3 ± 16.88
04	132.0 ± 17.24	131.6 ± 19.39	122.8 ± 17.53	120.3 ± 16.77
05	134.3 ± 16.72	134.5 ± 19.34	126.4 ± 18.51	125.3 ± 16.89
06	138.0 ± 17.91	138.1 ± 19.87	127.1 ± 18.78	126.9 ± 16.26
07	143.6 ± 18.13	144.7 ± 20.76	130.4 ± 18.26	129.5 ± 17.06
08	149.0 ± 17.57	149.5 ± 20.70	135.3 ± 18.18	133.8 ± 16.27
09	151.7 ± 16.22	151.6 ± 19.97	140.7 ± 17.88	139.8 ± 17.80
24-h mean	146.2 ± 19.37	146.6 ± 22.86	128.3 ± 18.72	127.9 ± 17.95

The overall group effect and effects by time point were all within the range of the estimates of the 100 repeat samples.

4 Discussion

In a robust model for simulation of 24-h ABPM, diurnal differences in reduction of bp_{sys} were demonstrated in the comparison of bisoprolol and metoprolol CR/ZOK, though the average blood pressure reductions were the same for the two groups. The demonstrated temporal discrepancies indicate the potential for differences in the impact on the prevention of CV events and the risk of adverse effects between the two treatments.

The exact mechanism by which β-blockers reduce blood pressure is not known. It is, however, obvious that it is caused by interference with the adrenergic system and the antagonistic effect these drugs have on the β_1-receptors. Thus, the effects of β-blockers are dependent on the degree of receptor antagonism, which, in turn, ultimately depends on pharmacokinetic properties.

The characteristic pharmacokinetic properties of bisoprolol are rapid absorption and, as consequence of delayed receptor dissociation, protracted elimination [6, 14–18]. These two properties are well reflected in the effects of the drug, with an early peak corresponding to the maximal concentration and immediate uptake, followed by a gradual tapering off until the next dose.

The pharmacokinetics of metoprolol CR/ZOK are dominated by a protracted uptake period extending over >10 h and (in comparison with bisoprolol) rapid elimination, with the net result of a more flat plasma concentration curve and a less varying effect profile [5, 19]. Thus, when compared with bisoprolol, metoprolol CR/ZOK is likely to have a temporally less varying blood pressure-lowering effect over the 24-h day. The average 24-h effect will be the same for the two compounds, with bisoprolol being more effective during the initial hours after drug intake and metoprolol CR/ZOK showing a greater impact during the latter part of the dose interval [20, 21].

The predilection of CV events to occur during late night and early morning periods makes it attractive for a β-blocker drug to have an effect during those hours, and is an

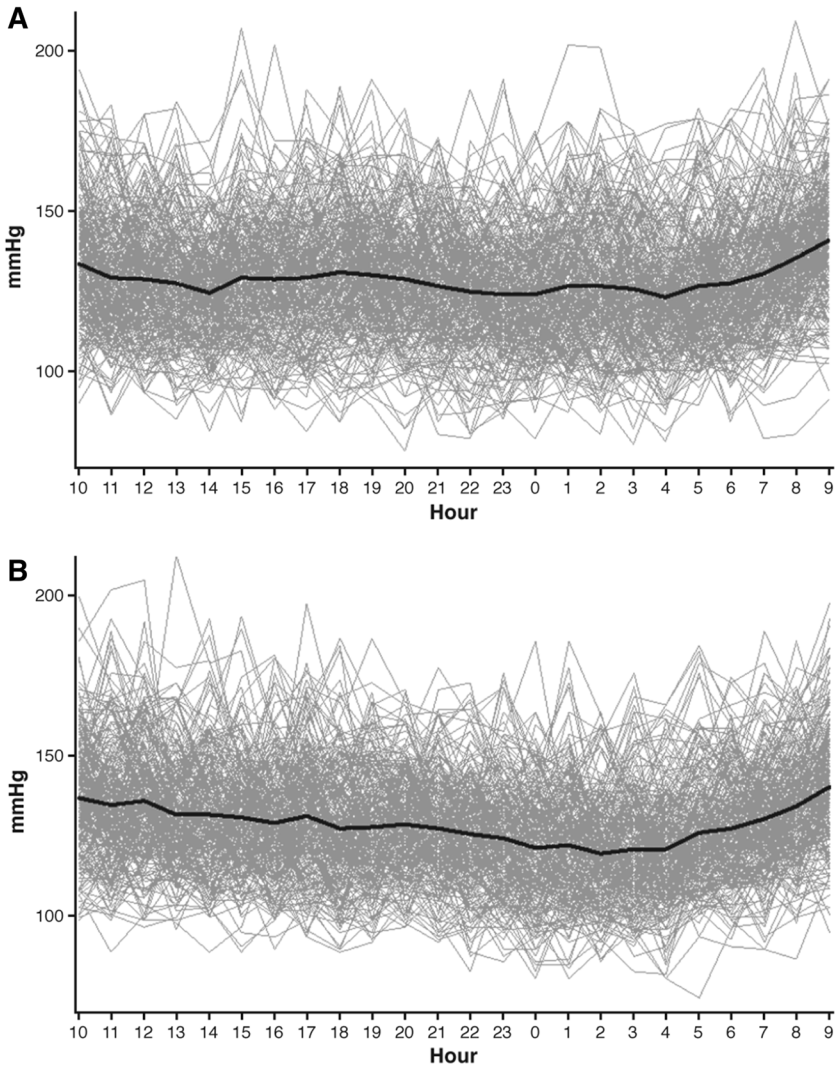

Fig. 2 Simulated systolic blood pressure (bp_{sys}) values for bisoprolol and metoprolol (mean and individual). **a** Simulation of bisoprolol bp_{sys} by subject and time of day (hours). **b** Simulation of metoprolol bp_{sys} by subject and time of day (hours)

important reason why some β-blockers that are efficacious as once-daily treatments for uncomplicated hypertension need to be administered twice daily in patients with ischemic heart disease. With regard to isolated blood pressure lowering, it would appear to be of value for a drug to have a pronounced effect during the early and mid-daytime to counteract the blood pressure-raising effects of daytime activities. Two related factors may, however, increase the risk of adverse reactions: (1) associated β-receptor-dependent adverse reactions, such as bradycardia, can contribute to symptoms such as dizziness, fatigue, and syncope; and (2) to achieve a 24-h effect with once-daily dosing, higher doses are required, with the potential for excess effects in the hours following administration. The possibility of bisoprolol being associated with these negative effects might be suggested by results from the CIBIS-ELD trial, where dose escalation is reported to have been hampered by bradycardia [22, 23].

Various measures based on ABPM, such as the trough-to-peak ratio and smoothness index, have been suggested as a means to assess sufficient blood pressure-lowering effects over the full 24-h dose interval. These single-item variables appear to have lost much of their attractiveness because of the undesirable properties inherent in ABPM [24]. Some of these can be appreciated through the present simulation. Despite a crossover model and a fairly large study emulation, some time point recordings fall outside the expected range, which, in a real study, can—depending on when the random outlier occurs—have important effects on the interpretation of the results.

It has been suggested that smoothing by combination of measurements over several hours should be employed to mitigate these kinds of outliers [2, 4]. That approach, however, has the significant drawback of reducing the information on the temporal effects of the drug under investigation. Alternatively, the number of pressure recordings per hour can be increased to allow for smoothed hourly values. This modality runs the risk of disturbing the diurnal blood pressure pattern of patients, particularly during the night, as the repeated cuff

Table 2 Estimates of changes in systolic blood pressure (Δbp_{sys}) values

Bisoprolol versus baseline				Metoprolol versus bisoprolol			
Time of day (hours)	Δbp_{sys}	95 % confidence limit		Time of day (hours)	Δbp_{sys}	95 % confidence limit	
		Lower	Upper			Lower	Upper
11	−4.1	−6.1	−2.1	11	2.1	−0.7	4.8
12	−4.7	−7.2	−2.2	12	4.0	0.5	7.5
13	−6.1	−8.8	−3.4	13	1.2	−2.6	5.0
14	−8.9	−11.7	−6.0	14	3.8	−0.2	7.9
15	−4.5	−7.4	−1.6	15	−1.3	−5.4	2.8
16	−4.9	−7.9	−1.9	16	−2.7	−6.9	1.4
17	−4.4	−7.4	−1.4	17	−1.1	−5.3	3.1
18	−2.4	−5.4	0.6	18	−7.1	−11.3	−2.9
19	−3.5	−6.5	−0.4	19	−5.3	−9.6	−1.1
20	−4.8	−7.8	−1.8	20	−3.2	−7.4	1.1
21	−7.0	−10.0	−4.0	21	−2.5	−6.8	1.8
22	−8.7	−11.7	−5.6	22	−2.4	−6.7	1.9
23	−9.3	−12.4	−6.3	23	−3.0	−7.2	1.3
00	−9.4	−12.4	−6.4	00	−6.1	−10.4	−1.9
01	−7.1	−10.1	−4.0	01	−7.6	−11.9	−3.3
02	−6.9	−10.0	−3.9	02	−10.1	−14.4	−5.8
03	−7.9	−11.0	−4.9	03	−7.8	−12.1	−3.5
04	−10.6	−13.6	−7.6	04	−5.2	−9.5	−0.9
05	−7.0	−10.0	−4.0	05	−3.7	−8.0	0.5
06	−6.3	−9.3	−3.2	06	−2.9	−7.2	1.3
07	−2.9	−5.9	0.1	07	−3.6	−7.9	0.7
08	1.9	−1.1	4.9	08	−4.2	−8.4	0.1
09	7.3	4.3	10.4	09	−3.6	−7.9	0.7
Baseline	133.4	131.2	135.5				

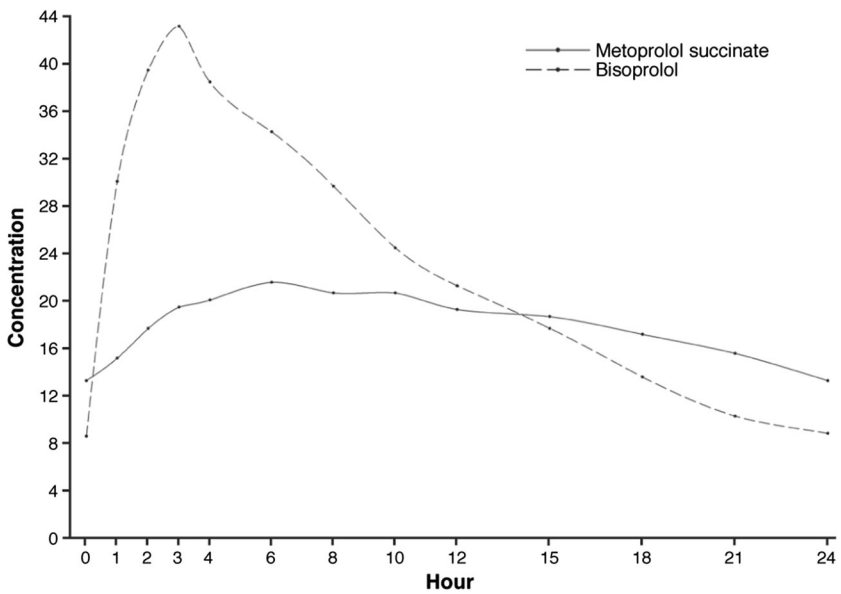

Fig. 3 Plasma concentrations at steady state over the 24-h dose interval: bisoprolol and metoprolol succinate

inflations may interfere with rest and sleep. The likely outcome is elevated pressures due to discomfort from the inflations.

A second consequence of the variance of ABPM recordings is shown by the bootstrapping model. Both the overall between-groups effect, as well as the time point

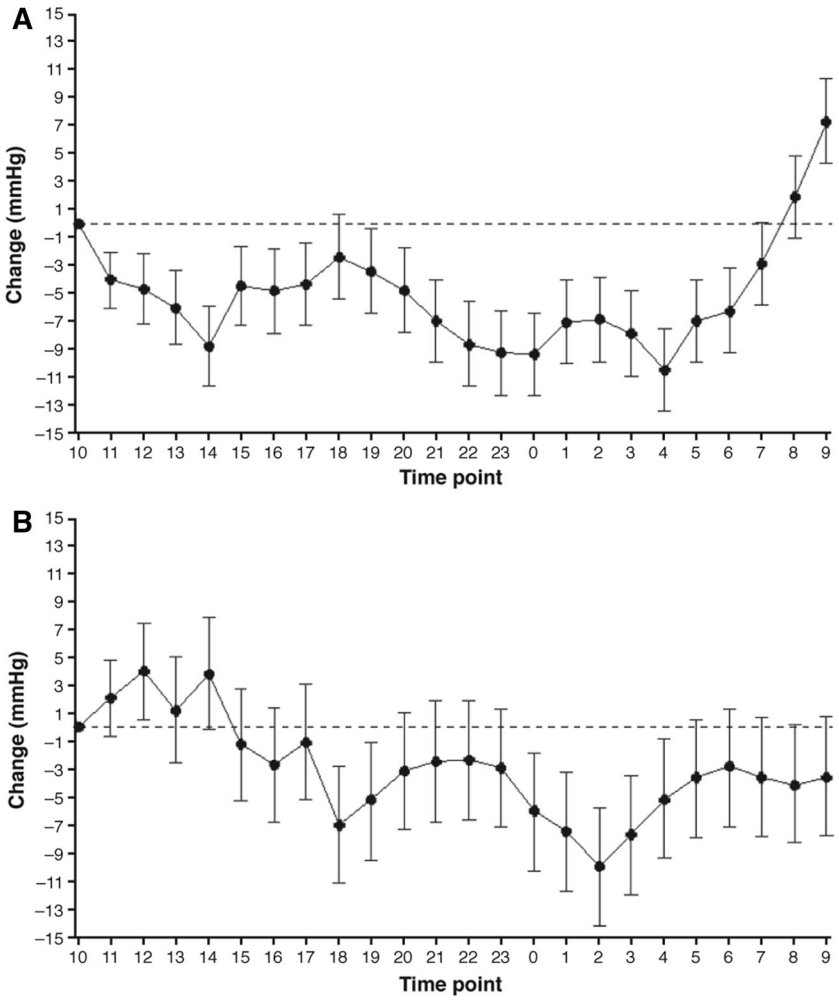

Fig. 4 Estimates (±95 % confidence intervals) of changes in systolic blood pressure (Δbp_{sys}) values. **a** Bisoprolol. **b** Metoprolol versus bisoprolol

estimates, vary over wide ranges, indicating the need for large sample sizes if robust comparisons between active substances are to be obtained.

An important contributor to the potential issues with ABPM can be seen from simulations of individual subjects' blood pressures. Some values are clinically unlikely but are not physiologic impossibilities. These outlier results will, in most instances, have to be included in the analyses, despite being unreasonable and heavily contributing to the error margins.

Apart from not being a prospective clinical trial, this simulation has some shortcomings that need to be taken into consideration. No raw data were available for bisoprolol, and no major ABPM study has been conducted with metoprolol CR/ZOK. This necessitated the use of summary data for simulation, which is the common situation in many simulations. However, blood pressure has a well described distribution, and the use of individual raw data as seeds in the data generation is believed to have provided sufficient background for the generation of sufficiently representative data values. The reported variances generally reflected office blood pressure recordings or smoothed values from ABPM. As these variance values were smaller than those observed in ABPM of untreated patients, the variances were expanded by normally distributed random values to better emulate the distribution of observed ABPM. Finally, the validation bootstrap used subsamples and not full sets. This was done to make the computational process more manageable and is not believed to have had a significant impact on the reliability of the validation.

5 Conclusion

In this simulation study of the effects of bisoprolol and metoprolol CR/ZOK on 24-h bp_{sys}, the mean effects were the same, while the diurnal patterns differed between the two treatments. This difference may be of clinical relevance, given the recognized diurnal pattern of CV events.

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