Clinical implications of pleomorphic ventricular tachycardias on oral sotalol therapy

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In 90 consecutive patients with coronary artery disease and sustained monomorphic ventricular tachycardia, who were treated with oral sotalol and underwent programmed stimulation to determine drug effectiveness, the influence of sotalol on induced ventricular tachycardia morphology was retrospectively examined. In 54 patients (60%) sotalol rendered the tachycardia non-inducible. However, contrary to drug-testing with class I antiarrhythmic agents, induction of multiple morphologies at baseline study did not predict failure of subsequent drug-testing with sotalol. In the remaining 36 patients (40%), in whom sotalol did not modify inducibility, 21 patients (i.e. a total of 23%) manifested at least one new morphology during electropharmacological testing on sotalol. This effect was independent of the degree of left ventricular dysfunction, infarct location and numbers of morphologies at baseline, but corresponded with drug-induced changes in refractoriness. This observation may be related to a proarrhythmic effect of sotalol. Slowing of ventricular tachycardia rate and changes in morphology may have implications in patients receiving implantable cardioverter-defibrillators or those undergoing ablative procedures.

Introduction

Patients with coronary artery disease and ventricular tachycardia often have morphologically distinct (pleomorphic) types of tachycardia[1,2]. However, data on the manifestation of new morphologies of ventricular tachycardia during electropharmacological testing in these patients are limited[3]. Class I agents have been reported to produce different morphologies[2], but the effect of the class II-III agent sotalol is unknown. Therefore, first we retrospectively investigated the relationship between pleomorphism and successful drug testing, as well as the effect of sotalol, on the morphology of inducible ventricular tachycardia in patients with coronary artery disease. Secondly, we investigated the possible determinants of pleomorphism, such as left ventricular dysfunction, type of infarct location, tachycardia cycle length and ventricular refractoriness.

Methods

PATIENT POPULATION

Ninety consecutive patients with coronary artery disease referred for evaluation of symptomatic sustained monomorphic ventricular tachycardia, unrelated to acute myocardial infarction, underwent drug testing with oral sotalol. Patients with disease of the left main coronary artery, or severe three-vessel disease, and those with a history of ischaemia-induced ventricular tachycardia, were excluded. There were 80 men and 10 women, with a mean (± SD) age of 60.5 ± 8.6 years (range 34 to 75 years) and 69.4 ± 8.1 years (range 55 to 81 years), respectively. Eighty-seven patients had a history of remote myocardial infarction (localized anteriorly in 35, inferiorly in 30, anteriorly an inferiorly in 14, and undetermined in eight patients), presenting at 2 months to 27 years (mean 7.5 ± 6.8 years, median 5.0 years) following the acute myocardial infarction. Mean left ventricular ejection fraction (± SD) measured by contrast ventriculography was 44 ± 16% (range 12 to 76%).

ELECTROPHYSIOLOGICAL STUDY

After written informed consent was obtained, all patients underwent a complete electrophysiological study at baseline (approved by the Hospital of the University of Münster Ethics Committee). All antiarrhythmic drugs were discontinued at least five half-lives before the test, and no patient received a beta-receptor blocker or verapamil, but nifedipine was allowed.

One quadripolar and two bipolar electrode catheters were inserted percutaneously under local anaesthesia via a femoral vein and were positioned in the right atrium, at the His bundle position and in the right ventricle, respectively. The surface electrocardiographic leads I, II, V_s and V_o, and the intracardiac electrograms (filtered at 40–500 Hz) were recorded simultaneously on a Picker Schwarzer HKM 6000 recorder (Picker, München, Germany). A programmable stimulator (Biotronik UHS 20, Berlin, Germany) was used to deliver rectangular
pulses 2 ms in duration at twice diastolic threshold (always < 2 mA). Programmed ventricular stimulation was performed at the right ventricular apex and then at the outflow tract as given below.

A strict stepwise stimulation protocol, that has been previously discussed in detail\(^4\), was followed and included up to three premature stimuli. Briefly, this stimulation protocol began with the introduction of single and then double ventricular extrastimuli during sinus rhythm. Subsequently, single and double extrastimuli were introduced after an 8-beat drive train at cycle lengths of 500, 430, 370 and 330 ms, respectively. A third extrastimulus was delivered only at a basic drive cycle length of 500 ms. For each extrastimulus, diastole was scanned in 10 ms decrements to the point of ventricular refractoriness. The end point of stimulation was the reproducible initiation (at least twice) of sustained monomorphic ventricular tachycardia.

**ANALYSIS OF TACHYCARDIA MORPHOLOGY**

All ECGs were recorded at a standard speed of 50 mm s\(^{-1}\) and amplitude (1 mV cm\(^{-1}\)). Two or more monomorphic ventricular tachycardias were considered to have the same morphology if they exhibited the same bundle branch-like pattern in the precordial leads and the mean frontal axis differed by less than 45°. Variations beyond this range were considered to represent a distinct tachycardia morphology. Changes in QRS complex configuration associated with ventricular pacing during an established ventricular tachycardia were excluded from analysis.

**DEFINITIONS**

S1, S2, S3 and S4 are the stimulus artifacts of the last beat of the ventricular drive train and of the first, second and third extrastimulus, respectively.

The ventricular effective refractory period for S2 was the longest S1-S2 interval at which S2 failed to evoke a ventricular response. All measurements of the effective refractory period of the ventricle given in this study refer to the first extrastimulus, S2, at a paced basic cycle length of 500 ms in the right ventricular apex.

Sustained ventricular tachycardia was defined as a ventricular tachycardia lasting longer than 30 s or requiring termination because of haemodynamic collapse. Induced ventricular tachycardia was considered monomorphic if the QRS morphology was constant and the cycle length was greater than 200 ms.

Multiple morphologically distinct tachycardias (pleomorphic ventricular tachycardias) were considered to be present when two or more episodes of sustained monomorphic ventricular tachycardia in the same patient had a different QRS configuration by the criteria outlined previously.

From the baseline electrocardiogram, the sinus cycle length, the QT interval and the corrected QT interval, QTc, (Bazett formula) were measured. These criteria were remeasured from an ECG recorded during sotalol therapy immediately before the repeat electrophysiological study.

**PATIENT MANAGEMENT**

All patients underwent serial electropharmacological testing. After the baseline study, oral drug therapy with sotalol was started. The average dose (± SD) administered was \(472 ± 96\) mg day\(^{-1}\) (range 320 to 640 mg day\(^{-1}\)). After 72 h at the maximally tolerated dose, sufficient to achieve a steady-state drug level, new electrodes were inserted and a repeat study, using the same stimulation protocol as described above, was performed between 2 and 4 h following sotalol administration.

**ASSESSMENT OF DRUG EFFICACY**

The criteria for drug efficacy has already been defined by our laboratory\(^4\). Ventricular tachycardia was considered to be no longer inducible if less than 10 repetitive responses were observed during introduction of up to three extrastimuli at any of the basic drive cycles. These patients constituted the responders group. Those who did not fulfil these criteria were designated as non-responders.

**STATISTICAL ANALYSIS**

Continuous data are presented as ± standard deviation (SD). The two-sided t-test (paired or unpaired as appropriate) was used to test for inter-group differences of continuous variables if normal distribution of data was demonstrable (Kolmogorov-Smirnov goodness-of-fit test). Comparisons between proportions were performed using chi-square analysis. A \(P\) value \(\leq 0.05\) was considered significant; 95% confidence intervals for the difference in means are given if appropriate.

**RESULTS**

**INDUCIBILITY OF VENTRICULAR TACHYCARDIA DURING DRUG-FREE STATE**

Sustained monomorphic ventricular tachycardia was inducible in all 90 patients in the absence of antiarrhythmic drug therapy. Sustained ventricular tachycardia was induced during sinus rhythm in eight patients (by S2 in one and by S2S3 in seven). In another 52 patients, induction was achieved at a paced basic cycle length of 500 ms (by S2 in nine, by S2S3 in 34 and by S2S3S4 in nine). In 12 patients, ventricular tachycardia was induced at a paced basic cycle length of 430 ms (by S2 in one and by S2S3 in 11), in 15 patients, it was induced at a drive cycle length of 370 ms (by S2 in one and by S2S3 in 14), and in the remaining three patients, it was induced at a drive cycle length of 330 ms (by S2S3 in all). Ventricular tachycardia was inducible at the right ventricular apex in all but three patients, who were only inducible from the right ventricular outflow tract.
Sixty-five patients (72%) showed only one morphology of ventricular tachycardia during the baseline study, whereas 25 patients (28%) developed two or more (two morphologies in 21 patients and three morphologies in four patients). The mean cycle length of all 119 induced ventricular tachycardias during baseline study was 287 ± 72 ms (range 200 to 560).

The mean ventricular effective refractory period at baseline was 232 ± 21 ms (range 200 to 310).

### CHANGES IN INDUCIBILITY, MORPHOLOGY AND CYCLE LENGTH DURING DRUG TESTING ON SOTALOL

In S4 of the 90 patients (60%), ventricular tachycardia was no longer inducible (responders), and this control by sotalol was independent of the number of morphologies found during baseline study (chi-square test, \( P=\text{ns} \)) (Table 1).

In the remaining 36 patients (40%), in whom sotalol did not suppress induction of ventricular tachycardia (non-responders), sustained ventricular tachycardia was induced during sinus rhythm in two patients (by S2S3). In another 18 patients, induction was achieved at a paced basic cycle length of 500 ms (by S2 in one, by S2S3 in 10 and by S2S3S4 in seven). In 10 patients, ventricular tachycardia was induced at a basic cycle length of 430 ms (by S2 in one and by S2S3 in nine), in four patients at 370 ms (by S2 in one and by S2S3 in three), and in the remaining two patients, at a drive cycle length of 330 ms (by S2S3). Ventricular tachycardia was inducible at the right ventricular apex in all but four patients, who were only inducible at the right ventricular outflow tract. Twenty-two patients exhibited only one morphology, 13 patients showed two and one patient showed three morphologies on drug. The mean cycle length of all 51 induced ventricular tachycardias was 346 ± 83 ms (range 220 to 470) which was significantly longer than the mean cycle length at baseline study (302 ± 74 ms) (t-test, \( P<0.001 \)). There was no significant difference in mean cycle between non-responders with ventricular tachycardias of altered morphology on drug and those with morphologies already known from the drug-free study (346 ± 86 ms vs 346 ± 79 ms) (Table 2).

In the drug-free state, 26 of the non-responders showed only one induced morphology of ventricular tachycardia with a mean cycle length of 301 ± 85 ms (range 200 to 540). Ten patients showed two or more distinct morphologies, with a mean cycle length at baseline study of 303 ± 64 ms (range 230 to 430) (\( P=\text{ns} \)). The number of morphologies at baseline did not predict the number of different morphologies during drug testing (chi-square test, \( P=\text{ns} \)) (Table 3). Twenty-one patients (i.e. a total of 23%) manifested at least one new morphology of ventricular tachycardia during electrophysiological testing on sotalol, as defined before (16 patients had exclusively a different morphology on drug, five patients had both a new morphology and morphologies identical to baseline) (Fig. 1).

In this study, induction of ventricular tachycardia on sotalol was found to be significantly easier in the group of non-responders with morphologies different from baseline, in comparison to non-responding patients with morphologies identical to baseline. In the former group, seven of 21 patients were inducible at an earlier step of the stimulation protocol during sotalol therapy than during baseline study, whereas in the latter group this was true only for one of 15 patients (chi-square test, \( P\leq0.05 \)).

### RESULTS OF PROGRAMMED STIMULATION IN RELATION TO LEFT VENTRICULAR FUNCTION

There was no correlation between left ventricular ejection fraction and the number of morphologies of ventricular tachycardia during baseline (mean left ventricular ejection fraction in patients with only one morphology was 44 ± 18% vs 43 ± 14% in patients with two or more morphologies; t-test, \( P=\text{ns} \), 95% confidence interval −9 to +10%) or during sotalol therapy (46 ± 15% vs 41 ± 18%, \( P=\text{ns} \), 95% confidence interval −6 to +15%). Mean left ventricular ejection fraction in responders was 45 ± 14%. In non-responders, mean left ventricular ejection fraction was 43 ± 19% in patients with only one induced morphology at baseline and 40 ± 18% in patients with two or more distinct morphologies at baseline study (\( P=\text{ns} \)).

There was a moderate but non-significant difference between patients who developed at least one new morphology of ventricular tachycardia on sotalol (mean left ventricular ejection fraction 39 ± 17%) and those who did not (mean 47 ± 20%) (\( P=\text{ns} \), 95% confidence interval −9 to +27%).

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**Table 1** Relationship between number of morphologies of ventricular tachycardia during baseline study and number of responding patients on drug (percentage in parenthesis) (chi-square test, \( P=\text{ns} \))

<table>
<thead>
<tr>
<th>Baseline study</th>
<th>1 morphology</th>
<th>≥2 morphologies</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (60%)</td>
<td>39 (43.3%)</td>
<td>15 (16.7%)</td>
<td>54</td>
</tr>
<tr>
<td>Non-responders (40%)</td>
<td>26 (28.9%)</td>
<td>10 (11.1%)</td>
<td>36</td>
</tr>
<tr>
<td>Total (100%)</td>
<td>65 (72.2%)</td>
<td>25 (27.8%)</td>
<td>90</td>
</tr>
</tbody>
</table>
Table 2 Comparison of left ventricular ejection fraction and electrophysiological variables in the two different groups of non-responders during sotalol therapy

<table>
<thead>
<tr>
<th>VT-morphology identical to baseline (n=15)</th>
<th>VT-morphology different from baseline (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>47 ± 20</td>
<td>39 ± 17</td>
</tr>
<tr>
<td>Mean CL (ms) of VT at baseline study</td>
<td>310 ± 66</td>
<td>295 ± 81</td>
</tr>
<tr>
<td>Mean CL (ms) of VT in sotalol study</td>
<td>346 ± 79</td>
<td>346 ± 86</td>
</tr>
<tr>
<td>Increase in CL (ms) (%)</td>
<td>36 ± 72</td>
<td>51 ± 83</td>
</tr>
<tr>
<td>Mean VERP (ms) at baseline</td>
<td>12 ± 23</td>
<td>17 ± 28</td>
</tr>
<tr>
<td>Mean VERP (ms) in sotalol study</td>
<td>232 ± 19</td>
<td>235 ± 21</td>
</tr>
<tr>
<td>δVERP (ms)</td>
<td>260 ± 22</td>
<td>281 ± 21</td>
</tr>
<tr>
<td>Mean QTC (ms) at baseline</td>
<td>30 ± 21</td>
<td>47 ± 20</td>
</tr>
<tr>
<td>Mean QTC (ms) in sotalol study</td>
<td>422 ± 32</td>
<td>409 ± 35</td>
</tr>
<tr>
<td>δQTC (ms)</td>
<td>438 ± 37</td>
<td>448 ± 43</td>
</tr>
<tr>
<td>Mean daily dose (mg) of sotalol</td>
<td>15 ± 34</td>
<td>39 ± 37</td>
</tr>
<tr>
<td></td>
<td>517 ± 132</td>
<td>480 ± 78</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation *P<0.02 vs baseline; **P<0.001 vs baseline.

CL = cycle length; LVEF = left ventricular ejection fraction;
VERP = ventricular effective refractory period;
δVERP = difference between VERP-values at baseline study and on drug, QTC = corrected QT interval (Bazett) during sinus rhythm,
δQTC = difference between QTC-values at baseline study and on drug;
VT = ventricular tachycardia.

RELATIONSHIP TO INFARCT LOCATION

There was no significant correlation between infarct location and the number of morphologies at baseline study or on drug or inducibility on sotalol. Emergence of new morphologies on the drug was also independent of infarct location.

RELATION TO CHANGES IN REFRACTORINESS

The mean ventricular effective refractory period in all patients on sotalol was 276 ± 24 ms (range 220 to 330), which was significantly longer than at baseline (232 ± 21 ms) (P≤0.001, 95% confidence interval +35 to +54 ms). There was no significant difference between responders and non-responders in respect to lengthening of the mean ventricular effective refractory period on drug vs baseline (Table 4). The corresponding differences of these values at baseline study and on drug, between non-responders and responders, were greater in the latter, but just missed statistical significance (38 ± 22 ms vs 48 ± 22 ms, P=0.06, 95% confidence interval -0.5 to +20 ms).

Surprisingly, within the group of non-responders there was a significant difference in the mean ventricular effective refractory period on sotalol between patients who developed at least one new morphology on drug (mean 281 ± 21 ms) and those who did not (260 ± 22 ms) (P≤0.01, 95% confidence interval +4 to +39 ms), whereas the corresponding values in the drug-free study did not differ significantly (235 ± 21 vs. 232 ± 19 ms, P=ns). The corresponding values of the difference between these values were 47 ± 20 ms vs 30 ± 21 ms (P≤0.03) (Table 2).

The drug-induced alterations of the QTc interval were parallel to changes in the ventricular effective refractory period in all different groups of patients, whereas the extent and significance differed slightly (Tables 2 and 4).

Table 3 Number of different morphologies of ventricular tachycardias in non-responders (36 patients) during baseline study vs drug therapy (chi square test, P=ns)

<table>
<thead>
<tr>
<th>Baseline study</th>
<th>1 morphology</th>
<th>≥ 2 morphologies</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study on sotalol</td>
<td>17</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>≥ 2 morphologies</td>
<td>9</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>10</td>
<td>36</td>
</tr>
</tbody>
</table>
The page contains text discussing the implications of pleomorphic VT on oral sotalol, with a focus on the relationship between drug testing and the inducibility of ventricular tachycardia. The text is structured with a discussion section at the beginning, followed by a table and a figure.

**Discussion**

This study demonstrates that in this homogeneous patient cohort with coronary artery disease and sustained monomorphic ventricular tachycardia, oral sotalol is effective in about 60% of patients, as based on electrophysiological criteria. Moreover, contrary to a recently published investigation concerning class I antiarrhythmic agents, the induction of multiple morphologies of monomorphic ventricular tachycardia at baseline electrophysiological study did not predict failure of subsequent drug testing with sotalol (Table 1). Patients with multiple morphologies of ventricular tachycardia at baseline study were as likely to be responders on sotalol as were patients with only one inducible monomorphic ventricular tachycardia. In both groups in 60% of patients tachycardia was rendered non-inducible during oral sotalol (Fig. 1).

Furthermore, almost one quarter of patients with one or more distinct morphologies of ventricular tachycardia at baseline manifested new morphologies of ventricular tachycardia during drug testing on sotalol. This effect was independent of the degree of left ventricular dysfunction, infarct location and number of morphologies during the drug-free study, but there was a significant difference in the ventricular effective refractory period on sotalol between patients who developed at least one new morphology on drug and those who did not. The lack of correlation between emergence of new morphologies and the degree of left ventricular dysfunction on sotalol contrasts with the strong correlation between these two variables during therapy with class I agents reported by Wilber et al.²

Patients with coronary artery disease and ventricular tachycardia often have morphologically distinct (pleomorphic) types of tachycardia. Theoretically, multiple morphologies of ventricular tachycardia could be a manifestation of different exit sites from a single reentrant circuit, or could arise from anatomically separate reentrant circuits. Mapping studies have provided evidence that morphologically distinct ventricular tachycardias often arise from the same circuit or from circuits that are within 1 to 2 cm of each other, and that only a minority of patients have disparate sites of origin located more than 5 cm from one another. Recent observations provide new insights into the possible mechanisms of pleomorphic ventricular tachycardias by demonstrating that a single region of slow conduction may indeed participate in the reentrant circuits of two or even three morphologically distinct ventricular tachycardias. Three different mechanisms by which morphologically distinct ventricular tachycardias might share the same region of slow conduction have been proposed. They may utilize varying lengths of the same region of slow conduction, which is activated in the same direction during both ventricular tachycardias. A second possibility is that the shared region of slow conduction is traversed in opposite directions during different ventricular tachycardias. Thirdly, the region of slow conduction may be similar in length and activated in the same direction during both ventricular tachycardias, and the pleomorphism may be related to changes in the epicardial activation (breakthrough) outside the region of slow conduction. By modifying these three mechanisms, antiarrhythmic drugs like sotalol may thus manifest new morphologies during serial electropharmacological testing.

Surprisingly, in those patients in whom new morphologies were induced on drug, a moderate but significant lengthening of ventricular refractoriness was observed compared to patients whose morphologies on drug were identical to baseline study; however, cycle lengths of ventricular tachycardias were the same on drug in both groups. Our hypothesis is, that in patients with new morphologies on sotalol, due to marked

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**Table 4 Mean ventricular effective refractory periods in responders and non-responders at baseline study and on drug**

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=54)</th>
<th>Non-responders (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERP (ms) at baseline study</td>
<td>230 ± 19</td>
<td>234 ± 25</td>
</tr>
<tr>
<td>VERP (ms) on sotalol</td>
<td>279 ± 23**</td>
<td>272 ± 25**</td>
</tr>
<tr>
<td>δVERP (ms)</td>
<td>48 ± 22</td>
<td>38 ± 22</td>
</tr>
<tr>
<td>QTc (ms) at baseline study</td>
<td>397 ± 35</td>
<td>414 ± 34</td>
</tr>
<tr>
<td>QTc (ms) on sotalol</td>
<td>431 ± 59*</td>
<td>443 ± 40*</td>
</tr>
<tr>
<td>δQTc (ms)</td>
<td>34 ± 48</td>
<td>29 ± 38</td>
</tr>
<tr>
<td>Daily dose (mg) of sotalol</td>
<td>456 ± 87</td>
<td>495 ± 106</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. P values are not significant. Abbreviations as in Table 2.
lengthening of refractoriness in the normal myocardium, new areas of block in normal tissue were created, leading to different exit sites from the reentrant circuit. The influence of sotalol on the reentrant waveform in the abnormal tissue was similar in non-responders with and without new morphologies, therefore cycle length was about the same in both groups. The possible explanation, that non-responders with a longer ventricular effective period had new morphologies on drug, merely due to a more complete stimulation protocol (perhaps because induced ventricular tachycardias on sotalol were slower and so haemodynamically better tolerated), could therefore be excluded. One might argue that inducibility of multiple morphologies is due to aggressiveness of the stimulation protocol. However, all patients in the present study underwent the same stimulation protocol with well-defined stimulation steps and endpoints in baseline and drug studies.

Any argument that helps to explain the mechanisms that influence the interplay between sotalol and the arrhythmogenic substrate in respect to the emergence of new morphologies, especially the exact role of the potassium channels, remains speculative. Several observations in this study suggest that sotalol may have potential proarrhythmic effects as far as emergence of new inducible ventricular tachycardias and their readiness of induction are concerned. Although sotalol suppressed induction in a large proportion of patients, more than half of the non-responders manifested new morphologies after sotalol. This latter observation is compatible with previous studies that have demonstrated a similar proarrhythmic effect after administration of amiodarone. On the other hand, changes in refractoriness may be only a marker for other unknown influences that modulate induction of tachycardia.

CLINICAL IMPLICATIONS

First, induction of multiple morphologies of sustained monomorphic ventricular tachycardia at baseline study does not predict failure of subsequent drug testing with sotalol, contrary to drug testing with class I agents.

Second, slowing of rate of ventricular tachycardia and changes in morphology during therapy with sotalol may have implications in patients receiving implantable cardioverter-defibrillators or those undergoing ablative procedures. Most automatic implantable cardioverter-defibrillators incorporate a morphology-and rate-discriminating detection algorithm. Thus, a different sequence of myocardial activation may interfere with recognition of ventricular tachycardia by devices using morphology criteria for termination.

LIMITATIONS

An important limitation of this study is the retrospective analysis. Because the stimulation protocol was performed according to current clinical practice with only one baseline study and a placebo group was lacking, one cannot account for spontaneous random temporal variations in induced morphologies, which may happen even in the absence of a concomitant drug regimen. Because of the limited sample size, statistical power to detect small differences between groups was only moderate, but it seems improbable, that clinically relevant differences have been missed.

References