



Effects of endothelin A receptor blockade in patients with ST-elevation acute coronary syndrome – A rhythmologic substudy

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ABSTRACT

Aims: Ventricular arrhythmias are common after acute myocardial infarction (AMI). Endothelin (ET) is a mediator of microvascular dysfunction and cardiac remodeling with arrhythmogenic potential. The aim of this study was to assess safety and feasibility of selective ET-A receptor blockade in ST-elevation acute coronary syndrome (STE-ACS) within a larger randomized trial.

Main methods: Patients with posterior-wall STE-ACS were randomly assigned to receive intravenous BQ-123 at 400 nmol/min or placebo over 60 min, starting immediately prior to primary percutaneous coronary intervention. Twenty-four hour Holter recordings were performed during hospitalization for STE-ACS and after 6–8 weeks. The predefined primary endpoint was the documentation of ventricular tachycardia and/or late potentials at follow-up.

Key findings: There was no significant difference in the predefined primary endpoint at 45 (33–62) days (0/16 (0%) in BQ-123 treated patients vs. 1/14 (7%) in the placebo group, $p = 0.465$). At 2 (1–3) days, an increase in the total number of supraventricular extrasystoles (SVES)/24 h in patients randomized to BQ-123 (45 (17–165) beats vs. 11 (5–72) beats in placebo treated patients, $p = 0.025$) occurred. This increase was also observed at 45 days (105 (37–216) beats vs. 11 (3–98) beats in placebo treated patients, $p = 0.037$). There was no significant difference regarding other rhythmologic secondary endpoints between the two groups. **Significance:** Based on the analysis of long-term ECG data, short-term administration of BQ-123 after AMI was safe. Because of the small sample size, no firm conclusion regarding antiarrhythmic efficacy can be drawn.

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Introduction

Ventricular arrhythmias represent a severe and common form of complications after acute myocardial infarction (AMI). While sudden cardiac death, mostly caused by ventricular tachycardia or ventricular fibrillation (VF), poses an immediate risk in the early phase, chronic phase arrhythmogenesis develops in a proportion of patients (Adabag et al., 2008; Bloch Thomsen et al., 2010; Camm et al., 2004; Solomon et al., 2005). The most important factor leading to ventricular arrhythmias in the chronic phase is the size of the infarcted area (Roberts et al., 1975; Crawford et al., 2010), which is determined, amidst other

factors, by ischemia/reperfusion injury; large infarcts result in ventricular remodeling and myocardial substrate formation.

Endothelin-1 (ET-1), one of the most potent known vasoconstrictors, was found in acute coronary thrombi and was significantly elevated in re-perfused ischemic myocardium (Adlbrecht et al., 2007; Keltai et al., 2004; Tonnessen et al., 1995). Additionally, ET-1 was identified as a predictor of long-term clinical outcome after AMI (Khan et al., 2007). When intravenously administered to dogs, it induced ventricular tachycardia (Toth et al., 1995). It was shown that ET-1 dose-dependently increases the norepinephrine release in the myocardium after ischemia/reperfusion injury and thereby increases the incidence of VF in isolated guinea pig hearts (Isaka et al., 2007).

ET receptor blockade was demonstrated to reduce infarct size and exert antiarrhythmic effects in some animal models, however, it is unclear whether a protective effect exists in patients (Alberola Aguilar et al., 2000; Baltogiannis et al., 2005; Crockett et al., 2001; Gelzer et al.,

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2004; Lee et al., 2008; Ozdemir et al., 2006; Singh et al., 2006). Interestingly, when studied in the setting of ischemic arrhythmia in rats, the selective ET-A receptor blocker BQ-123 attenuated arrhythmias only at the lowest dose, while significantly increasing the incidence of irreversible VF at higher doses (Garjani et al., 1995).

Our group has recently observed that ET receptor blockade has beneficial effects on microvascular flow, enzymatic infarct size and long-term outcome in patients with AMI (Adlbrecht et al., 2012; Adlbrecht et al., 2014).

Arrhythmia following myocardial infarction is associated with worse prognosis. Nonsustained ventricular tachycardias (nsVTs) represent an independent predictor for mortality and late potentials are a widely used electrophysiological risk stratification tool after myocardial infarction (Makikallio et al., 1999; Denniss et al., 1986; Gomes et al., 2001; Steinberg et al., 1992). Although somewhat reduced in sensitivity, they remain an independent risk factor in the reperfusion era (Bauer et al., 2005).

In the present study, we evaluated safety and feasibility of ET-A receptor blockade using the ET-A receptor antagonist BQ-123 using a predefined combined endpoint consisting of the occurrence of nsVT, late potentials or both.

Materials and methods

Patients and inclusion criteria

One hundred seventeen men or post-menopausal women aged 18 years and above with posterior or inferior wall STE-ACS were screened for eligibility between 2007 and 2009. 57 patients were randomized (Adlbrecht et al., 2012). Three protocol violations occurred in patients who were included into the study despite an onset of pain more than 12 h ago. All three were in the placebo arm. Importantly, all patients had either TIMI 0 or 1 coronary flow in the infarct related coronary artery before insertion of the guide-wire (Adlbrecht et al., 2011).

Immediately prior to PCI, all patients received unfractionated heparin to reach an activated clotting time of 300 s, 500 mg of acetylsalicylic acid and 600 mg of clopidogrel.

Of the 57 patients enrolled in this randomized, placebo controlled, double-blind study, 30 patients received 24-hour electrocardiograms (ECG) and were included in the electrophysiologic substudy with a predefined primary endpoint. Patients who were included early during the main trial did not receive Holter recordings, as the electrophysiologic substudy was initiated at a later time-point.

Study protocol

The study was approved by the ethics committee of the Medical University of Vienna and the Austrian Federal Office for Safety in Health Care (AGES) and was conducted in accordance with the Declaration of Helsinki. After informed consent had been obtained, patients were randomly assigned to either active treatment or placebo in a double-blind fashion. Patients were randomized to receive BQ-123 (Clinalfa, Läufelfingen, Switzerland) dissolved in 50 mL of 0.9% NaCl at 400 nmol/min intravenously or placebo (NaCl) over 60 min, initiated immediately before guidewire insertion (Adlbrecht et al., 2011).

Study drug dosing was based on published data showing that intravenous applications of BQ-123 above 300 nmol/min had reproducible systemic effects and that dosages of 1000 nmol/min lowered systemic blood pressure (Spratt et al., 2001).

Short-term administration was chosen to cover the crucial phase of reperfusion during which the largest myocardial endothelin burden has been found (Tonnessen et al., 1995). This also avoids side effects (e.g. liver function impairment) of long-term endothelin receptor antagonism (Hoepfer, 2009). It was shown that intra-venous administration of BQ-123 for 15 min induced hemodynamic effects for up to

4h (Spratt et al., 2001), indicating an effect beyond its plasma half-life. It is therefore plausible that direct effects are measurable at two days when the first recording was conducted. These influences on inflammation, remodeling and microvascular function are possible explanations for long-lasting effects.

Concomitant medical therapy was given according to standard of care.

Study procedure

Twenty-four hour Holter recordings (Del Mar Avionics, Del Mar Medical Systems, Irvine, CA) were performed on two occasions, during index hospitalization and at 6–8 weeks, to assess both immediate and delayed effects of ET receptor blockade. Analysis was performed by experienced physicians blinded to the trial randomization.

Study endpoints

The primary endpoint of this electrophysiologic substudy was the presence of nsVT (defined as a tachyarrhythmia originating from the ventricles for a duration of <30 s), late potentials or both at 6–8 weeks after STE-ACS (Exner et al., 2007).

In addition to the Holter recordings at follow-up, recordings were also performed in the subacute phase of STE-ACS during the initial hospital stay in order to account for both potential immediate and delayed effects of the study drug.

Late potentials increase in prevalence at 7 to 10 days after AMI and remain stable thereafter (Kuchar et al., 1986). Consequently, the time-point for the predefined primary study endpoint consisting of the presence of nsVT, late potentials or both was chosen to be 6–8 weeks after STE-ACS and the presence of nsVT in the Holter ECG recorded during the index hospitalization alone served as a secondary endpoint. Other secondary endpoints were the heart rate variability (HRV) parameter standard deviation of normal-to-normal intervals (SDNN) and routinely assessed ECG variables, including ventricular extrasystoles (VES), supraventricular extrasystoles (SVES) and sustained ventricular tachycardia (sVT) runs, defined as a tachyarrhythmia originating from the ventricles for a duration of >30 s.

Statistical analysis

Fisher's exact test was used for evaluation of the primary study endpoint. Continuous outcome measures are expressed as median (25th–75th percentile) and the Mann–Whitney U test was used for comparison between the two treatment groups. A p-value of <0.05 was considered as indicating statistical significance.

Results

Patient population

Of the 30 patients in whom Holter recordings were available, 14 were randomized to receive placebo and 16 were assigned to receive peri-interventional BQ-123. Median patient age was 61 (51–71) years, and 7 patients (23%) were female. The ischemic time, defined as the period from onset of chest pain to first balloon inflation or thrombectomy, was 4 (2.5–5.6) hours. Left ventricular ejection fraction of patients in the two treatment arms at baseline was comparable. Patient characteristics are presented in Table 1.

Primary endpoint

At 45 days after AMI, no difference in the occurrence of late potentials, nsVT or both was observed between the patients randomized to receive either BQ-123 or placebo (0/16 (0%) vs. 1/14 (7%), $p = 0.467$). Late potentials could be detected in only one patient. This patient had been randomized to the placebo group.

Table 1
Patient clinical characteristics.

Therapy	Control	BQ-123	p-value
Age (years)	65 (52.8–72.5)	55.5 (50.8–71.8)	0.755
Male n (%)	12 (86%)	11 (69%)	0.399
Ischemic time (hours)	4.25 (2.25–5)	4 (2.5–6.25)	0.675
IRA			0.642
RCA n (%)	11 (79%)	14 (88%)	
CX n (%)	3 (21%)	2 (12%)	
CKmax (U/L)	2261 (1607–3139)	1371 (828–2081)	0.138
Hypertension n (%)	11 (79%)	9 (56%)	0.260
Hyperlipidemia n (%)	13 (93%)	12 (75%)	0.336
Diabetes mellitus n (%)	3 (21%)	1 (6%)	0.315
Current smoker n (%)	5 (36%)	10 (63%)	0.272
On dual antiplatelet therapy	14 (100%)	16 (100%)	1
On beta-blocker n (%)	14 (100%)	15 (94%)	1
On ACE inhibitor	12 (86%)	15 (94%)	0.586
On lipid lowering therapy	14 (100%)	15 (94%)	1
LVEF (%)	54 (50.8–61.5)	55.5 (52–59)	1

IRA: infarct related coronary artery, RCA: right coronary artery, CX: circumflex coronary artery, CKmax: peak creatine kinase value, ACE: angiotensin converting enzyme, and LVEF: left ventricular ejection fraction. Values are median (25th–75th percentile) or number (percent) respectively. Percentages are rounded values.

Secondary endpoints

In the acute phase of myocardial infarction one patient experienced asystole following PCI. The sinus pause occurred 2 min after the start of BQ-123 infusion and was treated by 0.5 mg of intra-arterial atropine to which the patient responded promptly, no further treatment was necessary. Another patient experienced a ventricular tachycardia and was re-admitted to the hospital – both patients had been randomized to receive BQ-123. The need for peri-interventional atropine was similar in the BQ-123 treated group compared to the placebo group (8 (50%) versus 8 (57%), $p = 0.730$).

At 2 days after AMI, Holter recordings revealed no difference regarding the presence of nsVT (1 (7.15%) in the BQ-123 group vs. 0 (0%) in the placebo group, $p = 0.517$) or sVT (1 (7.15%) vs. 0 (0%), $p = 0.517$).

The total number of SVES per 24 h recording was significantly increased in the BQ-123 treated group at both time-points: 2 days (45 (17–165) vs. 11 (5–72), $p = 0.025$) and 45 days (105 (37–216) vs. 11 (3–98), $p = 0.037$, Fig. 1).

Grouping for >100 SVES yielded no significant difference at either time-point (5 patients in the BQ-123 group at 2 days vs. 2 in the placebo

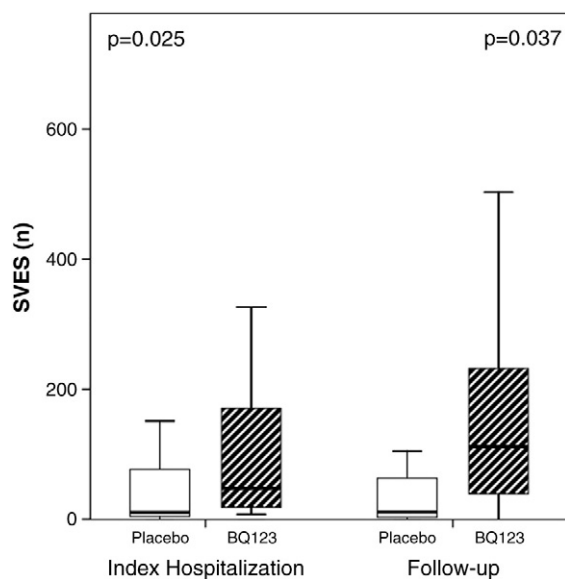


Fig. 1. Box plot presenting the total number of supraventricular extrasystoles (SVES) per 24 h recording during the index hospitalization and at post-discharge follow-up.

treated group, $p = 0.390$; and 7 vs. 2 at 45 days, $p = 0.208$). There was no significant difference in the total number of VES at either time-point ($p = 0.595$ and $p = 0.311$, respectively).

We classified the patients according to their beta-blocker dosage (no beta blocker, 1–49% of target dose according to guidelines, 50–99% of target dose and 100% target dose). After applying Spearman's rho, we found no correlation between beta-blocker dosage and the occurrence of SVES ($r = 0.075$, $p = 0.721$). There was no significant difference in the occurrence of supraventricular tachycardia.

No third-degree atrioventricular (AV) block occurred in any patient. Second-degree AV block type Mobitz 1 occurred in two patients, one in the treatment group and one in the placebo group. Both events occurred two days after AMI during the night. Second degree-AV block type Mobitz 2 occurred in one patient randomized to receive BQ-123 three days after the event. Pacemaker implantation was performed in this patient.

Two patients randomized to receive BQ-123 experienced episodes of atrial fibrillation (AF). One patient's Holter recording at two days after AMI showed AF from the beginning of recording in the morning, lasting for 7 h, converting spontaneously into sinus rhythm at around 3 p.m. In the second patient, AF occurred at 11:20 a.m., preceded by isolated premature ventricular contractions and one single premature supraventricular contraction. One patient in the treatment group developed a sinoatrial block.

Episodes of bradycardia were found in two patients in the treatment group. Detailed electrocardiographic results of the follow-up are presented in Table 2.

Discussion

This is the first trial assessing the electrophysiological effects of short-term systemic ET-A receptor blockade in patients with STE-ACS undergoing primary PCI. While animal studies provided conflicting results regarding the effect of ET receptor blockade on infarct size, or their antiarrhythmic potential, the current electrophysiologic sub-study suggests that the short-term use of BQ-123 in this setting is safe.

In a murine model of myocardial infarction, a decrease in the incidence of VF and infarct size and mortality from VF episodes was demonstrated for animals under ET-A receptor blockade (Baltogiannis et al., 2005). In patients with STE-ACS treated with an ET-A receptor blocker our group recently found an improvement in microvascular perfusion, a decrease in the enzymatic infarct size and an increase in left ventricular ejection fraction after 6 months (LVEF) of 63% vs. 59% ($p = 0.047$) (Adlbrecht et al., 2012). Infarct size, measured by both serum enzyme levels and MRI, and LVEF are known to be predictors of ventricular arrhythmia after AMI (Roberts et al., 1975; Crawford et al., 2010). Apart from a potential direct benefit of the blockade of pro-arrhythmic effects of ET-1, this could be another mechanism contributing to the lower incidence of ventricular arrhythmias reported in some studies (Alberola Aguilar et al., 2000; Baltogiannis et al., 2005).

Table 2
Electrocardiographic results.

	BQ-123	Placebo	p-value
Average heart rate (bpm)	68 (62–78)	64 (63–74)	0.936 ^a
P-wave width (ms)	119 (109–127)	114 (100–124)	0.792 ^a
PQ interval (ms)	165 (148–180)	162 (152–182)	0.719 ^a
QRS duration (ms)	99 (90–109)	94 (92–96)	0.200 ^a
QTc (ms)	420 (407–433)	428 (398–443)	0.434 ^a
ST-segment changes			
Elevation n (%)	7 (47%)	6 (55%)	0.691 ^b
Depression n (%)	4 (27%)	0 (0%)	0.091 ^b

bpm: beats per minute, ms: millisecond, QTc: QT interval corrected for heart rate. Values are median (25th–75th percentile) or number (percent) respectively. Percentages are rounded values.

^a Fisher's exact test.

^b Wilcoxon test.

Conversely, various doses of the ET-A receptor blocker BQ-123 were compared in rats and a distinct pro-arrhythmic effect at higher doses was observed (Garjani et al., 1995). In healthy human volunteers high doses of BQ-123 (3000 nmol/min) led to a moderate increase in heart rate (+18%) compared to the placebo group (Spratt et al., 2001). This increase may be explained by the concurrent decrease in systemic blood pressure.

The lack of consistency in data on the effect of ET receptor blockers in AMI may be explained by species differences. However, more importantly, there exist vast differences in the ischemia (+/– reperfusion) protocol as well as the timing and receptor selectivity of ET receptor antagonists. In some animal models, the investigators applied the study drug before coronary artery ligation, an approach of scientific interest, however, an unrealistic setting in view of the clinical situation. It must be emphasized that many of the published animal models of AMI are not representative in the modern era of primary PCI, as in many cases they represent ligation-only models. This resulted in relatively large infarct sizes and frequent arrhythmic complications, and might have therefore led to an overestimation of the pro- or antiarrhythmic potential. Additionally, the patient population included into the present study (Table 1) was treated quickly (mean ischemic time of 4 h) in a setting of guideline recommended door-to-balloon times, optimal medical therapy and frequent utilization of thrombectomy devices impacting on short- and long-term outcome (Kalla et al., 2006; Adlbrecht et al., 2010). As a result, one would expect to see very few arrhythmic complications in the first place. This is supported by the fact that there were no nsVT runs detected in the placebo group after 2 days. These considerations provide an explanation for the lack of difference in the combined endpoint between the two groups. Furthermore, no significant changes in routinely determined Holter ECG parameters were observed (Table 2).

Our pilot study revealed that a relatively high number of patients would be necessary for a phase III study evaluating clinical efficacy. We want to therefore emphasize that this sub-study should be primarily regarded as a safety and feasibility study.

When interpreting the discrepancies of animal data, it is of interest that experiments in rats showed a decrease in ventricular ectopic beats after treatment with BQ-123 but also after pre-treatment with ET-1 itself (Sharif et al., 1998). SVES (or premature atrial contractions (PACs)) were found to be predictors of AF (Perez et al., 2009). At 2 days, short episodes of AF were recorded in two patients (both BQ-123 treated), whereas there was no documented AF at 45 days. While in-vitro experiments showed a strong arrhythmogenic effect of ET-1 on rat atrial myocytes (Mackenzie et al., 2002), no atrial fibrillation could be observed after intra-coronary infusion of ET-1 in a dog model (Kiss et al., 2004). We found no effect on the development of AF but an increase in SVES. This might be explained by the many different systems that play a pathophysiologic role in this setting, including but not limited to, atrial remodeling, inflammation, neurohumoral signaling and electrophysiologic conduction. In a cohort of healthy individuals, the occurrence of excessive supraventricular ectopic activity, defined as ≥ 30 supraventricular ectopic complexes per hour, increased the risk for AF or stroke in a follow-up period of 6.3 years (Binici et al., 2010). In the present study, a mean value of 1.87 PAC per hour at two days and 4.62 at 45 days was observed in the treatment group. Although this represents a statistically significant difference compared to placebo-treated patients, it may not be clinically relevant. In two studies, one including patients after AMI and the other recruiting patients without structural heart disease, >100 PACs per day were established as a cutoff for prediction of a decrease in LVEF or of the occurrence of AF or adverse cardiovascular events, respectively (Zoni Berisso et al., 1988; Chong et al., 2012). After classifying our patients according to this scheme, we found only a non-significant trend towards a higher occurrence of >100 PACs per day in the treatment group at both time-points.

Infarct location is an important predictor of arrhythmic complications after AMI. Anterior infarct location is associated with an increased

risk of ventricular tachycardia and patients are more prone to develop AF (Jabre et al., 2011), whereas posterior infarcts increase the incidence of AV blocks (Hreybe and Saba, 2009). Therefore, the inclusion of patients with anterior infarct location is warranted for a subsequent protocol assessing the complete spectrum of effects of ET-1 receptor blockade in the setting of AMI.

The HRV parameter SDNN, calculated as the standard deviation of all normal beats during the recording, is a very well established prognostic marker after AMI (Bigger et al., 1992). The highest mortality rates were observed in patients with a SDNN of <70 ms (La Rovere et al., 1998). ET-1 plasma levels were inversely correlated to SDNN in a patient population with coronary slow-flow (Pekdemir et al., 2004). Very recently, a positive correlation between SDNN and the quality of life was reported in patients with chronic heart failure (Chrysohoou et al., 2010). While the difference in SDNN in the present study did not reach statistical significance, it does show a trend towards higher SDNN in the treatment group at the earlier time-point, leaving the placebo-treated patients within the high-risk group. One may argue that within 48 h after the infusion of BQ-123, its positive effects on microvascular flow and anti-inflammatory effects are ongoing.

Limitations

The study is limited by its small size, single center design and surrogate endpoints, as it was designed as a “proof-of-concept” study. However, the present study is a prospective sub-study of the randomized clinical trial assessing the effects of ET-A receptor blockade in STE-ACS. Patients with anterior wall myocardial infarctions were excluded for safety reasons because of data suggesting adverse cardiac remodeling in anterior infarctions after ET receptor blockade (Nguyen et al., 1998).

Conclusion

Based on the analysis of long-term ECG data, short-term administration of BQ-123 after AMI was safe. Because of the small sample size, typical for a phase II study, no firm conclusion regarding antiarrhythmic efficacy of ET receptor blockade can be drawn.

Conflict of interest statement

There are no conflicts of interest.

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Appendix A. Supplementary

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.lfs.2014.02.015>.

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