The Nephroprotective Effects of Oral Urinary Alkalization with Blemaren® on the Outcome of Patients with Severe Myocardial Infarction

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Abstract: *Objectives*: Acute cardiac dysfunction often leads to acute kidney injury (AKI). The harmful effect of myoglobin seems to be dependent on the acidic urine pH. This study aimed to discover whether urinary alkalinization with an oral combination of sodium citrate, citric acid and potassium hydrogen carbonate (Blemaren®) reduces the prevalence of AKI in patients with severe myocardial infarction.

Methods: In this retrospective cohort study, the data from >6.600 consecutive patients between 09/2005-06/2015 were analyzed. Finally, 359 patients with severe myocardial infarction (defined as creatine kinase- levels CKmax> 80µkat/l) could be included. To prevent AKI, 307 patients received Blemaren® treatment. The following statistical methods were used to compare the cohorts: Mann- Whitney- U- test with confirmation by t-test; chi- square- test based on Pearson; statistical correlation analysis based on Pearson; linear and binary logistic regression and Log- Rank- test for comparison of cumulative survival.

Results: No significant association between the development of urea, creatinine and GFR with oral urinary alkalization using Blemaren® (p=0.898; p=0.962; p=0.645) was found. Furthermore, in subgroup analyses, Blemaren®- treatment contributed no benefit for high-risk groups (arterial hypertension, cardiogenic shock and initial renal impairment) in terms of development of AKI (p>0.05). Finally, Blemaren® treatment did not improve in-hospital survival, mid-term mortality of about 1 and 2 years or cumulative survival (all p>0.05).

Conclusion: Oral urine alkalization with Blemaren® in severe myocardial infarction to prevent AKI and to improve patients' outcome is no longer appropriate.

Keywords: Urinary alkalization, myocardial infarction, nephroprotection, acute kidney failure, cardiorenal syndrome, Blemaren®.

INTRODUCTION

Acute cardiac dysfunction often leads to acute kidney injury (AKI). Patients, particularly those with acute coronary syndrome (ACS) can develop an AKI from 9.6 to 43.2 % of cases [1,2]. The rapid deterioration of cardiac function, which consequently leads to an acute harmful effect on renal function, is known as cardiorenal syndrome type 1 (CRS type 1) [3]. It is associated with a significantly worse prognosis, increased rehospitalization and costs [4]. In addition, the quality of life in affected patients is decreased [5]. Both renal hypoperfusion and toxic tubular necrosis due to myoglobinuria in the context of myocardiolysis are suspected to play key roles in the pathophysiology of AKI. The results of a small clinical study from Damman *et al*. suggest that the decrease in glomerular filtration rate (GFR) in acute heart failure is caused by a decrease in cardiac output as well as venous congestion due to elevated right atrial pressure. In summary, Damman *et al*. recognized both renal blood flow and right atrial pressure as independent factors influencing the GFR [6]. Several recent studies have investigated the role of rhabdomyolysis in AKI following an alternative approach. Between 10 and 50% of patients with rhabdomyolysis suffer AKI; conversely 5 to 25% of all AKI are caused by rhabdomyolysis [7]. As a consequence of muscle necrosis, the release of creative kinase (CK) and myoglobin occur in serum and urine [8]. However, to date clear cut-off values defining rhabdomyolysis serologically are lacking. In their study on AKI following heart surgeries, Hajjar *et al*. defined a cut-off level of >2500U/l (42µkat/l) for the presence of rhabdomyolysis [9]. However, this CK cut-off may even be lower in ICU patients. Based on the data from 1700 ICU- patients, El- Abdellati and coworkers reported a 40% increased risk of AKI at least even at a low CK activity of 170 - 1000U/1 (2.83 - 16.7µkat/l) [10]. It is, therefore, hypothesized that the necrosis in severe myocardial infarction (MI) with serum CK values exceeding 80µkat/l is similarly harmful to kidney tubules as rhabdomyolysis. The toxic effect of free myoglobin possibly results from acidic pH of urine [11].

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Zager *et al*. studied the mechanisms and therapeutic options in myoglobinuric AKI. He explained the protective effect of urine alkalization using bicarbonate with an increased myoglobin excretion in the alkaline medium [12]. Another potential target of the urine alkalization in myoglobinuric AKI is a reduced occurrence of methemoglobin, and therefore, a decreased formation of pigment cylinders, as well as less proximal tubular necrosis due to a reduced endocytic uptake of hemoglobin and fewer iron-radical-induced damage owes to the formation of insoluble iron hydroxide in neutral/alkaline urine and simultaneously smaller increase of free radicals via the Haber-Weiss-reaction [13].

So far there are several therapeutic approaches for the prevention of AKI, which have the potential however no proven effect according to current published evidence. These approaches include the oxygen radical scavenger N-acetyl-cysteine (NAC) and sodium bicarbonate. Sehirli *et al*. demonstrated a positive effect on renal function after renal ischemia and reperfusion in a rat model [14]. Thereupon, NAC has also been applied to patients with risk of acute cardiorenal syndrome (CRS) in heart surgery. While Burns *et al*. observed a significant benefit of NAC for the prevention of postoperative AKI, the results by Wijeysundera *et al*. 2 years later couldn`t demonstrate a preventive effect of NAC-treatment [15]. Because currently there is no convincing evidence for a clear benefit of NAC supplementation in CRS, the oral or intravenous application of NAC is not recommended for the prophylaxis of postoperative AKI [16] by the KDIGO (Kidney Disease: Improving Global Outcomes).

In addition, the urine alkalizing agent sodium bicarbonate showed promising effects with positive influences on ischemic nephropathy in rats with significantly lower increases of creatinine [17]. Therefore, Haase *et al*. studied the influence of urine alkalization by sodium bicarbonate in patients with high risk of type 1 CRS in the context of cardiopulmonary bypass surgeries. Of note, in this double-blinded randomized and controlled trial significantly fewer patients in the sodium bicarbonate group were found to have an increased creatinine >25% of baseline in the first 5 days after surgery (p=0,043) [18]. This investigation contained a small cohort of 100 cardiac surgical patients at increased risk of postoperative acute renal dysfunction.

Blemaren® (oral combination of 835,5mg sodium citrate; 1197,0 mg citric acid and 967,5mg potassium hydrogen carbonate per tablet), also an urine alkalizing agent, is approved for treatment and prevention of urolithiasis. In several intensive care units it is routinely used for the prevention of AKI after severe myocardial infarction. Until now, there was no scientific evidence that proved the use of the medication for prevention of AKI.

Therefore, the aim of this study was to evaluate whether the administration of Blemaren® protects patients from the development of AKI after severe MI. Furthermore, we studied whether the administration of the combined preparation has an effect on length of hospital stay, ICU stay and midterm mortality as well as cumulative survival.

METHODS

We retrospectively analyzed data from 6647 consecutive patients in the period 09/2005- 06/2015 using the Myocardial Infarction Registry of the Heart Center Dresden, University Hospital Dresden, Germany. Troponin- positive acute coronary syndrome with a highly increased creatine kinase CKmax ≥80µkat/l was a key inclusion criterion. A total of 359 patients were included of which 307 patients received on average 18 tablets of Blemaren® (containing overall 21,0g citric acid, 15,0g sodium citrate, 17,4g potassium hydrogen carbonate) to prevent the AKI, whereas 52 patients received no Blemaren®- treatment.

Kidney function within 7 days after admission was evaluated based on creatinine increase ≥50%, RIFLE-criteria and dialysis recommendations of the National Kidney Foundation. Furthermore, glomerular filtration rate (GFR), creatinine and urea levels during the observation period were analyzed. Comparing the cohorts' Mann- Withney- U- test with confirmation by t-test for non- categorical values and chi-square-test based on Pearson for categorical values were used. Further statistical correlation with analysis based on Pearson and performed linear or binary logistic regression was examined. The cumulative survival in the first 2 years after infarction was shown using the Kaplan-Meier- procedure. Comparison of survival distributions was performed in log- rank- test. $P<0.05$ was considered statistically significant and indicated as*.

RESULTS

Study Participants and Subgroups

The studied cohort of patients with severe myocardial infarction is characterized by a typical

Table 1: Comparison of the Average Patient Characteristics

Baseline charakteristics	with Blemaren®	without Blemaren®	Significance of group difference p=
Age, years	61	64	0,165
Gender, male, %	81	73	0,181
Arterial hypertension, %	66	67	0,832
Diabetes mellitus 2, %	27*	40*	0,044
BMI, kg/m^2	27,8	27,8	0,768
Triglycerides, mmol/l	1,9	1,7	0,320
Cholesterol, mmol/l	4,4	4,4	0,706
Nikotine abuse, %	45	48	0,675
LVEF initial, %	37	36	0,393
TAPSE initial, mm	22*	20*	0,012
Cardiogenic shock, %	43	50	0,381
CKmax, µkat/l	131,5*	110,5*	0,0001
CK-MBmax, µkat/l	10,9	10,7	0,692
Renal impairment at admission, %	83	81	0,730
Amount of contrast agent, ml	127	131	0,484

*Significant at p<0.05 affect merely distribution of diabetes mellitus, TAPSE und CKmax- level; relatively balanced cohort.

cardiovascular risk profile (refer to Table **1**). Additionally, an initial GFR- impairment <90ml/min/1,73m^2 was seen in 83% of patients with severe myocardial infarction. On average, the GFR was 68ml/min/1,73m^2. During an observation period of 7 days after myocardial infarction, 14,2% of patients (51 out of 359 patients), showed a worsening in renal function according to RIFLE-criteria 1-3 (Figure **1**).

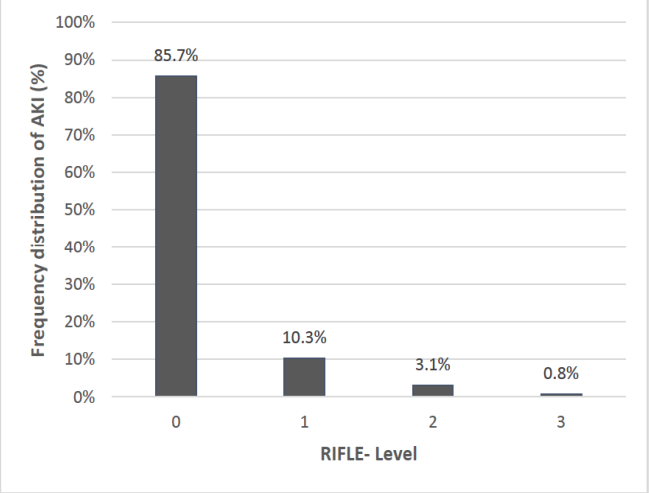

Figure 1: Frequency distribution of acute kidney injury (AKI) according RIFLE- levels in our cohort with severe myocardial infarction, nearly 14% of our patients suffered an AKI according RIFLE- criteria. Additionally, the figure demonstrates decrease of affected patients in increasing RIFLE- levels.

Moreover 7% of patients (26/359) suffered from an increase of creatinine ≥50%. A total of 7% of patients (26/359) showed decreases of the GFR, where dialysis should be considered. About 1% (3/359) underwent necessary hemodialysis.

The results of our statistical analysis indicates an association between certain patient characteristics (Age, initial GFR- impairment <90ml/min/1,72m^2, magnitude of LVEF- restriction and TAPSE- decline, CKmax- level) and a higher risk of developing AKI after myocardial infarction.

The risk of AKI-development, according to RIFLE-criteria, rises by 33% (p=0,017) with a 10 year age increase. In addition, the risk of dialysis necessity increases with each passing year by 3% (p=0,038).

An initial GFR- impairment of 30ml/min/1,73m^2 raises the risk of at least 50% creatinine increase by 98% (p=0,006). The odds of dialysis necessity even increases 9.2-fold respectively by 800% with a GFR reduction of 30ml/min/1,73m^2 (p=0,0001).

Provided that left ventricular ejection fraction (LVEF) rises up by 10%, the risk of AKI according RIFLE-criteria decreases by almost 30% (p=0,047). The odds of dialysis necessity decreases by more than 40% in this circumstance (p=0,013).

Table 2: Overview of the Primary Outcome after Severe Myocardial Infarction

Primary Outcomes	with Blemaren® (n=307)	without Blemaren® (n=52)	p- value (U- test t- test)
Average urea increase, mmol/l	1,3	1,4	0,538 0,898
Average GFR increase, ml/min/1,73m^2	2,0	0	0,956 0,923
Average creatinine increase, µmol/l	5	4	0,608 0,926
Creatinine increase ≥50%, %	6,8 (21)	9,6 (5)	0,560
AKI according RIFLE- criteria, %	14,0 (43)	15,4 (8)	0,792
Necessity of dialysis, %	9,6 (5)	7,8 (24)	0,638

Comparison of cohorts using U- test, t-test and categorical parameters with chi-square test (AKI according RIFLE- criteria, dialysis necessity) p= not significant so there is no evidential effect on taking Blemaren® for renal function.

With an increase of the initial Tricuspid annular plane systolic excursion (TAPSE) by 10 mm the risk of AKI-development according RIFLE- criteria growths by 60% (p=0,045). Patients with cardiogenic shock had an increased risk of AKI according to RIFLE- criteria by 220% (p=0,0003) as well as an increase in change of creatinine ≥50% by 10th (p=0,0001). The odds of dialysis necessity also rose considerably by 8-fold (p=0,0001). In our analyzed group of patients with CKmax ≥80µkat/l, the risk on dialysis necessity was increased with a CKmax- rise of 10µkat/l by 8.6% (p=0,00002). CKmax also correlates with AKI and creatinine escalation. CKmax- rise by 10µkat/l increases both the chance of AKI according RIFLE-criteria and at least 50% creatinine increase about 5% (p=0,013; p=0,005).

Cohorts

In the retrospective analysis, the total cohort of 359 patients is divided into 307 patients who received Blemaren® and 52 patients without Blemaren®-treatment. The patient group without Blemaren® had a significantly higher prevalence of diabetes than the group without Blemaren® (27 vs 44%, p=0.044). Moreover the patients with Blemaren® had a higher initial TAPSE although the absolute difference is only small (22 vs 20mm, p=0,012). Patients with Blemaren®- treatment showed on average a 20µkat/l higher CKmax (131,5 vs. 110,5, p=0,0002); Table **1**.

Primary Outcome

The average accumulation of urea in serum differs between the 2 cohorts by 0.1mmol/l (1.4mmol/l without and 1.3mmol/l with Blemaren®- treatment). This difference was not statistically significant (U- Test p=0.538; t- Test p= 0.898) and we could not identify any significant relationship between the individual urea difference and Blemaren® treatment (p=0,898).

In addition, the differences of absolute creatinine development during the first 7 days after myocardial infarction were not significant (U- Test p=0.608, t- Test p=0.926). Both absolute levels of creatinine and the increase of creatinine were not significantly influenced by the treatment with Blemaren® (4µmol/l without und 5µmol/l with Blemaren®, as shown in Figure **2**). Furthermore, there was no significant relationship between the absolute difference of creatinine levels and the treatment (p=0.962).

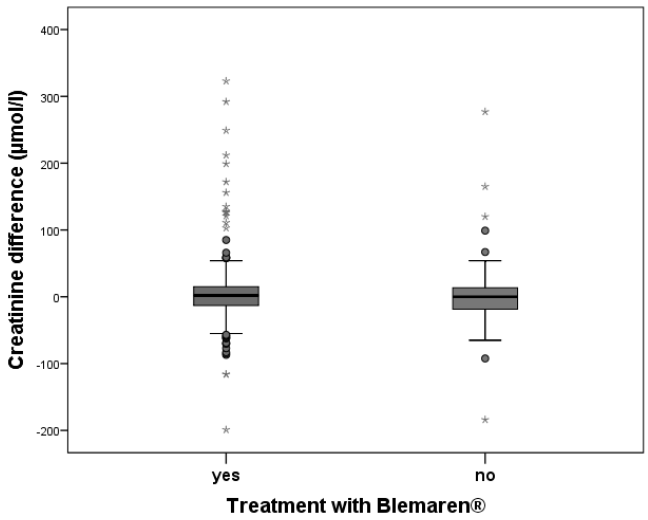

Figure 2: Development of absolute creatinine value as difference during first 7 days after myocardial infarction, p= not significant, so Blemaren®- treatment shows no significant effect.

We recorded an increase of creatinine by ≥50% in 7% of patients with Blemaren®- treatment (21 patients) and 10% (5 patients) of patients without urine

alkalization. However, the difference did not reached significance (p= 0,560). The administration of Blemaren® had no effect on creatinine increase ≥50% (Pearson correlation p=0.477; binary logistic regression p=0.477).

Approximately, half of each cohort suffered a GFR decrease (51% of Blemaren®- patients, 48% without Blemaren®; p=0.116). The absolute GFR- differences are at 150ml/min/1.73m^2 with Blemaren®- treatment and 100ml /min /1.73m^2 without Blemaren®- treatment, which is considerable in view of the standard value at ≥90ml/min/1.73m^2 (see Figure **3**). But overall, the groups' changes did not differ significantly in terms of GFR (p=0.956 U-test; t-test p=0.923) and there was no significant association between Blemaren®-treatment and the development of GFR (p=0.645).

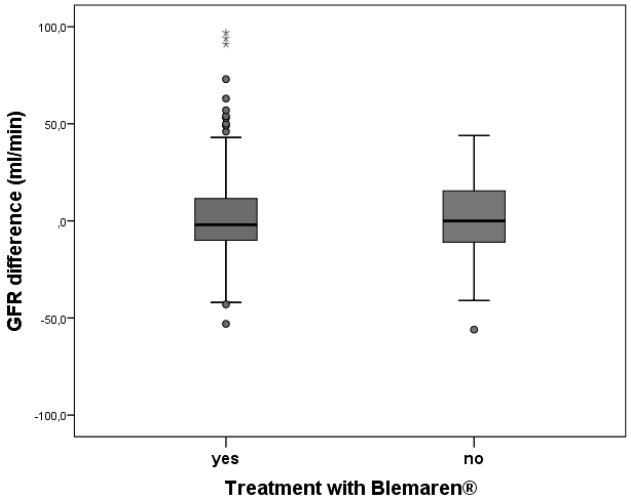

Figure 3: Development of GFR as difference during first 7 days after myocardial infarction, p= not significant, so Blemaren®- treatment shows no significant effect.

AKI according to RIFLE- criteria was encountered in 14.2% of patients (n=51; p=0.792; see Figure **4**) without statistically significant differences between the patient groups and the different treatment with or without Blemaren®. Around 15% of patients were not treated with Blemaren® (8 patients) and 14% of the AKI- patients received Blemaren®- treatment (43 patients). Furthermore, the development of AKI according RIFLE- criteria was independent from using Blemaren® (Pearson correlation p=0.793; binary logistic regression p=0.792).

In 7.9% and 9.6% of the cohort with and without Blemaren®- treatment (2 patients per group), respectively, dialysis had to be considered due to low GFR. This was not statistically significant between patient groups (p=0.638) and there is no significant

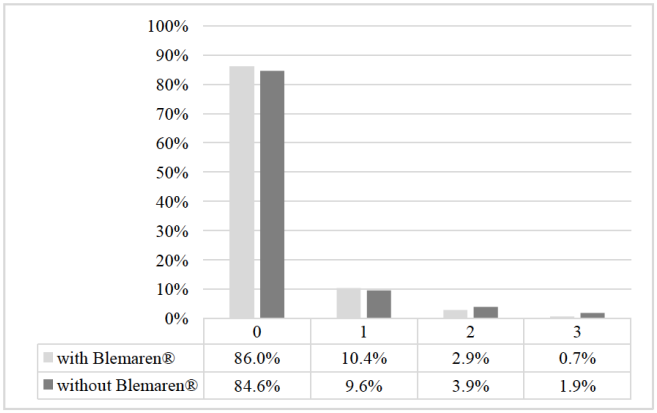

Figure 4: Frequency distribution of RIFLE- levels depending on treatment with Blemaren®, p = not significant, so Blemaren®- treatment shows no significant effect.

relationship between treatment and dialysis necessity (p=0.639).

In conclusion, we observed no significant differences in the distribution of patients developing AKI after myocardial infarction depending on Blemaren® treatment (Table **3**). We also identified no influence of Blemaren® in patients with certain risk factors to AKI according to RIFLE- criteria or creatinine increase ≥50% of baseline (Table **4**), although the patient group without Blemaren® had a significantly higher prevalence of diabetes than the group with Blemaren®-treatment(27 vs 44%, p=0.044).

Secondary Outcome

The median length of hospital stay was not significantly different (8 days with and 7 days without Blemaren®; U- test p=0.06; t- test p=0.146) and we revealed no significant effect of the medicament on length of hospital stay (Pearson correlation p=0.146; linear regression p=0.146).

All patients with severe MI also required care in the intensive care unit (ICU). The length of stay in ICU did not differ significantly among the various treatment groups (Blemaren®- patients 7 days, patients without Blemaren® 6 days; U- test p=0.210; t-test p=0.372). We also identified no association between urine alkalization and the length of stay in ICU (Pearson correlation p=0.372; linear regression p=0.372).

Overall, hospital mortality was 17% (62 of 359 patients) in this patients group with severe myocardial infarction, defined with a CKmax>80 µkat/l. Among the 52 patients without Blemaren®- treatment, 27% (14 patients) died, while 16% (48 of 307 patients) in the group with Blemaren (p=0.072).

Table 3: Significance of Blemaren®- Influence on AKI in Binary Logistic Regression Controlling Potential Risk Factors

risk factors	Creatinine- increase ≥50% p=	AKI according RIFLE- criteria p=
Gender, male	0,447	0,787
Nikotine abuse	0,445	0,747
Arterial hypertension	0,480	0,785
anamnestic myocardial infarction	0,469	0,779
Obesity	0,466	0,775
Diabetes mellitus	0,428	0,717
Hypertriglyceridemia	0,210	0,935
Hypercholesterinemia	0,154	0,386
Cardiogenic shock	0,627	0,936
Necessity of catecholamines	0,568	0,883
Renal impairment at admission GFR <90ml/min/1,73m^2	0,451	0,787

p= not significant so no special group of patients benefits from Blemaren®- treatment.

Table 4: Overview of Secondary Outcome after Severe Myocardial Infarction

Secondary Outcomes	with Blemaren®	without Blemaren®	p- value
Hospital length of stay in days	11	9	0.146
ICU length of stay in days	7	6	0.372
Hospital mortality, %	16 (48 pts.)	27 (14 pts.)	0.072
One year mortality, %	28 (66 pts.)	43 (16 pts.)	0,081
Two year mortality, %	44 (70 pts.)	61 (16 pts.)	0,137

Comparison of cohorts using U- test, t-test and categorical parameters with chi-square test (hospital mortality, one year mortality, two year mortality), p= not significant so there is no evidential effect on taking Blemaren for secondary outcome, pts. stands for patients.

During the first year after myocardial infarction, 28% of patients who had taken Blemaren® died (66 out of 236 evaluable patients, lost to follow up: 71 patients), whereas 43% of patients without Blemaren® died (16 out of 37 patients, lost to follow up: 15 patients). There was no significant difference in 1-year- mortality between both cohorts (p=0.081), Thus, we conclude that urine alkalization has no improving effect on mortality in the first year after myocardial infarction.

Although only patients of the Blemaren®- group died (4 patients with Blemaren®; 0 patients without taking Blemaren®) in the second year after myocardial infarction, the 2-year mortality was not significantly different (p=0.137). Based on these data we noticed no convincing positive effect of Blemaren®- treatment on 2-year mortality (lost to follow up: 174 patients respectively 48% of the cohort in 2 years of observation). However, the current retrospective analysis was not powered for a mortality analysis.

Cumulative survival with and without Blemaren®-treatment considering lost to follow up is also not significantly different (log rank test p=0.058).

DISCUSSION

The summarized findings of the present study are that the treatment of patients with severe acute myocardial infarction with Blemaren® had no influence on kidney function, development of AKI, creatinine levels or clinical outcomes up to two years.

Examined patients with severe MI (level of CKmax>80 µkat/l) show an accumulation of typical cardiovascular risk factors such as diabetes mellitus, arterial hypertension and increased levels of serum lipids. Whereas various long- term studies on cardiovascular risk exist, specific risk factors for AKI after myocardial infarction have not yet been established. The definition of CRS type 1 indicates that

the kidney damage is caused by the rapid deterioration of cardiac function [19]. The restriction of left ventricular function can be estimated based on echocardiographic parameters such as left ventricular ejection fraction (LVEF) or TAPSE. In our population of patients, we found that a 10% decrease in LVEF is associated with increased odds of 10% for AKI according to RIFLE-criteria. Additionally, the odds in dialysis-necessity even increases by 40%. Consequently, we regard LVEF as a potential predictive marker of AKI after severe myocardial infarction.

In a clinical study of 51 patients, Damman *et al*. demonstrated that renal blood flow depends on cardiac output, but also that right atrial pressure is an independently influencing factor of GFR [6]. We evaluated the echocardiographic parameter TAPSE for the quantitative assessment of right ventricular function in the examined patient groups. The analysis shows that an initial 10 mm higher TAPSE reduces the chance of AKI in myocardial infarction by 60%. Accordingly, restriction of right ventricular function has quite a significant impact on AKI in severe myocardial infarction and might be considered as a risk factor.

Depending on the location of the coronary occlusion, a combined right and left heart failure can develop in the context of myocardial infarction. As a result, both lower renal blood flow as well as venous congestion can occur in the kidneys. Damman *et al*. observed the lowest GFR and thereby the highest risk of AKI, particularly, in patients with this hemodynamic profile [6]. This profile typically exists in cardiogenic shock. Examined patients with cardiogenic shock had an increased risk of AKI according to RIFLE- criteria by 220%, as well as an increased chance of creatinine-increase ≥50% by 10th. The odds ratio of dialysis necessity is also raised considerably by 8- fold. Accordingly, these results confirm the assumption of the research group led by Kevin Damman: Global heart failure with hemodynamic decompensation has the greatest impact on the development of AKI, among all previously considered risk factors.

The insights on myoglobin-induced renal failure offer another approach of AKI- pathogenesis following severe myocardial infarction. Respectively, de Meijer *et al*. demonstrated a connection between elevated serum CK and the development to AKI in patients with median CK- levels around 83µkat/l [20]. Furthermore, the research group of El- Abdellati showed that even a CK activity of about 2,8µkat/l increases the chance of AKI by at least 40% [10]. In agreement with these results, patients in our cohort with a CK- activity level ≥80µkat/l showed a significant correlation between CKmax- level and the formation of AKI according to RIFLE- criteria and creatinine increase ≥50%. In addition, CK activity correlates with chance of dialysis necessity. Therefore, our current analysis is in line with previous studies from de Meijer and El- Abdellati *et al*., which reported the close connection between elevated CK- activity and development of AKI. However, treatment with Blemaren® was without effects.

Furthermore, we examined a raised risk of AKI in patients with already impaired GFR <90ml/min/1,72m^2 on hospital admission. These patients showed a significant higher chance of suffering creatinine increase ≥50%. A GFR impairment of 30ml/min/1.73m^2 doubles the chance of creatinine escalation. The chance of dialysis necessity even rose to 9.2 fold. Similar findings were reported by Palomba *et al*. in patients with enlarged AKI- risk following cardiac surgery. They noticed a tripled chance for subsequent AKI in patients with GFR less than 60ml/min/1.73m^2 before surgery [21].

Currently, there are no other studies on the prevention of AKI in patients with myocardial infarction by urine alkalization using Blemaren®. By contrast, the problem of an increased rate of AKI following cardiac surgery with cardioplegia has been studied from various sides. Critical decrease in renal perfusion is assumed to be one major cause of AKI as it occurs in the context of severe myocardial infarction [22]. One remarkable therapeutic approach for the prevention of postoperative AKI is urine alkalization. Regarding this Haase *et al*. compared creatinine development in patients with intraoperative cardioplegia in a double-blinded, randomized, and controlled trial. The relative creatinine- increase could be significantly affected by sodium bicarbonate infusions [18]. This is contradicted to the results of a prospective study from 2012, which also assessed the development of creatinine in patients after intraoperative cardioplegia. Heringlake *et al*. reported an increased creatinine serum value ≥50% in 9.6% of the patients. This result is similar to our examination on patients with severe myocardial infarction (creatinine increase ≥50%: 7% with Blemaren®-, 10% without treatment, p=n.s.). Furthermore, the relative increase of creatinine was not significantly affected by sodium bicarbonate treatment in these patients [23]. Likewise, Blemaren® did not show any significant effect on creatinine increase ≥50%.

Wijeysundera *et al*. investigated the possible influence of N-acetylcysteine (NAC) on the development of GFR and prevention of type 1 CRS following intraoperative cardioplegia. In their prospective placebo- controlled trial they found a slightly better performance in urine alkalizing group (medially 5% less GFR decrease in NAC -group). In congruence with Wijeysundera's results, we revealed a higher GFR of 2ml/min/1.73m^2 in the Blemaren®-group. Nevertheless, there were no significant differences due to alkalization in both studies [15]. There is no significant association between Blemaren® treatment and the development of GFR (p=0.645). Neither NAC nor Blemaren® seems to be suitable for the prevention of GFR- decline in context of CRS type 1.

According to standard practice, we evaluated AKI using the RIFLE- classification to measure creatinine and estimated GFR changes. Similarly, McGuinness *et al*. investigated the influence of urinary alkalization by sodium bicarbonate in a multicenter double blinded randomized and controlled phase II trial. Similarly, there was no significant difference in the frequency distribution of RIFLE- levels on sodium chloride (p = 0.41). Consequently there was no benefit using bicarbonate for the prevention of AKI in CRS by urinary alkalization [24]. In agreement with these results frequency distribution of patients with urinary alkalization taking Blemaren® are not significantly different (p=0.792). Nearly equal shares of cohorts suffered an AKI according to RIFLE- classification (14% of patients with and 15% without Blemaren®). Therapy with Blemaren® and the occurrence of AKI according to RIFLE- criteria are independent (p=0,792). Therefore it seems plausible that Blemaren®-treatment is not suitable for the prevention of AKI following severe myocardial infarction. Furthermore, it is no longer advisable for the prevention of dialysis in the context of myocardial infarction. These results are in agreement with a placebo- controlled trail examining the prevention of CRS following coronary artery bypass surgery. In this trial Burns *et al*. reported no significant advantages in the frequency of patients on dialysis taking the radical scavenger NAC [25]. Furthermore, no advantage was observed by taking Blemaren® in the prevention of AKI for investigated risk groups (e.g. obesity, diabetes mellitus, and hypercholesterinemia). Accordingly, we cannot recommend Blemaren® to any risk group of patients for the prevention of AKI following severe myocardial infarction.

Besides, the secondary outcome was not significantly affected by Blemaren®. We could not detect any significant effect of Blemaren® on the length of hospital stay. This result is congruent to the findings of McGuinness *et al*., who could not demonstrate any significant impact on urine alkalization to the median length of hospital stay [24]. Even prevention of AKI by NAC in patients with cardiac surgery and cardioplegia showed no significant effect on the length of hospital stay [15]. Pursuant to these results, there is still no appropriate medication to reduce the duration of hospital care in CRS type 1.

Moreover, our study couldn`t demonstrate a significant difference in the mean length of ICU stay between patients with and without treatment, similarly to previous trials [15, 24]. No convincing pharmacological treatment has been found for patients with risk of CRS that can reduce the intensive care period yet.

In our cohort, Blemaren®-treatment did not reduce the odds ratio of in-hospital-mortality following a severe myocardial infarction (p=0.050). Similarly, Heringlake *et al*. could not find any significant differences on hospital mortality due to urine alkalization. In both cohorts, 4 patients died in the hospital (1,3% of placebo- group; 1,4% with bicarbonate- treatment) [23]. In the trial of Burns *et al*., hospital mortality also did not significantly improve by taking NAC following intraoperative cardioplegia [25]. In contrast, a randomized controlled study of nearly 200 patients on NAC-treatment from 2007 showed a significant influence on hospital mortality. Whereas non-patients under treatment passed away, 8% (7 of 87 patients) in the placebo- arm died following cardiac surgery with intraoperative cardioplegia [15]. In the synopsis of several recent studies, data seem to be inconsistent. Further studies of the issue are necessary.

Observing 1-year mortality the cohorts of our study differ not significant (p=0.081). McGuinness found with reference to 90-day mortality of patients after coronary arterial bypass graft also no mortality reducing effect of urine alkalization using sodium bicarbonate (p = 0.61) [24]. Therefore, the approach of urine alkalization does not seem to have an effect on mortality in the first year either in oral or in intravenous administration. Likewise, Blemaren® shows no significant relationship and influence on the development of 2-year mortality (p=0.101).

The cumulative survival, considering the loss of follow up, is not significantly different (p=0.058). Finally, the Blemaren®- treatment is not beneficial for the long-term survival of patients with myocardial infarction.

LIMITATIONS OF THE STUDY

This study has some limitations. As this is a retrospective study on a real life- collective, we had to accept significant differences in patient characteristics. Indeed, it can be assumed that it is a representative cohort with the usual composition of patients with severe myocardial infarction because the observation goes back more than 10 years and involves more than 6000 consecutive patients. Remarkably, there were significant more patients with diabetes mellitus in the group without Blemaren®. Nonetheless this group did not suffer an increased rate of AKI. Even in this constellation treatment with Blemaren® couldn`t demonstrate a positive trend in the group with less diabetics.

One weakness of the study is the small number of patients who didn`t receive Blemaren®-treatment. However, studies on off- label use of medications can be performed for ethical reasons only retrospectively, what amounts to a certain inequality. Because we had to work with the submitted parameters of renal function, we could not use cystatin C for assessing these, even though it reflects the kidney performance more adequately than creatinine and GFR. Cystatin C had not yet been established at the beginning of our study in 2005. Besides, the loss to follow up was high with 174 patients (48%) in the 2 years of follow up. At the same time, there were only a few events to make substantial statements about mortality. Prospective, randomized studies designed with a larger number of patients and a blinded procedure should be performed. However judging from the results of this study and others major effects are unlikely.

Parametric tests of correlation analysis according to Pearson and also linear regression required normal distribution. Some of the patients' characteristics such as age, weight and BMI were not normally distributed. This can shift the level of significance which is why we validated the results of these tests in a multistage procedure. We confirmed the results of parametric U-test by non-parametric t-test to perform further parametric tests of correlation and regression analysis.

CONCLUSION

Overall, we found no convincing effects of the combined preparation of sodium bicarbonate, potassium bicarbonate and citric acid (Blemaren®) on the outcome of patients after severe myocardial infarction. The treatment could not reduce the incidence of AKI not in the whole group of patients nor in risk groups. Also clinical outcomes were not significantly altered. The treatment also had no adverse effect on our patients.

Based on this study, the prescription of Blemaren® in severe myocardial infarction for the prevention of AKI is no longer appropriate.

AUTHORS' CONTRIBUTIONS

A.N. and S.W. acquired the data and conceived and designed the research. A.N., F.M.H. and S.W. performed statistical analysis and drafted the manuscript. R.H.S. and S.W. supervised the patients' analysis and contributed critical revisions to the manuscript.

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DISCLOSURES

None.

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