



## OPEN Analyzing the association of critical illness and cardioversion success in patients with atrial fibrillation at the emergency department

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In critically ill patients with atrial fibrillation (AF), standard treatment algorithms might not be applicable. Emergency departments (ED) play a crucial role in implementing individualized treatment approaches. The aim of this study was to assess the association of lactate and cardioversion success rates in AF patients presenting to an ED. This was a retrospective single-center study analyzing 3535 AF episodes between 2012 and 2022. The main outcome was cardioversion (CV) to sinus rhythm (SR) depending on serum lactate levels (mmol/L). Lactate levels were divided into quintiles (lac < 1.1, 1.1–1.3, 1.4–1.7, 1.8–2.3 and > 2.3 mmol/L). Overall CV success declined with rising lactate levels (SR: lac < 1.1 79% (n = 547), 1.1–1.3 76% (n = 579), 1.4–1.7 73% (n = 562), 1.8–2.3 66% (n = 447), > 2.3 mmol/L 61% (n = 393);  $p < 0.001$ ). Electrical CV (eCV) was conducted in 1021 (SR 95%), medical CV (mCV) in 706 (SR: 72%), facilitated CV in 523 (SR: 88%) and spontaneous conversion was observed in 591 (46% of all patients without treatment) cases. ECV was effective independent of lactate levels (SR: lac < 1.1 96% (n = 225), 1.1–1.3 93% (n = 253), 1.4–1.7 97% (n = 228), 1.8–2.3 92% (n = 154), > 2.3 mmol/L 95% (n = 106);  $p = 0.716$ ). However, for mCV, conversion success decreased with increasing lactate levels (SR: lac < 1.1 84% (n = 95), 1.1–1.3 80% (n = 109), 1.4–1.7 75% (n = 115), 1.8–2.3 67% (n = 93), > 2.3 mmol/L 59% (n = 97);  $p < 0.001$ ). Overall cardioversion success was less likely with rising lactate levels; especially medical cardioversion success rates decreased. Therefore, AF in critically ill may benefit from either electrical cardioversion, treatment of the underlying condition, or primary rate control.

**Keywords** Atrial fibrillation, Dysrhythmia, Cardioversion, Critical illness, Lactate, Emergency medicine

Approximately 20% of intensive care unit (ICU) patients develop a form of dysrhythmia, with atrial fibrillation (AF) being the most common<sup>1–4</sup>. Factors like illness severity and systemic inflammatory response syndrome have been found to be predisposing for AF development<sup>2,5</sup>. AF in critically ill patients has been shown to increase in-hospital- as well as long-term mortality, ICU length of stay, and the risk of stroke and systemic embolism<sup>6–9</sup>. Critically ill patients represent a distinct subgroup of the general AF population, as they are often in a state requiring intermediate or intensive care and therefore standard treatment algorithms may not be applicable. However, data on the management of this specific subgroup is scarce<sup>1,10</sup>.

Emergency departments (ED) play a crucial role in the acute care of AF, as the whole range of disease severity is covered, and initial treatment might have an impact on outcomes<sup>11</sup>. In an ED setting, AF patients require special attention in terms of individualized treatment options and identification of those at risk for further clinical deterioration<sup>12</sup>. However, there is controversy if AF is only a marker of underlying illness severity with no direct associations with outcome, or if it has an impact on mortality itself in these individuals<sup>5,13</sup>. Current literature does not provide a general recommendation for either rhythm- or rate control in critically-ill AF patients,

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since neither treatment has shown superiority<sup>14,15</sup>. Guidelines by the European Society of Cardiology (ESC), the European Resuscitation Council (ERC), and the American Heart Association (AHA) describe electrical cardioversion (eCV) as the therapeutic gold standard in hemodynamic instability in the general AF population and in post-operative AF (POAF)<sup>16–18</sup>. Nevertheless, these recommendations, especially those covering POAF, cannot be directly applied to the overall critical care population, and statements on AF in general critical illness are far less concise<sup>10</sup>. Moreover, eCV success rates in critical illness seem to be low (ranging from 30 to 37%)<sup>19,20</sup>, and identifying potentially reversible AF triggers and treating the underlying condition may be crucial for successful rhythm control<sup>10</sup>.

There is no general marker of critical illness, however, lactate as a surrogate of anaerobic metabolism and oxygen mismatch has been studied extensively in this context<sup>21–23</sup>. Intermediate and high lactate levels were associated with increased mortality in ED patients with symptoms of sepsis. Moreover, lactate was useful for identification of patients requiring urgent medical attention and therefore suggested as a useful biomarker for ED risk stratification<sup>21–23</sup>. However, to our knowledge data on association of AF and lactate in the setting of an ED is to date lacking.

### Study aim

The aim of this study was to analyze the association of AF cardioversion success at different lactate levels as a surrogate of critical illness in ED patients.

### Methods

Of overall 4048 patients, 513 had to be excluded due to missing data. In total, 3535 AF episodes between 01/2012 and 04/2022 were analyzed in this registry-based retrospective analysis. The primary study outcome was CV success (defined as restoration of SR as a direct consequence (<24 h) and achieved via electrical CV (eCV), medical CV (mCV), or facilitated CV) in relation to serum lactate levels in mmol/L. Lactate levels were divided into quintiles (lac < 1.1, 1.1–1.3, 1.4–1.7, 1.8–2.3 and > 2.3 mmol/L).

For eCV, biphasic defibrillators were used in an escalating Joule strategy (100, 150, 200 Joule) following the clinic's respective standard operating procedure (SOP). A maximum of three shocks was applied, and electrode position was anterior-apical in almost all cases.

For mCV, amiodarone, ibutilide and vernakalant were used. Dosing was chosen according to the clinic's SOPs: 300 mg amiodarone were given intravenously (i.v.) and potentially repeated up to a maximum of 900 mg/24 h if primarily unsuccessful. Three mg/kg of i.v. vernakalant were initially administered and repeated with two mg/kg if unsuccessful. One mg of i.v. ibutilide was initially administered and potentially repeated with another one mg if no return of SR occurred. Cardioversion was defined as facilitated if mCV (with one of the above-mentioned drugs) was attempted without return of SR and eCV was then performed consecutively. There is no standardized observation time at our department before proceeding to an eCV. The time that is waited after antiarrhythmic treatment depends on the patient's condition and the overall clinical situation; commonly up to a maximum of 6 h. In total, eight patients were excluded for further analysis because they had received sotalol, ajmaline, or flecainide instead of the above-mentioned drugs, and four patients had received multiple different drugs as subsequent cardioversion attempts (those were included in the respective drug groups). MCV was regarded successful when SR occurred < 24 h.

Conversion to SR was regarded as spontaneous if no attempt of CV was made. Moreover, conversion to SR after either receiving rate controlling agents ( $\beta$ -blockers, non-dihydropyridine calcium channel blockers or digitalis glycosides) and/or after fluid-/electrolyte-substitution was considered spontaneous.

### Study population

This single-center cohort study is based on an observational registry. In this registry, all consecutive patients ( $\geq 18$  years) presenting to the ED of the Medical University of Vienna, Austria, due to an AF episode and who provide written informed consent are prospectively included. For this specific analysis, only patients  $\geq 18$  years who had serum lactate levels drawn were eligible for the further analyses.

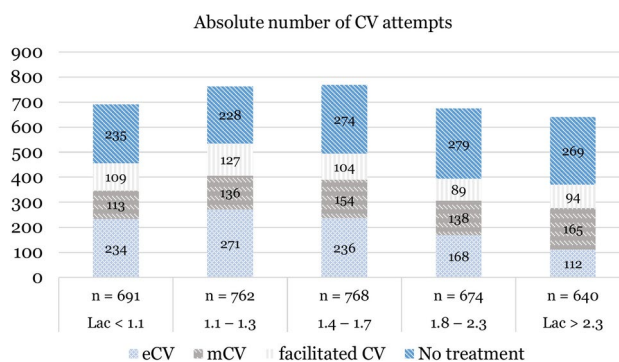
Of all patients ( $n = 4048$ ), 513 had to be excluded due to missing lactate levels. Study fellows then retrospectively document basic characteristics including vital signs and comorbidities. Routine laboratory results are imported automatically from the hospital's electronic patient documentation system. The study protocol complies with the Declaration of Helsinki. All data reporting was conducted in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline<sup>24</sup>. Moreover, the study followed proposed strategies by Worster et al.<sup>25</sup>: Approval for the registry was provided by the Ethics Committee of the Medical University of Vienna. Data acquisition and medical records are described in detail, thus results are reproducible and can be validated. Missing data is addressed above.

### Statistics

For categorical data, absolute and relative frequencies are given. The results are visualized using (grouped) bar charts. For metric variables, medians with interquartile ranges (IQR) are provided in tabular form. Pearson's chi-squared test was used to compare the conversion success of different groups. Calculations were performed with the statistical software R (RStudio Version 1.2.5033, RStudio Inc., Boston, MA, U.S.A.). A two-sided  $p$ -value of < 0.05 was considered as statistically significant.

Lactate levels (mmol/L)	Overall n = 3535	Lac < 1.1 n = 691	1.1–1.3 n = 762	1.4–1.7 n = 768	1.8–2.3 n = 674	Lac > 2.3 n = 640
Age, years [IQR]	68 [58–76]	67 [56–74]	68 [56–75]	68 [58–76]	69 [59–76]	69 [60–76]
Male gender, n (%)	1982 (56)	349 (51)	423 (56)	418 (54)	390 (58)	402 (63)
BMI, kg/m <sup>2</sup> [IQR]	26.9 [23.9–30.9]	26.5 [23.6–31.0]	27.0 [24.4–30.9]	26.8 [23.8–30.1]	27.4 [23.9–31.2]	26.8 [23.5–30.8]
HR max, bpm [IQR]	131 [112–148]	125 [104–139]	125 [107–141]	133 [115–148]	136 [116–150]	140 [120–158]
HR mean, bpm [IQR]	126 [105–145]	117 [99–134]	121 [100–138]	128 [109–146]	131 [111–147]	137 [115–157]
Systolic BP, mmHg [IQR]	133 [120–150]	134 [120–150]	134 [120–150]	132 [120–150]	134 [120–150]	130 [113–149]
NT-proBNP, ng/L [IQR]	1078 [365–2674]	873 [317–2012]	938 [341–2237]	1092 [368–2700]	1099 [346–2854]	1626 [478–3790]
Potassium, mmol/L [IQR]	4.0 [3.7–4.3]	4.0 [3.8–4.3]	4.0 [3.7–4.3]	4.0 [3.7–4.3]	4.0 [3.7–4.3]	4.0 [3.7–4.4]
Creatinine, mg/dl [IQR]	1.00 [0.85–1.20]	0.98 [0.85–1.13]	0.97 [0.84–1.15]	0.99 [0.82–1.20]	1.02 [0.85–1.24]	1.09 [0.91–1.34]
pH, [IQR]	7.40 [7.37–7.43]	7.40 [7.38–7.42]	7.40 [7.38–7.43]	7.40 [7.37–7.43]	7.40 [7.37–7.43]	7.38 [7.34–7.43]
Arterial hypertension, n (%)	2223 (63)	420 (61)	478 (63)	483 (63)	430 (64)	412 (64)
Heart failure, n (%)	678 (19)	118 (17)	145 (19)	148 (19)	126 (19)	141 (22)
Diabetes mellitus, n (%)	551 (16)	57 (8)	83 (11)	112 (15)	129 (19)	170 (27)
History of stroke, n (%)	203 (6)	38 (5)	43 (6)	43 (6)	36 (5)	43 (7)
COPD, n (%)	325 (9)	67 (10)	54 (7)	65 (8)	51 (8)	88 (14)

**Table 1.** Study population characteristics—overall and stratified into lactate level groups. Variables are presented as counts (n), relative percentages (%), medians and interquartile ranges (IQR). Variables are given for the overall population and then divided into lactate quintiles of < 1.1 mmol/L, 1.1–1.3 mmol/L, 1.4–1.7 mmol/L, 1.8–2.3 mmol/L and > 2.3 mmol/L. Abbreviations: COPD: chronic obstructive pulmonary disease.



**Fig. 1.** Absolute numbers of cardioversion (CV) attempts (successful and non-successful) stratified into lactate quintiles. ECV = electrical cardioversion; mCV = medical cardioversion; facilitated cardioversion = mCV and eCV subsequently; “no treatment” = except fluids/electrolytes.

## Results

### Characteristics of the overall study population

All in all, 3535 individuals were included for analysis. Table 1 presents basic study population characteristics as a total overview, as well as stratified into lactate level subgroups.

### Cardioversion attempts

Absolute numbers of CV attempts are presented in Fig. 1. A decrease in the number of eCV attempts with rising lactate levels could be seen: 234 patients (34%) underwent eCV in the group of lac < 1.1 mmol/L in comparison to 112 patients (18%) in the quintile with the highest lactate levels of > 2.3 mmol/L ( $p < 0.001$ ). MCV attempts were rising with increasing lactate: 113 (16%) in lac < 1.1 mmol/L vs. 165 (26%) in lac > 2.3 mmol/L. In patients receiving no treatment a difference between lactate groups was seen, but no specific tendency with increasing or decreasing lactate was found. In facilitated CV no significant difference was found ( $p = 0.292$ ).

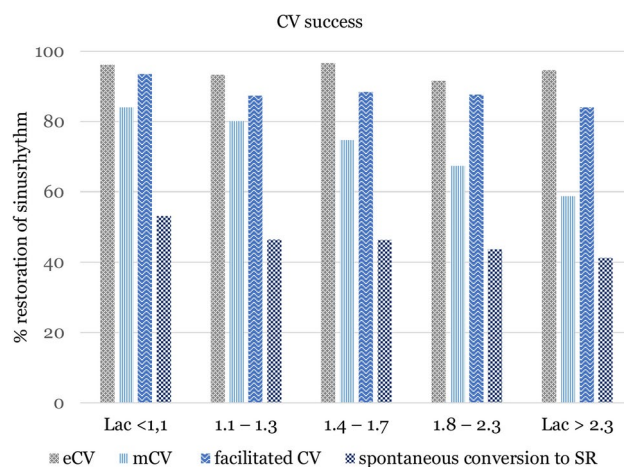
### Cardioversion success

Of the 3535 analyzed patients, 2732 (77%) patients successfully converted to SR. Cardioversion success rates are presented in Table 2. In general, overall conversion to SR was less likely with rising lactate levels: Cardioversion success decreased from 79% for lac < 1.1 mmol/L to 61% for lac > 2.3 mmol/L ( $p < 0.001$ ).

ECV was conducted in 1021 patients (successful conversion to SR in 95%), mCV was conducted in 706 (SR 72%), and facilitated CV in 523 (SR 88%) individuals. Spontaneous conversion to SR was observed in 591 (46% of all patients without treatment) cases. For eCV, no significant difference was seen in relation to lactate levels (SR: lac < 1.1 mmol/L 96% vs. lac > 2.3 mmol/L 95%;  $p = 0.716$ ). However, for mCV, conversion

Lactate levels (mmol/L)	Overall n = 3535	< 1.1 n = 691	1.1–1.3 n = 762	1.4–1.7 n = 768	1.8–2.3 n = 674	> 2.3 n = 640	p-values
Overall CV success, n (%)	2528 (72)	547 (79)	579 (76)	562 (73)	447 (66)	393 (61)	<b>&lt; 0.001</b>
eCV, n (%)	1021 (29)	234 (34)	271 (36)	236 (31)	168 (25)	112 (18)	<b>&lt; 0.001</b>
SR, n	966	225	253	228	154	106	0.156
(% eCV)	(95)	(96)	(93)	(97)	(92)	(95)	
mCV, n (%)	706 (20)	113 (16)	136 (18)	154 (20)	138 (21)	165 (26)	<b>&lt; 0.001</b>
SR, n	509	95	109	115	93	97	<b>&lt; 0.001</b>
(% mCV)	(72)	(84)	(80)	(75)	(67)	(59)	
Facilitated CV, n (%)	523 (15)	109 (16)	127 (17)	104 (14)	89 (13)	94 (15)	0.292
SR, n	462	102	111	92	78	79	0.315
(% facilitated CV)	(88)	(94)	(87)	(89)	(88)	(84)	
No treatment, n (%)	1285 (36)	235 (34)	228 (30)	274 (36)	279 (41)	269 (42)	<b>&lt; 0.001</b>
SR, n	591	125	106	127	122	111	0.094
(% no treatment)	(46)	(53)	(47)	(46)	(44)	(41)	

**Table 2.** Cardioversion (CV) success rates for lactate quintiles. Relative counts in percent are given for the respective lactate subgroups, as well as the relative counts in percent of successful CV to sinus rhythm (SR) in each CV-group. ECV = electrical cardioversion; mCV = medical cardioversion; facilitated CV = mCV and eCV subsequently; “no treatment” = except fluids/electrolytes. Significant values are in bold.



**Fig. 2.** Cardioversion (CV) success for the groups of electrical CV, medical CV, facilitated CV (mCV + eCV), and spontaneous conversion to sinus rhythm (SR) stratified into lactate quintiles.

success decreased with increasing lactate levels (SR: lac < 1.1 mmol/L 84% vs. lac > 2.3 mmol/L 59%;  $p < 0.001$ ). Graphical illustration of cardioversion success rates is presented in Fig. 2.

### Cardioversion drugs

Amiodarone was used in 56% of mCV and was shown to be less effective in rising lactate levels (63% SR in lac < 1.1 mmol/L vs. 49% in lac > 2.3 mmol/L;  $p = 0.126$ ). Ibutilide (SR 94%) and vernakalant (SR 99%) were shown to be effective, irrespective of lactate levels. Cardioversion success rates of the respective drugs are presented in Table 3.

### Discussion

In the current study, we could show that overall CV success rates in an ED setting seem to decline with the severity of critical illness, surrogated via lactate levels. Identifying patients at risk for further deterioration and specific subgroups of acutely ill individuals seems crucial for a personalized AF management<sup>26,27</sup>. However, specific recommendations of either rhythm- or rate control in management of subgroups are to date lacking<sup>16</sup>. Data extrapolated from studies involving non-critically ill populations might not be fully applicable, and the specific ED setting is often not assessed at all<sup>10,11,28</sup>.

In our study population, general CV success declined with rising lactate levels. This is comparable to data highlighted in the “European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in the critically ill and post-surgery patient”, where reported CV

Lactate levels (mmol/L)	Overall study population	Lac < 1.1	1.1–1.3	1.4–1.7	1.8–2.3	Lac > 2.3	<i>p</i> -values
		n = 113	n = 136	n = 154	n = 138	n = 165	
Amiodaron, n (%)	395 (11)	46 (41)	56 (41)	77 (50)	86 (62)	130 (79)	<b>&lt; 0.001</b>
SR, n (%)	207 (52)	29 (63)	32 (57)	40 (52)	43 (50)	63 (49)	0.662
Ibutilide, n (%)	159 (4)	33 (29)	40 (29)	40 (26)	26 (19)	20 (12)	<b>&lt; 0.001</b>
SR, n (%)	150 (94)	32 (97)	36 (90)	38 (95)	26 (100)	18 (90)	0.388
Vernakalant, n (%)	148 (4)	32 (28)	37 (27)	34 (22)	26 (19)	19 (12)	<b>0.003</b>
SR, n (%)	146 (99)	32 (100)	35 (95)	34 (100)	26 (100)	19 (100)	0.193

**Table 3.** Overview of used cardioversion drugs stratified into lactate quintiles. The lines named “SR” (= sinus rhythm) mean the fraction of successful conversion to SR after drug administration in the respective drug group. Significant values are in bold.

success rates in critical illness were shown to be as low as 30 to 37%<sup>10</sup>. The effect of worsening CV success rates in our study was mostly carried by the mCV success rates. ECV success was—irrespective of lactate levels—higher (up to 96%) than estimated when comparing with previous data, where success rates range from 71% immediately after cardioversion to only 23% at 24 h<sup>10,29</sup>. In contrary, the number of eCV attempts was significantly lower with increasing lactate levels. This might have been due to the need of sedation and concomitant unfavorable hemodynamic or respiratory side effects, but stands in clear contrast to recommendations on the handling of hemodynamically unstable patients<sup>10,16</sup>.

Interestingly, we found an increasing number of mCV attempts with rising lactate levels: 16% in lac < 1.1 mmol/L vs. 26% in lac > 2.3 mmol/L. However, the success of mCV decreased with rising lactate levels. In current literature, an astonishing variation in mCV success rates ranging from 18 to 96% is found, but notably in general AF populations and not critical illness<sup>30,31</sup>. In line with literature<sup>32,33</sup>, amiodarone was used in 56% of mCV attempts in our study—this reflects our impression of clinical practice, where amiodarone is often being used as a first line medication in unclear situations. Amiodarone was less effective with rising lactate levels: 63% SR in lac < 1.1 mmol/L vs. 49% SR in lac > 2.3 mmol/L. In comparison, ibutilide and vernakalant were shown to be effective irrespective of lactate levels. This leaves room for thought about the ideal medication for critically ill AF patients: Vernakalant has in the past produced good results in POAF ICU patients<sup>34</sup>, but has several contraindications. Further randomized trials are warranted to figure out the clinical significance of vernakalant and ibutilide in the critically ill population.

Considering these findings, it can be stated that in evaluation of the ideal treatment approach, several factors have to be taken into account: inciting events, potentially reversible triggers, comorbidities, as well as hemodynamic effects of AF. Our results suggest that in clinical routine, treating the underlying condition potentially triggering AF should be the first step towards optimal management. If the underlying condition is considered to be reversible (and therefore also AF is considered intermittent), rate control could be the preferred initial treatment target. However, for a specific subgroup of critically ill patients, where restoration of SR seems beneficial, an attempt of rhythm control can be made. In this case, eCV seems—after exclusion of potential contraindications—a reasonable option to provide relevant benefits in conversion to sinus rhythm in the setting of an ED with acute and critically ill AF patients.

Moreover, our findings only represent the first step towards comprehensive management of critically ill AF patients since they highlight the need for further studies. As patients acutely presenting to an ED with AF are very heterogeneous, consecutive research should focus on the distinct subgroup of critically ill AF patients. Treatment protocols and optimized strategies are needed to ensure safe and effective management of these patients in the specific setting of an ED. As already mentioned, there is evidence suggesting a potential benefit of vernakalant even in critically ill or postoperative intensive care patients, however, we believe that more data regarding specific conditions potentially triggering AF, like sepsis or myocardial infarction, is warranted to provide future benefit.

### Strengths and limitations

First, our study was conducted at a single-center tertiary care hospital, therefore a clinical practice bias is possible. However, patients presented with a sufficient heterogeneity leading to a real-world study design and making a potential confounder in the inclusion criteria unlikely. Second, the results concerning the medication subgroups in mCV could have been underestimated, and a potential statistical significance might not have been seen. Considering the nature of a retrospective study design, a potential confounder in our study results cannot be excluded.

### Conclusion

Overall cardioversion success was less likely with rising lactate levels in ED patients, and especially medical cardioversion success rates decreased. The effectiveness of electrical cardioversion was, however, not associated with lactate levels. Therefore, AF in the critically ill may benefit from either electrical cardioversion, a primary treatment of the underlying condition, or primary rate control, rather than medical cardioversion attempts. Further research into this specific topic is warranted.



## Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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### Author contributions

Conceptualization, S.S. and J.N.; methodology, J.O.; software J.O.; validation, S.S. J.O. H.D. and J.N.; formal analysis, J.O.; investigation, S.G., M.L.; resources, F.C., A.S.; data curation, S.G., M.L.; writing—original draft preparation, S.G., M.L., S.S.; writing—review and editing, S.S., J.N.; visualization, J.N., P.S.; supervision, H.D., A.S., J.N.; project administration, J.N. All authors have read and agreed to the published version of the manuscript.

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