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Impact of Rate Control in Hospitalized Patients with Atrial Fibrillation and Sepsis

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Corresponding Author:	Marco Proietti, M.D. University of Milan Milan, ITALY
First Author:	Giulio Francesco Romiti
Order of Authors:	Giulio Francesco Romiti Marco Proietti, M.D.



Milan, 13th March 2021

To Professor Giancarlo Agnelli

Editor-in-Chief

European Journal of Internal Medicine

Dear Prof. Agnelli,

RE: Impact of Rate Control in Hospitalized Patients with Atrial Fibrillation and Sepsis

Following your suggestion, we submit the current paper in the form of the “Letter to the Editor”, after having submitted it as a Full Research Paper (Manuscript N. EJINME-D-21-00361). We hope that the manuscript in its current form would be eligible for publication in your authoritative journal.

Patients with atrial fibrillation and sepsis require complex pharmacological management, often characterized by the use of antiarrhythmics. However, at present, there are no clear recommendations that can guide physicians in the choice of these drugs, especially about outcomes. In our study, we investigated the association between the use of antiarrhythmics and intra-hospital outcomes in this complex clinical scenario, through a systematic review and meta-analysis of the literature.

We believe that our study, the first to aggregate the evidence available so far, provides an important summary of current knowledge, and offers clinicians pivotal data to inform their therapeutic choices in this clinical setting. Furthermore, it will represent a benchmark for future studies that aim to investigate this issue, which remains largely unsolved.

Even though we do recognize that the limited number of studies identified limits the solidity and generalizability of our results, we do believe that the lack of evidence we



identified is the most relevant results that can be gathered from this work. In particular in these difficult times we are living, with infectious diseases being one of the most prominent public health issues, is even stronger the need for well-designed studies to establish evidence to inform guidelines and guide clinicians.

We confirm the following: 1) the paper is not under consideration elsewhere, 2) none of the paper's contents have been previously published, 3) all authors had access to all the study data, take responsibility for the accuracy of the analysis, had authority over manuscript preparation and the decision to submit the manuscript for publication and 4) have read and approved the manuscript; 4) the full disclosure of any potential conflict of interest has been made.

Yours sincerely

Marco Proietti MD PhD FESC FEHRA

Assistant Professor in Internal and Geriatric Medicine

Department of Clinical Sciences and Community Health

University of Milan, Italy

Honorary Senior Research Fellow in Cardiology

Liverpool Centre for Cardiovascular Science,

University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool

Impact of Rate Control in Hospitalized Patients with Atrial Fibrillation and Sepsis

Running Head: Rate Control in AF Patients with Sepsis

Giulio Francesco Romiti^{1*} MD, Marco Proietti^{2,3,4*} MD, PhD

¹Department of Translational and Precision Medicine, Sapienza – University of Rome, Rome, Italy; ²Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; ³Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy; ⁴Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom.

Corresponding Author

Marco Proietti MD PhD FESC FEHRA

IRCCS Istituti Clinici Scientifici Maugeri

Via Camaldoli 64, 20138, Milan, Italy

ORCID: 0000-0003-1452-2478

Twitter Handle: @MProiettiMD

e-mail: marco.proietti@unimi.it

*Both authors equally contributed to each aspect of the manuscript.

1 Sepsis is defined as a dysregulated host response to several types of infections¹, still representing
2 a challenging issue in Medicine. Atrial Fibrillation (AF) frequently occurs in patients with sepsis and
3
4 septic shock,² representing one difficult challenge for treating physicians: increased heart rate and
5
6 loss of atrial kick worsen myocardial function and cardiac output.³ Unsurprisingly, AF has been
7
8 consistently associated with worse outcomes in sepsis patients.³
9

10 In this clinical scenario, antiarrhythmics are used to achieve prompt rate or rhythm control.

11 However, which antiarrhythmic represents the most suitable choice in patients with sepsis and AF
12
13 remains unclear. Indeed, several data suggest how the current knowledge and evidence related to
14
15 “usual” AF patients don’t apply easily to sepsis patients.⁴
16
17

18 We conducted a systematic review and meta-analysis, to explore the relationship between the use
19
20 of antiarrhythmics and in-hospital mortality in patients with AF during sepsis, according to the
21
22 Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and
23
24 recommendations.⁵
25
26

27 We performed a systematic literature search on Pubmed and EMBASE databases, from inception
28
29 to 27th October 2020. A set of keywords were combined, including ‘Sepsis’ and ‘Atrial Fibrillation’.
30
31 According to titles and abstracts, all records retrieved were systematically assessed independently
32
33 by two authors and then evaluated for full-text eligibility. We included all studies reporting
34
35 outcomes according to the antiarrhythmic drug received during sepsis (including beta-blockers
36
37 (BBs), non-dihydropyridine calcium channel blockers (CCBs), class I-C antiarrhythmic agents (I-C),
38
39 amiodarone, and digoxin) in patients with AF and sepsis. Data from the studies included were
40
41 extracted independently by two co-authors. We evaluated the risk of bias using the Newcastle-
42
43 Ottawa Scale (NOS) for Cohort Studies:⁶ studies with a NOS ≤ 6 were categorized at high risk of
44
45 bias. Numbers of events and total number of patients were pooled and compared using a random-
46
47 effects model. Pooled estimates were reported as Odds Ratios (OR) and 95% Confidence Interval
48
49 (CI). Additionally, to give the proper account of each study sample-size, we also performed a
50
51 secondary analysis according to fixed-effects models. The inconsistency index (I^2) was calculated
52
53 to measure heterogeneity. All the statistical analyses were performed using R 4.0.3 (The R
54
55 Foundation, 2020).
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1 4,166 studies were retrieved from the literature search; after duplicates removal, 3,717 records
2 were assessed for eligibility. Finally, 68 full-texts were screened, and 2 studies were included in the
3 systematic review and meta-analysis. We added 1 other article according to the author's
4 knowledge, with a total number of 3 studies included⁷⁻⁹. Two studies showed low risk of bias^{7,9},
5 while one study had a high risk, mainly due to selection and comparability sources of bias⁸.
6
7 Walkey and colleagues performed a retrospective, multicenter cohort study⁷ to describe patterns of
8 antiarrhythmics prescription and associated outcomes in AF patients hospitalized with sepsis
9 (59.2% enrolled in an intensive care unit (ICU)). In the final propensity-matched multivariable
10 analysis, use of BBs was associated with reduced hospital mortality compared to other drugs.
11
12 Balik and colleagues performed a retrospective, single cohort study⁸ on the comparison between
13 propafenone, amiodarone, and metoprolol for the treatment of supraventricular arrhythmias (88.5%
14 AF or atrial flutter; 69.7% acute onset AF) in 234 septic shock patients admitted to ICU. The mean
15 (SD) SOFA score was 10.7 (4.0), with 27.3% of patients who underwent renal replacement
16 therapy. While at 28 days there were no significant differences, patients treated with amiodarone
17 showed a significantly lower survival after 12 months.
18
19 Finally, Bosch and colleagues⁹ reported a multicenter retrospective analysis on antiarrhythmics'
20 efficacy in patients with sepsis, AF, and rapid ventricular response. In-hospital mortality was lower
21 among patients treated with digoxin and CCBs compared to those treated with BBs or amiodarone.
22 After pooling studies using random-effects model, no significant differences in term of in-hospital
23 mortality were observed between BBs and CCBs [Figure 1, Panel A] and between BBs and digoxin
24 [Figure 1, Panel B], showing high heterogeneity. When compared to amiodarone, BBs resulted
25 associated with a 45% reduction of in-hospital mortality across three studies, showing no
26 heterogeneity (OR 0.52, 95%CI: 0.46-0.58) [Figure 1, Panel C]. Fixed-effect models showed no
27 difference for the comparison of BBs and amiodarone, and a significant reduction in risk of in-
28 hospital death for BBs compared with CCBs (OR: 0.90, 95%CI: 0.84-0.97) [Figure 1, Panel A] and
29 digoxin (OR: 0.75, 95%CI: 0.70-0.81) [Figure 2, Panel B].
30
31 Our research showed that despite the clinical relevance of this issue, only few studies examined it
32 with no randomized trials and with a limited number of patients. This analysis showed that patients

1 treated with BBs presented a significant reduction of in-hospital mortality compared to amiodarone
2 users; regarding the other comparisons, a trend of lower risk for in-hospital mortality emerged, with
3 fixed-effects suggesting a beneficial effect of BBs even in comparison with CCBs and digoxin. The
4 analysis of the individual studies evidenced controversial data regarding the in-hospital and long-
5 term occurrence of death. Indeed, Walkey and Balik suggested that BBs would be safer in terms of
6 in-hospital mortality^{7,8}, while Bosch and colleagues showed that patients treated with digoxin
7 experienced the lowest mortality rate, even though they did not perform any regression analysis to
8 adjust for baseline characteristics⁹. Given the large difference of sample sizes, we believe that the
9 fixed-effects estimates may suggest a possible beneficial effect of BBs over other antiarrhythmic
10 drugs.
11

12 The individual studies' differences may also offer an interesting perspective about current
13 uncertainties in managing AF during sepsis. Indeed, Walkey et al. enrolled both ICU and non-ICU
14 patients, with an overall higher burden of comorbidities;¹¹ contrarywise, Bosch and colleagues
15 enrolled exclusively ICU patients, with less comorbidities but higher rates of mechanical
16 ventilation⁹. These differences might have driven the differential rates of antiarrhythmic prescription
17 and the consequential impact on outcomes.
18

19 Our study is limited by the low number of studies available, and their non-randomized design.

20 Differences in the study design and indications for the use of different antiarrhythmics may have
21 biased our results; however, we feel it is informative to outline these differences, since it may
22 reflect heterogeneity in these patients' real-world management.
23

24 In the context of a significant lack of evidence, our meta-analysis underlines some significant
25 aspects. We found out that only few, non-randomized studies, examined the impact of rate control
26 drugs on the risk of outcomes. However, our meta-analysis may support the indication of BBs as
27 first-line therapy, suggesting a possible beneficial effect compared to any other agent.
28

29 Notwithstanding this, the most relevant finding is the *urgent need* for more evidence: given the
30 epidemiological relevance of this issue, answers from large randomized clinical trials are pivotally
31 due to inform guidelines and help physicians in daily clinical life.
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AUTHORS CONTRIBUTIONS

GFR and MP had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

GFR and MP both contributed substantially to the conceiving of the study, data analysis and interpretation, and the writing of the manuscript.

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CONFLICT OF INTERESTS

None of the authors declares relevant conflict of interests.

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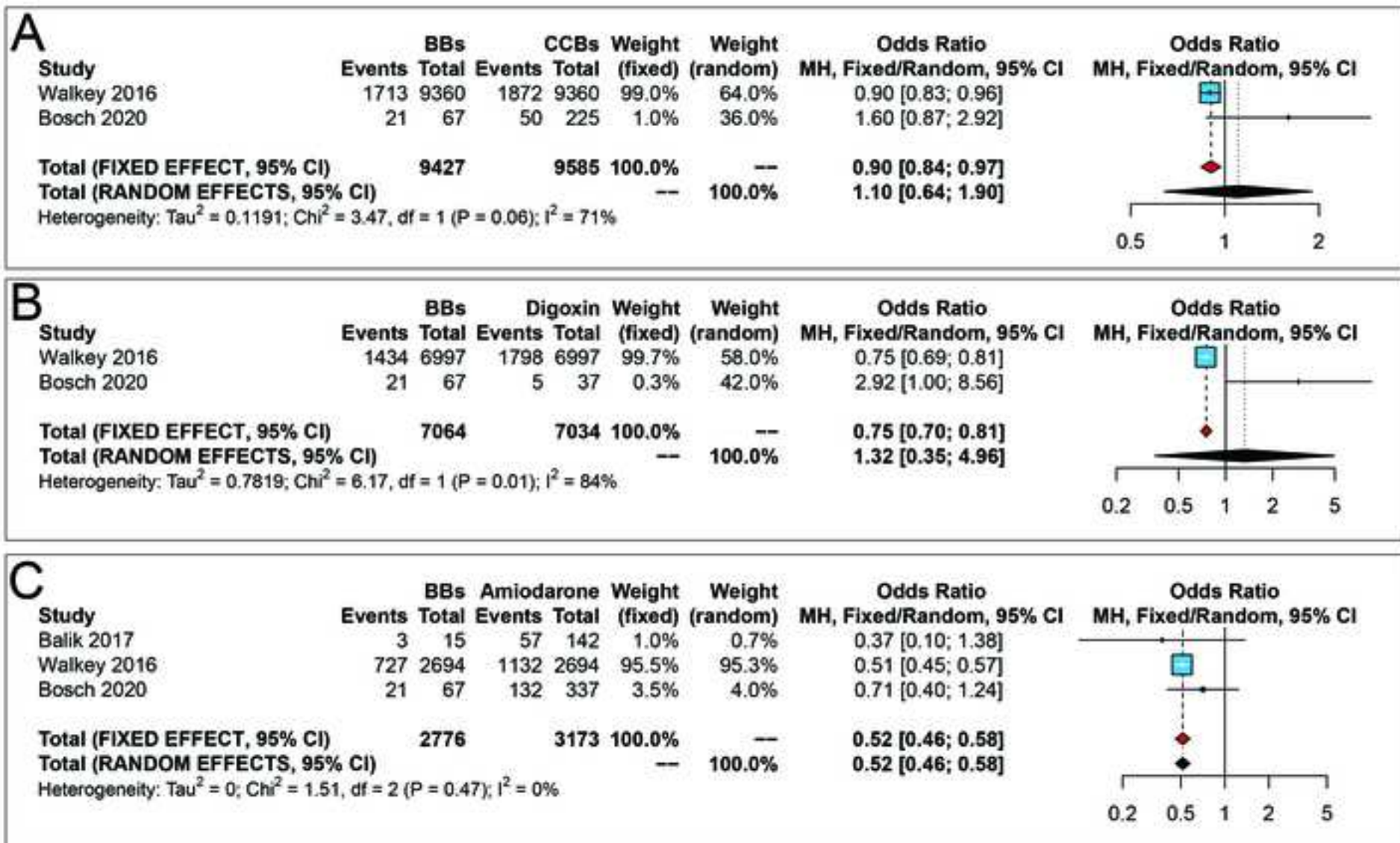
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FIGURE LEGENDS

Figure 1 – Random-Effects and Fixed-Effect Analysis for the Comparison between Antiarrhythmic Drugs for In-hospital Mortality

Legend: BBs= Beta-Blockers; CCB= Calcium-Channel Blockers; CI= Confidence Interval; M-H= Mantel-Haenszel.

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