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Uso de antiagregantes plaquetários numa coorte de doentes críticos/ Antiplatelet use in a cohort of critically ill patients

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TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Antiplatelet use in a cohort of critically ill patients

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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A nós!

Antiplatelet use in a cohort of critically ill patients

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Declarations of interest: none

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Abstract

Objective

Evaluate the association of different antiplatelet drugs and critically ill patients' mortality during their intensive care medicine department (ICMD) stay and global mortality at 28 and 90 days.

Design

Retrospective, descriptive, single center cohort study was performed from January 2014 to December 2014

Setting

A 65 bed ICMD.

Patients

Total of 942 adult patients admitted to the ICMD through the emergency department.

Main variables of interest

Clinical variables at ICU admission were extracted from the medical records. Primary outcomes were ICMD mortality and global mortality at 28 and 90 days. Adjusted mortality with a cox regression was also calculated.

Results

Chronic antiplatelet therapy (APT) had no difference on patient mortality. In patients presenting with infection at admission, stopping their APT had higher ICMD mortality than patients that continued APT (21.4% vs 4.1%, *p*=0.011). Cox regression after adjusting to SAPS II and other variables showed no difference in chronic APT (HR: 1.321, 95%CI: 0.847-2.060) and a lower adjusted mortality in patients receiving APT during ICMD stay (HR: 0.364, 95%CI: 0.203-0.653). Patients receiving acetylsalicylic acid had lower adjusted mortality (HR: 0.272, 95%CI: 0.135-0.551) than patients receiving clopidogrel (HR: 3.396, 95%CI: 1.317-8.761).

Conclusions

Our results show that chronic APT had no effect on patient mortality. Patients presenting with infection at admission, stopping their chronic APT may be detrimental. Patients receiving APT during ICMD stay had lower adjusted mortality. This benefit is present in patients receiving acetylsalicylic acid and not in those receiving clopidogrel.

Keywords

Intensive Care Unit, Antiplatelet Drugs, Mortality

Introduction

The role of platelets in hemostasis and thrombosis has long been studied[1]. There's growing evidence of their importance in inflammation and immunological responses to infection[2]. Critically ill patients with systemic inflammation and sepsis show platelet activation. Such widespread activation results in thrombocytopenia which is associated with a poor outcome [3, 4].

The capability of antiplatelets agents in reducing platelet activation has been hypothesized to have a beneficial effect in critically ill patients. However, after several studies there is still no clear evidence regarding the clinical effect of antiplatelets on critically ill patients during intensive care medicine department (ICMD) stay. A recent meta-analysis by Du F. *et al.* showed that critically ill patients receiving antiplatelet therapy (APT) had reduced mortality compared with the control group, mainly on the subgroup of patients with sepsis[5]. However, other studies found that there is no benefit to patients in receiving APT prior to their ICMD admission and during their ICMD stay.

The aim of this study was to evaluate the effect of different antiplatelet drugs on critically ill patients regarding their ICMD mortality and global patient mortality at 28- and 90-days post admission on an unselected population admitted to an ICMD with critical illness.

Patients and Methods

Subjects and protocol

We performed a retrospective study analyzing the records of 942 adult patients who were admitted between January 1st 2014 to December 31st 2014 to the Intensive Care Medicine Department, with a total of 65 beds, through the emergency department of Hospital de São João, an urban tertiary care centre. The study was approved by the local ethics committee with a waiver of informed consent. Patients transferred from another hospital and those admitted to the neurocritical ward were excluded from this study.

Information regarding the status of APT prior to ICMD admission was obtained from the review of patients record history. Administration of acetylsalicylic acid (ASA), clopidogrel and ticagrelor during ICMD stay was obtained from patients' electronic medical record. Variables needed to calculate Simplified Acute Physiology Score (SAPS) II were recorded within the first 24 hours post ICMD admission. Other variables were collected, such as age, sex, the presence of infection on admission (defined by the prescription of antibiotics or the diagnosis at admission). Emergency medical procedures were recorded, such as use of mechanical ventilation, orotracheal intubation, use of a central venous catheter and use of vasopressor and inotropic drugs.

The primary outcomes of the study were ICMD mortality, mortality rate at the 28th day and mortality rate at the 90th day post ICMD admission.

Statistical analysis

Baseline characteristics of different study groups were assessed by the Chi-square test or Fisher's exact test for categorical variables. Post hoc analysis involved pairwise comparisons using z-test of two proportions or using multiple Fisher's exact tests (2 x 2) with a Bonferroni correction. Normal distribution of continuous variables was evaluated by the Kolmogorov–Smirnov test. Continuous variables were compared with the Wilcoxon-Mann-Whitney test or Krustkal-Wallis H test. Post hoc analysis with pairwise comparisons were performed using Dunn's [6] procedure with a Bonferroni correction for multiple comparisons.

Kaplan-Meier survival analysis [7] was conducted to compare the four different APT groups for their effectiveness decreasing mortality. A log-rank test was conducted to determine if there were differences in the survival distributions for the different types of APT.

Effects of APT on outcomes were further examined by multivariate Cox proportional hazards models [8]. Model were constructed by analyzing crude HR and including variables with a $p<0.20$ or that had biological plausibility. Endpoints of the survival analyses were date of admission to ICMD as the starting point and patients were follow up till 90 days post ICMD admission.

Statistical significance was defined at $p<0.05$. Statistical analysis was performed using SPSS™ software version 25.

Results

A total of 942 patients were included in the study. Of those, 282 patients were receiving antiplatelet drugs prior to their admission to the ICMD, 232 patients were receiving ASA (maximum dosage 160 mg/day), 82 were receiving clopidogrel 75mg/day and 2 were receiving ticagrelor 90mg/day. During the ICMD stay, 193 patients received ASA, 73 received clopidogrel and 22 received ticagrelor, resulting in 216 patients receiving antiplatelet drugs during ICMD stay. A total of 56 patients were treated with both ASA and clopidogrel.

Patients without antiplatelet therapy during ICMD stay had similar mortality as patients who received any antiplatelet drug during ICMD, particularly ICMD mortality (15.3% vs 11.8%; $p = 0.202$), global mortality at 28 days (14.4% vs 12.1%; $p = 0.402$) and global mortality at 90 days (21.8% vs 21.0%; $p = 0.805$), respectively. Regarding the APT status prior to ICMD admission, patients that didn't have any APT prior to ICMD admission had similar mortality as patients who were on chronic antiplatelet therapy prior to ICMD admission, particularly ICMD mortality (14.3% vs 15.0%; $p = 0.790$), global mortality at 28 days (14.2% vs 13.2%; $p = 0.677$) and 90 days (20.8% vs 23.6%; $p = 0.347$), respectively.

Patients were then grouped into 4 different groups accordingly to their APT status to understand possible effects of change of status of APT (A- patients not exposed to any APT; B- patients that started APT during ICMD stay; C- patients receiving chronic antiplatelets that stopped APT on ICMD admission; D- patients that maintained APT during their ICMD stay). Baseline characteristics between different APT groups can be seen in Table 1. Median SAPS II scores were significantly different between patients not exposed to APT and patients who stopped APT during ICMD stay (33 vs. 36, $p = 0.010$), respectively. No significant difference in ICMD mortality, global mortality at 28 and 90 days and length of stay (LOS) was seen between different APT groups. When comparing only the subset of patients who presented with infection at admission, patients who stopped APT had higher ICMD mortality than those that kept APT (21.4% vs 4.1%, $p=0.011$), respectively. In this subset of patients, no significant difference in global mortality at 28 and 90 days and LOS was seen between any groups.

We then compared the effects of ASA and clopidogrel therapy during ICMD stay, to differentiate individual antiplatelet drugs and ICMD patient's mortality. Patients were again divided into 4 different groups (no APT during ICMD, only ASA during ICMD, only clopidogrel during ICMD and patients taking both drugs during ICMD stay). Patients who were receiving only ASA had lower ICMD mortality than patients taking both ASA and clopidogrel (7.3% vs 23.2%, $p=0.002$).). No difference in global mortality at 28 days, mortality at 90 days and LOS was seen between different APT drugs during ICMD stay. Patients taking both ASA and clopidogrel also had higher rate of cardiopulmonary resuscitation than patients receiving only clopidogrel (12.5% vs 0%) or patients not receiving any APT (12.5% vs 1.9%, $p<0.05$). Different patient characteristics according to APT drugs during ICMD stay can be seen in Table 2.

Kaplan-Meier survival analysis was conducted to compare the different APT groups mortality. The survival distributions for the different groups were not significantly different ($p=0.228$), survival curves are portraited in Figure 1. To minimize the effect of cofounding variables, Cox regressions were constructed, adjusting for several variables, namely patient age, gender, SAPSII score , maximum lactate level in first 24 hours, presence of infection at admission, several emergency department procedures (arterial line placement, cardiopulmonary resuscitation, central venous catheter placement, inotropic therapy, mechanical ventilation, orotracheal Intubation, vasopressor therapy) and non-programmed surgery. Both crude and model adjusted hazards ratio (HR) can be seen in Table 3 and Table 4. While the adjusted model showed no difference on the HR of patients with chronic APT prior to ICMD admission, patients receiving APT during their ICMD stay had a decrease in the expected hazard of approximately 64%. Cumulative patient survival curves for APT

during ICMD stay adjusted with Cox regression are represented in Figure 2. Comparing the individual antiplatelet agents, patients receiving clopidogrel during ICMD stay had a risk of death more than 3 times greater than those who didn't receive clopidogrel. Patients receiving ASA during ICMD stay, had a decrease in the expected hazard of approximately 74 %. Patients on Ticagrelor showed no significant HR in the model. No difference in HR was seen regarding the usage of ASA, clopidogrel and ticagrelor prior to ICMD admission. Cumulative patient survival curves for therapy during ICMD stay with ASA and clopidogrel, adjusted with Cox regression, can be seen in Figure 3. Using the previously constructed model to evaluate the mortality of patients receiving double antiplatelet therapy during ICMD, the adjusted HR 0.813, 95%CI 0.392-1.686, *p*=0.577) showed no significant value.

Discussion

Prior studies have shown mixed results when comparing the effect of ATP on ICMD patient mortality. Some studies suggested that chronic antiplatelets may reduce patient mortality upon ICMD admission [5, 9]. Contrary findings by Wiewel et al.[10] whom with a propensity-matched analysis, showed no benefit of chronic ASA on critically ill patients during ICMD stay. Our study showed no difference in ICMD mortality and global patient mortality when comparing patients on chronic antiplatelet therapy.

We observed no mortality difference, when comparing the effect of APT therapy during ICMD stay. The fact that the groups showed differences in their baseline characteristics is an important consideration, mainly the higher SAPS II score and number of emergency department procedures on patients that stopped their APT upon ICMD admission.

When analyzing the subset of patients presenting with an infection on admission, we found that patients that stopped chronic APT upon ICMD admission had higher ICMD mortality than patients that continued APT during their ICMD stay. This result is somewhat concordant with the findings of Tsai et al. [11] and Fuchs et al.[12] who've seen a beneficial effect of antiplatelet therapy during ICMD on septic patients.

To try to better understand the difference on mortality of the different patients, a Kaplan-Meier survival analysis was conducted. No global difference was seen in the different APT groups. Trying to minimize possible confounding effects and adjusting to the different baseline characteristics of patients, namely the significant difference on SAPS II score between APT groups and different emergency department procedures, a Cox regression model was built. As previously mentioned, the adjusted HR of patients receiving APT during their ICMD stay were significantly lower, exhibiting a decrease of their expected hazard of approximately 64%. No difference was seen regarding the status of APT prior to admission. This could indicate a beneficial effect of APT on patients during their ICMD stay.

There is however compelling evidence showing a lower clinical efficacy of clopidogrel on critically ill patients. A recent clinical trial [13] showed that up to 80 % of critically ill patients responded poorly to clopidogrel treatment, with lower levels of clopidogrel active metabolite and perhaps an increased risk of cardiovascular complications. To better understand that phenomenon, we tried to differentiate the individual effect of clopidogrel versus ASA during ICMD stay and their effects on patient mortality. Despite lower crude ICMD mortality of patients receiving only clopidogrel during ICMD stay, no significant difference when comparing crude mortality at 28 and 90 days and crude hazards ratio was seen on global mortality. When using the Cox regression model adjusted for the previously mentioned confounding variables, we found that patients receiving clopidogrel during ICMD stay had a much higher risk of death than patients receiving ASA. The chronic use of ASA or clopidogrel prior to ICMD admission showed no significant difference in the crude or adjusted hazard ratio. These findings may imply that any beneficial effect of APT during ICMD is drug dependent. Clopidogrel appears to lack the beneficial effects of ASA in reducing patient mortality.

Some of this may be explained by the different patient characteristics, possibly with worse morbidities and different diseases. Double antiplatelet therapy is usually used in acute coronary syndrome and the higher model adjusted HR in patients receiving clopidogrel may only show a worse overall disease severity of this patients. However, when using the Cox regression model to evaluate the mortality of patients receiving double antiplatelet therapy during their ICMD stay, the adjusted HR showed no significant value (0.813, 95%CI 0.392-1.686, p=0.577). This fact may show

that, when adjusted to the model variables, patients receiving double APT had no difference in mortality. Considering this, it's clear that more studies are needed to clarify this finding and if other P2Y12 inhibitors also exhibit this effect.

As with every study, several limitations can be pointed out in ours. As a retrospective cohort, the lack of control of intervention limits the ability to adjust to confounding variables. The fact that several of the comparing groups didn't have the same size, somewhat hinders the validity of our findings. By using several covariate variables such as SAPSII, a score that showed to correlate to patient mortality and severity of illness, we can somewhat limit such confounding effect. Despite that, the lack of any information on other chronic medication use, no clear delimitation of patients with diagnostic of sepsis and no information of comorbidities is a clear limitation on our analysis that we cannot totality adjust for. The most evident of all is the lack of data on cause of patient admission, namely atherosclerotic disease, diagnosis of cardiovascular disease and acute coronary syndrome. We tried to overcome this handicap by adjusting for the other variables with the Cox regression model and by comparing the HR of patients receiving double APT as a surrogate variable of patients an ICMD secondary to an acute coronary syndrome.

In conclusion, in this study, chronic antiplatelet use prior to ICMD admission appears to lack an effect on reducing mortality of critically ill patients. We've seen that different antiplatelet agents possibly have different effects on critically ill patients. During ICMD stay, APT in general and particularly ASA, has shown to reduce the mortality of patients, when adjusted for confounding variables. Besides that, after admission, patients presenting with infection that continued their chronic APT during ICMD stay had lower mortality. There is an evident need for randomized control trials, as the ongoing clinical trial ANTISEPSIS [14], to clarify the effects on patient mortality and morbidity of different antiplatelet agents prior to admission and during ICMD stay, and their possible effect on septic patients.

Contribution of the authors

SA did the statistical analyses, analyzed and interpreted the data, made several drafts of the manuscript text body, the tables and figures and revised these several times. PM revised the manuscript critically, made a major contribution to the design and interpretation of the data. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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Tables

Table 1 Baseline characteristics the different groups according to their APT status prior and during ICMD stay

Variable	No APT exposure n=588	Started APT on ICMD admission n=72	Stopped APT on ICMD admission n=138	Continued APT on ICMD admission n=144	*p*
Age, years, median [IQR]	65 [51-78] [a]	71.5 [58-81.75] [a,c]	77.5 [67-83.25] [b,c]	74 [66-81.75] [b]	< .001
Gender. Male, n (%)	304 (51.7) [a]	44 (61.1) [a,b]	68 (49.3) [a]	91 (63.2) [b]	.031
ICMD mortality, n (%)	80 (13.6)	10 (13.9)	26 (18.8)	15 (10.4)	.129
Mortality 28 days, n (%)	81 (14.0)	11 (15.7)	22 (16.1)	15 (10.4)	.533
Mortality 90 days, n (%)	119 (20.6)	16 (22.5)	37 (27.0)	29 (20.3)	.408
ICMD LOS, median [IQR]	3.00 [2-5]	3.00 [2-5]	3.00 [1-5]	3.00 [2-5]	.425
Hospital LOS, median [IQR]	10.00 [6-18]	9.50 [6-14.75]	11.00 [7-19.25]	10.00 [6-15]	.573
ICMD readmission, n (%)	40 (6.8)	3 (4.2)	13 (9.4)	11 (7.6)	.531
Infection, n (%)	203 (34.5)	19 (26.4)	43 (31.2)	50 (34.7)	.503
Severity of disease in first 24 h					
SAPSII score, median [IQR]	33 [24-45] [a]	34.5 [24.-45.5] [a, b]	36 [30-47.25] [b]	35[27.25-46] [a, b]	.006
Max Lactate level, median [IQR]	1.94 [1.19-3.54]	3.25 [1.18-6.9]	1.94 [1.12-3.33]	1.88 [1.06-2.79]	.053
Procedures on ED					
CPR, n (%)	10 (1.7) [a]	12 (16.7) [b]	4(2.9) [a]	3(2.1) [a]	< .001
CVC placement, n (%)	91 (15.5)	13 (18.1)	22 (15.9)	19 (13.2)	.811
Arterial line placement, n (%)	131 (22.3)	20(27.8)	26(18.8)	31(21.5)	.524
Orotracheal Intubation, n (%)	89 (15.1) [a, b]	19 (26.4) [b]	12(8.7) [a]	15(10.4) [a]	.003
Mechanical Ventilation, n (%)	93(15.8) [a]	21(29.2) [b]	13(9.4) [a]	18(12.5) [a]	.002
Noninvasive Ventilation, n (%)	116(19.7) [a]	22(30.6) [a, b]	25(18.1) [a]	53 (36.8) [b]	< .001
Vasopressor therapy, n (%)	53 (9.0) [a]	15 (20.8) [b]	21 (15.2) [a, b]	11 (7.6) [a]	.003
Inotropic therapy, n (%)	6 (1.0) [a]	4 (5.6) [a]	5 (3.6) [a]	3 (2.1) [a]	.013
Non-programmed surgery, n (%)	145 (27.7)	21 (29.2)	35 (25.4)	23 (16.0)	.092
Admission type					
Medical, n (%)	446 (75.9)	68 (94.4)	110 (79.7)	140 (97.2)	#
Emergent Surgery, n (%)	42 (7.1)	0 (0)	12 (8.7)	1 (0.7)	#
Trauma, n (%)	52 (8.8)	1 (1.4)	11 (8.0)	0 (0)	#
Neurocritical, n (%)	39 (6.6)	3 (4.2)	4 (2.9)	3 (2.1)	#
Pot Organ Donor, n (%)	9 (1.5)	0 (0)	1 (0.7)	0 (0)	#

Abbreviations: APT, antiplatelet therapy; CPR, cardiopulmonary resuscitation; CVC, Central venous catheter; ED, emergency department; ICMD, intensive care medicine department; IQR, interquartile range; LOS, length of stay.

Notes: Each superscript letter denotes a subset of patients with different APT status whose column proportions do not differ significantly from each other at the 0.05 level. e.g. both columns containing "[a]" are not significantly different, while one column with "[b]" and other with "[b]" are significantly different.

#- unable to compute *p* value

Table 2 Characteristics of patients comparing different drugs during ICMD stay

Variable	No APT during ICMD n= 715	ASA during ICMD n= 135	Clopidogrel during ICMD n=17	ASA and Clopidogrel during ICMD n=56	*p*
Age, years, median [IQR]	68.5 [54-80] [a]	74 [65.5-83.5] [b]	71 [59.5-83.5] [a,b]	56 [62.25-77.75] [a,b]	< .001
Gender. Male, n (%)	372 (51.2) [a]	84 (61.3) [a]	12 (70.6) [a]	35 (62.5) [a]	.034
ICMD mortality, n (%)	106 (14.6) [a, b]	10 (7.3%) [a,]	1 (5.9) [a, b]	13 (23.2) [b]	.037
Mortality 28 days, n (%)	103 (14.4)	14 (10.4)	1 (5.9)	10 (17.9)	.360
Mortality 90 days, n (%)	156 (21.8)	23 (17.0)	4 (23.5)	17 (30.4)	.237
ICMD LOS, median [IQR]	3 [2-5]	3 [2-5]	3 [2-5.5]	3 [2-5.75]	.368
Hospital LOS, median [IQR]	10 [6-18.25]	10 [6-15]	6 [6-23]	9.5 [6-14]	.790
Infection, n (%)	246 (33.9) [a, b]	49 (35.8) [a, b]	9 (52.9) [b]	11 (19.6) [a]	.045
Severity of disease in first 24 h					
SAPSII score, median [IQR]	34 [25-45]	35 [27-46]	35 [28.5-40.5]	37.5 [25.25-48]	.375
Max Lactate level, median [IQR]	1.94 [1.17-3.51] [a, b]	2 [1.08-3.08] [a, b]	1.3 [0.8-1.5] [a]	2.42 [1.75-6.48] [b]	.007
Procedures on ED					
CPR, n (%)	14 (1.9) [a]	8 (5.8) [a, b]	0 (0) [a, b]	7 (12.5) [b]	< .001
CVC placement, n (%)	113 (15.6) [a]	18 (13.1) [a]	0 (0) [a]	14 (25) [a]	.056
Arterial line placement, n (%)	157 (21.6)	30 (21.9)	1 (5.9)	19 (33.9)	.071
Orotracheal Intubation, n (%)	101 (13.9) [a]	18 (13.1) [a]	0 (0) [a]	15 (26.8) [a]	.022
Mechanical Ventilation, n (%)	106 (16.6) [a]	22 (16.1) [a]	0 (0) [a]	16 (28.6) [a]	.015
Noninvasive Ventilation, n (%)	141 (19.4) [a]	53 (38.7) [b]	5 (29.4) [a, b]	16 (28.6) [a, b]	< .001
Vasopressor therapy, n (%)	74 (10.2)	15 (10.9)	0 (0)	11 (19.6)	.092
Inotropic therapy, n (%)	11 (1.5)	3 (2.2)	0 (0)	4 (7.1)	.057
Non-programmed surgery, n (%)	180 (24.8)	23 (16.8)	3 (17.6)	16 (28.6)	.153

Abbreviations: ASA, acetylsalicylic acid; APT, antiplatelet therapy; CPR, cardiopulmonary resuscitation; CVC, Central venous catheter; ED, emergency department; ICMD, intensive care medicine department; IQR, interquartile range; LOS, length of stay.
Notes: Each subscript letter denotes a subset of patients with different APT status whose column proportions do not differ significantly from each other at the 0.05 level

Table 3 Hazard ratios for mortality within 90 days after admission using Cox proportional hazards regression.

	Crude HR			Model adjusted HR[a]		
Variable	HR	95% CI	*p*	HR	95% CI	*p*
Age, years	1.014	1.003-1.025	0.016	1.007	0.992-1.023	0.334
Gender, male	1.362	0.959-1.935	0.085	1.373	0.912-2.067	0.128
SAPS II score	1.059	1.048-1.069	<0.0005	1.040	1.024-1.056	<0.0005
Max Lactate level	1.099	1.064-1.136	<0.0005	1.051	0.999-1.105	0.053
Home APT	1.062	0.734-1.537	0.749	1.321	0.847-2.060	0.220
ICMD APT	0.779	0.504-1.204	0.260	0.364	0.203-0.653	0.001
Infection	0.907	0.627-1.312	0.604	0.927	0.604-1.425	0.731
Non-programmed surgery	2.968	2.104-4.185	<0.0005	1.742	1.131-2.682	0.012
MV	5.358	3.790-7.574	<0.0005	0.784	0.247-2.493	0.681
ED CVC placement	3.609	2.529-5.150	<0.0005	0.796	0.419-1.511	0.485
ED Arterial line placement	3.106	2.200-4.385	<0.0005	0.867	0.467-1.610	0.652
ED Orotracheal Intubation	5.563	3.929-7.877	<0.0005	2.638	0.817-8.519	0.105
ED Mechanical Ventilation	5.358	3.790-7.574	<0.0005	0.784	0.247-2.493	0.681
ED Vasopressor therapy	5.400	3.755-7.766	<0.0005	1.394	0.753-2.579	0.290
ED Inotropic therapy	3.292	1.537-7.050	0.002	1.070	0.429-2.669	0.885
ED CPR	4.731	2.666-8.395	<0.0005	0.915	0.432-1.939	0.817

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ED, emergency department; HR, hazard ratio;
Notes: [a]- The model of Cox proportional hazards regression included age, gender, SAPSII score , maximum lactate level in first 24 hours, infection at admission, emergency department procedures (arterial line placement, cardiopulmonary resuscitation, central venous catheter placement, inotropic therapy, mechanical ventilation, orotracheal Intubation, vasopressor therapy), non-programmed surgery and chronic treatment with antiplatelet agents prior to hospital admission and during ICMD as independent variables.

Table 4 Hazard ratios for mortality within 90 days comparing APT with ASA or clopidogrel using Cox proportional hazards regression.

	Crude HR			Model adjusted HR[a]		
Variable	HR	95% CI	*p*	HR	95% CI	*p*
Previous chronic Clopidogrel	1.094	0.743-1.611	0.648	0.476	0.189-1.202	0.116
Previous chronic ASA	0.885	0.465-1.687	0.711	1.372	0.861-2.187	0.184
Clopidogrel during ICMD	1.437	0.826-2.502	0.200	3.396	1.317-8.761	0.011
ASA during ICMD	0.814	0.519-1.276	0.370	0.272	0.135-0.551	<0.0005

Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; HR, hazard ratio.

Notes: [a]-The model of Cox proportional hazards regression included age, gender, SAPSII score , maximum lactate level in first 24 hours, infection at admission, emergency department procedures (arterial line placement, cardiopulmonary resuscitation, central venous catheter placement, inotropic therapy, mechanical Ventilation, orotracheal Intubation, vasopressor therapy), non-programmed surgery and status of treatment during ICMD and prior to hospital admission with clopidogrel and acetylsalicylic acid as independent variables.

Figures

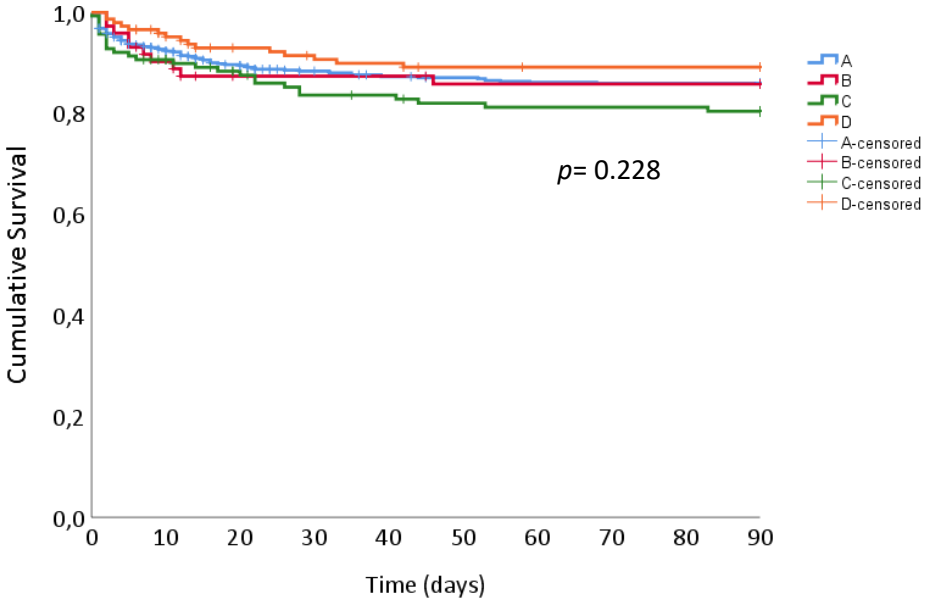

Figure 1 Kaplan-Meier plots of survival time up to 90 days after intensive care unit admission between different APT groups. A- No APT exposure; B- started APT on ICMD admission; C- stopped APT on ICMD admission; D- Continued APT on ICMD admission. Abbreviations: APT, antiplatelet therapy.

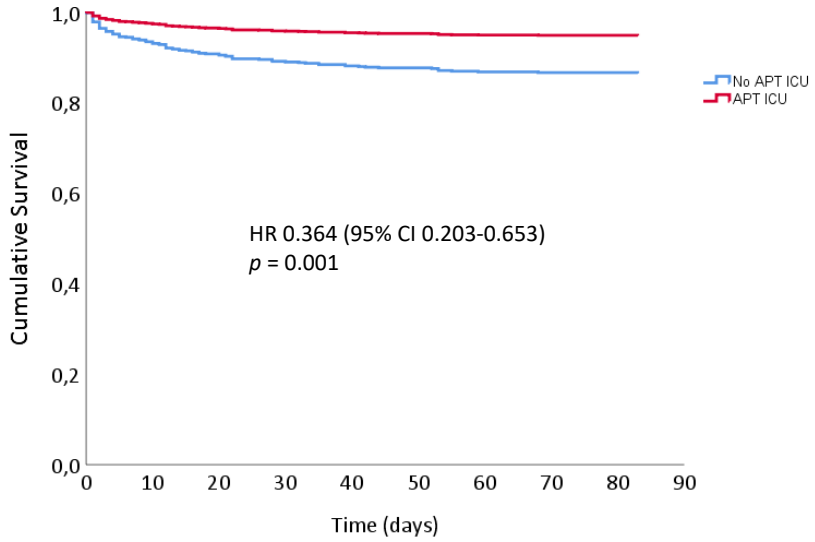

Figure 2 Impact of APT during ICMD stay on cumulative patient survival. HR, 95% CI, and *p* value obtained from the Cox proportional hazards regression model including age, gender, SAPSII score , maximum lactate level in first 24 hours, infection at admission, emergency department procedures (arterial line placement, cardiopulmonary resuscitation, central venous catheter placement, inotropic therapy, mechanical ventilation, orotracheal Intubation, vasopressor therapy), non-programmed surgery and chronic treatment with antiplatelet agents prior to hospital admission and during ICMD as independent variables.
Abbreviations: APT, antiplatelets therapy; CI, confidence interval; HR, hazards ratio; ICMD, intensive care unit.

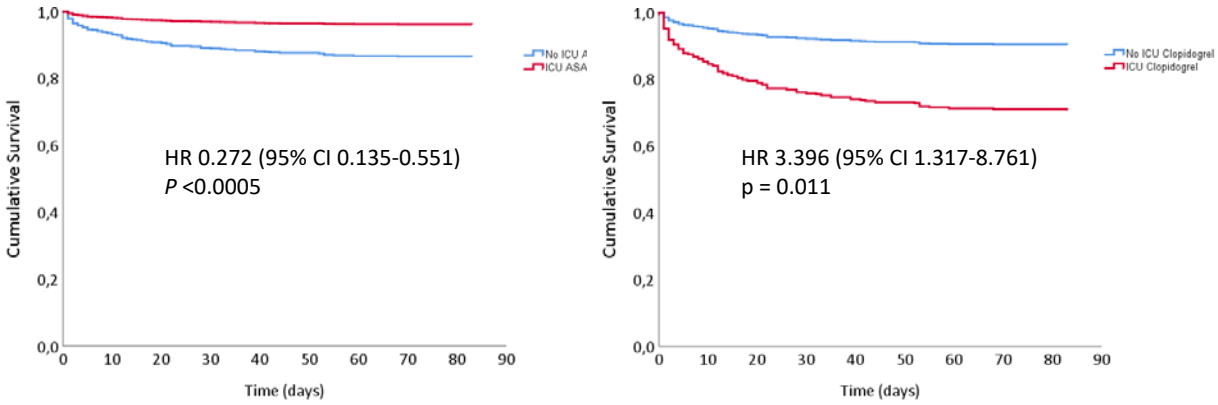

Figure 3 Impact of ASA and clopidogrel therapy during ICMD stay on cumulative patient survival. HR, 95% CI, and p value obtained from the Cox proportional hazards regression model including age, gender, SAPSII score, maximum lactate level in first 24 hours, infection at admission, emergency department procedures (arterial line placement, cardiopulmonary resuscitation, central venous catheter placement, inotropic therapy, mechanical Ventilation, orotracheal Intubation, vasopressor therapy), non-programmed surgery and status of treatment during ICU and prior to hospital admission with clopidogrel and acetylsalicylic acid as independent variables.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; HR, hazards ratio; ICMD, intensive care medicine department.

Este trabalho não seria possível sem a ajuda e apoio de muitas pessoas. Queria aqui deixar expresso o meu agradecimento a algumas.

Em primeiro lugar, à minha companheira de vida, Filipa, que para além de todo o apoio incondicional durante mais de metade da minha existência, teve um papel fulcral na idealização e criação deste trabalho.

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A todos o meu obrigado!

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1. Title
2. Abstract: a) Objective, b) Design, c) Setting, d) Patients or participants, e) Interventions, f) Main variables of interest, g) Results, h) Conclusions
3. Text: a) Introduction, b) Patients and Methods, c) Results, d) Discussion
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5. Funding
6. Conflict of Interest
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Acknowledgements

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1. Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. N Engl J Med. 2002;346:305–10. https://doi.org/10.1056/NEJMoa010877.

2. Bernard GR, Vincent JL, Laterre PF, La Rosa SP, Dhainaut JF, López-Rodríguez A, et al. Eficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344: 699–709. https://doi.org/10.1056/NEJMc063207.

Article in electronic journal
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4. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *Heliyon*. 2018;**19**:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205.

Study published by a corporation (author is not specified)
5. The hypothermia after cardiac arrest study group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346:549–56.

Books and other monographs

Personal authors
6. West JB. Ventilation/blood flow and gas exchange. Oxford: Blackwell Scientific Publications; 1977.

Corporative author
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Editors or compilers as authors
8. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB, editors. Evidence-based medicine. How to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone; 2000.

Chapter of a book
9. Chastre J, Fagon JY. Ventilator-associated pneumonia. En: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care. 2nd ed. New York: McGraw-Hill; 1998. p. 617–52.

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Reference to a dataset

[dataset] 11. Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/xwj98nb39r.1.

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HOSPITAL

Parecer da Comissão de Ética para a Saúde do
Centro Hospitalar de São João / Faculdade de Medicina da Universidade do Porto

Título do Projecto: Antiplatelet use in a cohort of critically ill patients.

Nome do Investigador Principal: António Simão Torgo Silva Soares de Abreu, aluno do Mestrado Integrado em Medicina da FMUP.

Onde decorre o Estudo: No Serviço de Medicina Intensiva (SMI) e nos Serviços Farmacêuticos do CHSJ. Dispõe de autorização da Dra. Teresa Honrado e do Dr. Paulo Carinha. O profissional de ligação no SMI será o Dr. Paulo Mergulhão, que é também o orientador.

Objectivos do Estudo: Estudo retrospectivo observacional que tem como principal objectivo avaliar os efeitos da toma de fármacos anti-agregantes plaquetários, antes e durante o internamento em Cuidados Intensivos, na mortalidade e na morbilidade dos doentes. O estudo será realizado no âmbito da elaboração do projeto de opção do Mestrado Integrado em Medicina da FMUP, sob orientação do Dr. Paulo Mergulhão.

Concepção e Pertinência do estudo: Evidência recente aponta para um papel importante dos fármacos anti-agregantes plaquetários na redução da mortalidade de doentes graves internados em Unidades de Cuidados Intensivos. No entanto, existem também efeitos laterais potenciais destes fármacos, que justificam uma análise mais aprofundada. Será avaliada retrospectivamente a influência da medicação com anti-agregantes palquetários na mortalidade e na morbilidade de doentes admitidos em CI, quer na UCI quer no hospital, bem como aos 28 dias.

Benefício/risco: Não aplicável.

Confidencialidade dos dados: Está previsto o acesso a dados clínicos dos doentes pelo investigador, através do elo de ligação, com respeito pela confidencialidade e anonimização.

Respeito pela liberdade e autonomia do sujeito de ensaio: Em face da natureza retrospetiva do estudo, a obtenção de CI é dispensável.

***Curriculum* do investigador**: Adequado à investigação.

Data previsível da conclusão do estudo: Dezembro de 2018

Conclusão: Proponho um parecer favorável à realização deste projecto de investigação.

Porto, 19 de Outubro de 2018

O Relator da CES, Prof. Manuel Pestana

Unidade de Investigação

Tomei conhecimento. Nada a opor.

30 de Outubro de 2018

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

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Nome do Investigador Principal:

António Simão Torgo Silva Soares de Abreu

Título da Investigação:

Antiplatelet use in a cohort of critically ill patients

Pretendendo realizar no(s) Serviço(s) de:

Serviço Medicina Intensiva e Serviços Farmacêuticos

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos. *O Investigador/ Promotor*

Porto, 17 *de* setembro *de* 2018 . António Simão Abreu

assinatura

Centro de Investigação HSJ

RECEBI

24/10/2018

Documento para Reunião de CA

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