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Juliana Pereira Macedo

Impacto Prognóstico da elevação da Troponina em doentes submetidos a endarterectomia carotídea sob anestesia regional – Um estudo prospectivo/

Prognostic effect of troponin elevation in patients undergoing carotid endarterectomy with regional anesthesia - A prospective study

Setembro, 2019

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

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

Prognostic effect of troponin elevation in patients undergoing carotid endarterectomy with regional anesthesia - A prospective study

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Faculdade de Medicina da Universidade do Porto, 02/11/2019

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Abstract

Background: Myocardial injury after noncardiac surgery (MINS) occurs in 15% of patients undergoing carotid endarterectomy (CEA) with general anesthesia. Short and long-term risk of myocardial infarction (MI) and stroke have been strongly associated with the presence of MINS, with an associated mortality rate superior to 10% in the first year. Due to the absence of studies concerning CEA with regional anesthesia (RA), the present study aimed to evaluate the incidence of MINS in patients with RA and its prognostic value on cardiovascular events or death.

Materials and Methods: From January 2009 to January 2018, 156 patients from a Portuguese tertiary care medical center who underwent CEA under RA were retrieved from a prospectively gathered database. Troponin I or high-sensitive troponin I values were systematically measured in the postoperative period and studied as a binary outcome in a logistic regression model. Survival analysis was used to study the impact of MINS in time-dependent clinical outcomes such as stroke and MI.

Results: The incidence of MINS after CEA was 15.3%. Multivariate analysis confirmed that chronic heart failure was strongly associated with MINS (OR: 4.458, 95% CI: 1,689 – 11.708, $P < 0.001$). A previously diagnosed MINS was associated with the long-term risk of MI and major adverse cardiovascular events (MACE) with hazard ratios (HR) of 3.318 (95% CI: 0.97-13.928, Breslow: $P = 0.025$) and 1.955 (95% CI: 1.01 – 4.132, Breslow: $P = 0.046$), respectively.

Conclusions: MINS is a long-term predictor of MI and MACE. Troponin assessment after CEA should be routinely monitored in patients with a cardiovascular risk superior to 5%.

Further studies concerning prophylaxis and management of MINS should be carried on, focusing on the effect of anesthetic procedure in postoperative troponin elevation.

Keywords: Carotid Stenosis – Carotid Endarterectomy – Myocardial Injury after Non-Cardiac Surgery – Major Adverse Cardiovascular Events

Highlights:

- Incidence of myocardial injury after carotid endarterectomy under regional anesthesia was 15.3%.
- Myocardial injury in carotid endarterectomy predicts long-term risk of cardiovascular events.
- Routinely troponin assessment after carotid endarterectomy should be performed in patients with a cardiovascular risk superior to 5%.

Abbreviations

AHF – Acute Heart Failure

ASA - American Society Of Anesthesiologists

BMI – Body Mass Index (Kg/M2)

CAD – Coronary Artery Disease

CEA – Carotid Endarterectomy

CHF – Chronic Heart Failure

CI – Confidence Interval

CKD – Chronic Kidney Disease

COPD – Chronic Obstructive Pulmonary Disease

DM – Diabetes Mellitus

ECG - Electrocardiography

GA – General Anesthesia

Hb – Hemoglobin

HR – Hazard Ratio

HsTnI – High Sensivity Troponin I

MACE – Major Adverse Cardiovascular Events

MI – Myocardial Infarction

MINS – Myocardial Injury In Non-Cardiac Surgery

OR – Odds Ratio

RA – Regional Anesthesia

TIA – Transient Ischemic Attack

Trop I – Troponin I

1. INTRODUCTION

Myocardial injury after noncardiac surgery (MINS) is defined as a relevant myocardial injury due to ischemia occuring during or within 30 days after surgery (1). This myocardial lesion in the perioperative period does not meet the classic diagnostic criteria for myocardial infarction (MI) (1, 2). The definition of MI is narrower than the definition of MINS, as the latter includes other relevant myocardial injuries related to ischemia (1), not including the perioperative myocardial injury due to documented non-ischemic aetiology such as pulmonary embolism, cardioversion, sepsis and others (1). In the large international study *V*ascular events *I*n noncardiac *S*urgery pat*I*ents c*O*hort evaluatio*N* (VISION), it was reported the optimal diagnostic criterion for MINS is an elevation of serum troponin (1, 3), a highly sensitive and specific marker of myocardial lesion (3). It was also found that MINS affects 8% of the patients and can predict 34% of deaths during the first 30 days after noncardiac surgery in adults (1). Moreover, 58.2% of patients with MINS did not fulfil the universal definition of MI (2) and, of these patients, 1 in 13 died within 30 days (1).

Vascular surgery is strongly associated with cardiovascular risk (3). Particularly, carotid endarterectomy (CEA), the treatment of choice for symptomatic and selected asymptomatic patients with severe ipsilateral carotid artery stenosis, (3, 4) was associated with a higher risk of silent periprocedural MI (3). Serum troponin was significantly elevated in 15% of patients under general anesthesia (GA) (3). These patients presented higher rates of major adverse cardiovascular events during a follow-up of 1.8 years when compared to patients without elevation of troponin (3).

Furthermore myocardial infarction (MI) is one of the most frequent complications after CEA, with substantial associated mortality (5-7), and a presenting a strong relation with the presence of MINS (1, 8). Nevertheless, incidence of MINS after CEA under regional anesthesia (RA) was never reported.

Therefore, this study aimed to determine the incidence of MINS after CEA under RA and estimate its prognostic value upon associated long-term adverse outcomes including MI, related cardiovascular events and mortality. Influence of baseline and procedure-related factors on postoperative troponin elevation was also analysed.

2. METHODS

2.1 Study Population. From January 2011 to January 2018, 156 patients from a tertiary care and referral center, who underwent CEA with RA for carotid artery stenosis were selected from a previous prospective cohort database. A *post-hoc* analysis was performed. From the original database, (n=188) patients with concomitant cardiac surgery (7 patients), missing troponin values (14 patients) and the absence of a first postoperative evaluation (11 patients) were excluded from the study. Sensitivity analysis was performed and non-significant. Patients were evaluated by a vascular surgeon and an anesthesiologist before the surgery and were under acetylsalicylic acid 100 mg and atorvastatin 40 mg for at least two days prior to surgery. Troponin I (Trop I) and high-sensitivity troponin I (hsTnI) values were measured and registered systematically during the following 48h. The median follow-up was 52 months [49 – 54] (reverse Kaplan-Meier). Clinical adverse events such as stroke, MI, acute heart failure (AHF), and all-cause mortality were assessed 30-days post-procedure and in the subsequent long-term surveillance period. This study was reported according with the STROCSS criteria (9). The study protocol was approved by the local Ethics Committee and respects the Declaration of Helsinki.

2.2 Definitions. Myocardial injury after noncardiac surgery is defined by a rising pattern of cardiac troponin values with at least one value above the 99th percentile upper reference limit (2). However, it did not include perioperative myocardial injury due to non-ischemic reasons such as sepsis, cardioversion and pulmonary embolism (1). Symptomatic carotid stenosis was defined according to the Clinical Practice Guidelines of the European

Society for Vascular Surgery (10), and MI was defined according to the Fourth Universal Definition of Myocardial Infarction (2018) (2).

On the postoperative days the levels of troponin were estimated and the highest value was registered (8). MINS was defined by the reference values of a Trop I chemiluminescent microparticle immunoassay (Architect Stat Troponin I, Abbot Laboratories, Wiesbaden, Germany) and a fourth-generation assay hSTnI (Abbot Laboratories, Wiesbaden, Germany): 0.032 μg/mL regardless of sex and 27 ng/mL (male) or 11.4 ng/mL (female), respectively, in accord to the references values of the hospital clinical laboratory. Cardiac troponin I has been previously demonstrated as a highly sensitive and specific marker for myocardial injury post-procedure in short and long-term periods in these patients (11, 12). The hSTnI commercial assay fulfills the criteria of the International Federation for Clinical Chemistry to be considered a high sensitivity assay for cardiac troponin, i.e., 10% total imprecision at the 99th percentile of a reference normal population and the detection of cardiac troponin in at least 50% of the individuals belonging to that population (2, 13, 14).

Major adverse cardiovascular events (MACE) is defined as the composite of MI, AHF and all-cause mortality (2). As postoperative anemia was considered determinant for possible association with troponin elevation, the hemoglobin (Hb) threshold related to cardiac ischemia (namely troponin elevation, ST deviations on ECG, and/or angina) was set to 10 g/dL (5).

2.3 Surgical Technique. All patients were subjected to CEA under RA with initial neurologic examination and further surveillance every 5 minutes and cerebral oximetry

monitoring (INVOS^{TM}, Medtronic, Minneapolis, MN, USA). The present department has a reported stroke rate in CEA of 1.10% and a death rate of 0.6% in symptomatic patients (15, 16). Regional anesthesia by deep cervical block was performed with the patient in supine position and head turned opposingly to the side of procedure. A 22 gauge insulated needle was perpendicularly inserted under ultrasound guidance in most cases. After, 4-5ml of ropivacaine 0.5% was administered per spinal level (C2-C4) in a total of 12-15mL (deep cervical blockade) and/or 5mL of ropivacaine 0.5% at the posterior border of the midportion of the sternocleidomastoid muscle (superficial cervical blockade) were injected (17).

Postoperative surveillance was performed resorting to clinical examination and Doppler Ultrasonography in the subsequent 30-90 days.

2.4 Statistical analysis.The necessary sample for a survival test was calculated resorting to WinPepi® V11.65 (18), aiming for a statistical power (β) of 80% and an $\alpha<0.05$. The sample was estimated (152) for an event rate difference of 20% between groups, although higher event rates differences are described (1, 19). Due to the low rate of 30-day-events, an increased sample size would be necessary to detect 30-day differences in outcome.

For statistics purposes, SPSS (IBM Corp., released 2017. IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, USA) was used and univariate analysis was assessed through $\chi 2$ or Fisher's test concerning qualitative data and Student's t-test for quantitative data. Patients with MINS were compared to patients without troponin rise upon baseline demographic and clinical characteristics (Table I). Multivariate analysis was performed

resorting to binary logistic regression using MINS as a binary outcome, variables with $p<0.05$ were included. The Log-rank and the Breslow estimators were applied to study the effect of MINS in time-dependent variables.

3. **RESULTS**

3.1 Demographics and perioperative determinants of MINS. The sample consisted of 156 patients, with a mean age of 69.58 ± 9.291 (range 45 – 89), including 119 men (76.3%). The incidence of MINS in this sample was 15.3% (24 patients). No significant differences in demographics were found between patients with or without MINS.

Concerning comorbidities, troponin elevation was significantly associated with the presence of coronary artery disease (CAD) (59.09% vs 34.65% P = 0.029) and chronic heart failure (CHF) (45.45% vs 15.75% P = 0.003). Multivariate analysis did not confirm CAD as a risk factor for MINS (CAD odds ratio (OR): 1.796, 95% confidence intervals (CI): 0.649 – 4.970, P = 0.260). CHF revealed an OR of 4.458, 95% CI: 1,689 – 11.708, P = 0.002. Regarding other comorbidities of the patients such as hypertension, diabetes or dyslipidaemia, no significant results were found (P = 0.719, P = 0.313 and P = 0.688, correspondingly). No association with MINS was found in patients with symptomatic presentation of the disease (P = 0.157). Additionally, pre-operative Hb levels and the occurrence of post-carotid clamping deficits were not significantly different (P = 0.367 and P = 0.432, respectively) (Table I). Concerning the use of anti-hypertensive therapy, only calcium channel blockers presented a significant association (23.10% vs 10.40%, P = 0.039), although, this finding was not confirmed by the multivariate analysis (OR: 2.28, 95% CI: 0.847 – 5.859, P = 0.104). Beta-blockers, angiotensin-converting enzyme inhibitors and diuretics did not predict or prevent significant MINS (P = 0.399, P = 0.901 and P = 0.975, correspondingly) (Table I).

3.2 Prognostic value of MINS upon short and long-term outcomes. At 30-days no significant differences were observed in major outcomes. Long-term rates of MI and MACE were found to be significantly increased in patients with reported MINS (for MI, HR: 3.318, 95% CI: 0.97-13.928, Breslow: P = 0.025; for MACE, HR: 1.955, 95% CI: 1.01-4.132, Breslow: P = 0.046). However, the presence of MINS could not predict the risk of isolated stroke and all cause death in a long-term period (for stroke, HR: 2.133, 95% CI: 0.565 – 8.052 P = 0.251; for death, HR: 1.699 95% CI: 0.772-3.743, log rank: P = 0.986) (Figure 1).

MINS was not associated with carotid restenosis (30% or higher) at 24 months after CEA (P = 0.587).

4. DISCUSSION

This prospective cohort study reports the incidence of MINS after CEA under RA and its determinants. Troponin elevations occurred in 15.3% of the patients and more frequently in patients with CAD, CHF and under calcium channel blockers, although only CHF persisted in multivariate analysis. Furthermore, this study confirms previous findings on the prognostic value of MINS upon long-term MI and MACE.

CAD is a strong risk-factor for postoperative myocardial complications (20, 21), and its prevalence in patients submitted to CEA might be as high as 93% (35% of them classified as severe CAD) (6). Another recent study has described a CAD prevalence of 77.5% in patients with severe carotid artery stenosis undergoing carotid artery stenting (22). The risk

of MI in patients undergoing vascular surgery has been ranged from 1% to 26% with an incidence of 14% to 47% for myocardial ischemia (23). However, a recently published large international prospective cohort did not confirm CAD as a predictor of MINS in patients undergoing vascular surgery with GA or RA (8). These findings are consistent with those found in this cohort. On the other hand, CHF was confirmed by multivariate analysis as an independent predictor of MINS. This finding is supported by a previous report, presenting CHF as having significant predictive role in the occurrence of MACE after CEA, regardless of the anesthetic method (24). Additionally, the National Health And Nutrition Examination Survey I (NHANES I) follow-up study has described CAD as the leading cause of heart failure, with an 8-fold risk increase in both genders (95% CI: 6.95-9.46, $P < 0.001$) (25). This finding suggests that CAD might be a confounding factor, which supports the significant reported risk for myocardial injury in patients with CHF ($P = 0.0002$).

Considering the action of antihypertensive drugs, none has shown consistent and significant differences between the groups, in line with previous findings(26, 27). A significant association with the duration of intraoperative hypotension was reported (28, 29), but direct relations between the different antihypertensive drugs and MINS were excluded (28). However, previous studies report that beta-blockers might present a cardioprotective role, due to its chronotropic effect, along with the reduced systolic pressure and ventricular contractile force (23, 30, 31). Furthermore, beta-blockers can be implicated in the prevention of the rupture of coronary plaques (30, 31) and display an anti-inflammatory action on the circulating levels of cytokines (30, 32). Moreover, in patients with CHF with impaired ventricular function, up to 50% the patients submitted to vascular surgery (33, 34), beta-

blockers have shown to reduce cardiac remodeling (35) and possibly reduce the impact of this risk-factor in the development of MINS.

In the present study, MACE and MI have shown to be associated with troponin I elevation. As described above, MI accounts for 24% of deaths after CEA with further diagnosis of MINS (16, 36). These findings are consistent with the results previously published by Grobben et al. (5). Some clinical trials such as the Coronary Artery Revascularization Prophylaxis (CARP) trial and the randomized Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echography (DECREASE)-V (37) studied the role of myocardial revascularization preceding vascular surgery to minimize these adverse outcomes (37, 38). Similar results were obtained in both trials, and no significant differences were found between patients who performed myocardial revascularization and patients undergoing only medical therapy, regarding a composite outcome of 30-day cardiovascular mortality and myocardial infarction (23). However, a randomized controlled trial reported significant postoperative benefit in patients undergoing CEA with asymptomatic disease who were routinely submitted to coronary angiography and supplementary revascularization (39, 40). Furthermore, long-term results demonstrated the reduction of the incidence of MI and the increase of survival in patients with asymptomatic CAD ($P = 0.01$) (40). However, larger controlled studies in order to confirm these results are necessary, which could lead to current practice change (40).

The present cohort did not demonstrate an association between MINS and the risk of late stroke. Other studies are in concordance with this finding (5, 12). In contrast, the large VISION study (1), reported a higher incidence of stroke in patients undergoing noncardiac

surgery. The reasons behind this finding are not clear and might be due to association with several factors such as advanced age, comorbidities or extensive vascular disease. It is important to note that the current evidence regarding MINS after CEA concerns patients submitted to GA. GA might predispose the occurrence of myocardial injury although current evidence is unclear (5, 12, 41). Since RA is feasible and offers safer outcomes, it would be expected a lower incidence of myocardial injury when compared with GA (42). Only one randomized trial that has compared the impact of these two types of anesthesia in CEA, reporting periprocedural troponin T levels and the occurrence of MI, but no significant differences were found (43). However, this study included a sample of only 60 patients, which is an important limitation to its external validity. Moreover, the General Anesthesia versus Local Anesthesia for Carotid Surgery (GALA) trial supports that the incidence of MI when undergoing CEA with GA does not differ from the RA approach (44). Although, it is suggested that RA has some disadvantages, such as periprocedural pain and anxiety, which could induce a higher risk of myocardial injury (44). Hence, only further prospective studies of MINS comparing RA with GA would clarify their relevance in myocardial injury.

As for the above-mentioned long-term cardiovascular events associated with MINS, assessment and management of MINS remains a matter of discussion. Selective post-CEA troponin measurement should be considered in order to avoid further cardiovascular morbidity and mortality, once MINS is also associated to a three-fold increased risk of 30-day mortality (45) and other major cardiac complications (1). According to the Canadian Cardiovascular Society Guidelines, patients with a cardiovascular risk superior to 5%

accessed by Revised Cardiac Risk Index, should undergo routine troponin evaluation. (46, 47)

Nonetheless, cost-effectiveness analyses regarding measurement of troponin and management of MINS are still widely limited. A cost-consequence analysis of troponin T monitoring, based on the VISION study (29), has demonstrated higher cost-effectiveness in patients at higher risk for MINS (age > 65 years, or history of atherosclerosis or diabetes) (48). Toborg et al. has reported that routine troponin surveillance was cost-effective in patients aged >45 years with a positive screening for MINS (49). It was also demonstrated a 25% reduction in MI and vascular mortality by initiating aspirin and statin therapy. (50)

Strengths of the present study are the long follow-up of the patients and the use of exclusively RA during CEA. Even though the data collection was prospective, it has some limitations since it is a *post-hoc* analysis. Although, no differences were reported regarding the excluded group.

5. CONCLUSIONS

The incidence of MINS was 15.3%. CHF is associated with the occurrence of MINS after CEA. MINS is a valid long-term predictor of MACE and MI in patients undergoing CEA with RA.

Due to its prognostic relevance, the authors recommend the reference to MINS incidence in the standards of report for CEA. Additionally, it is also recommended troponin assessment in the postoperative period of CEA for patients with RCRI≥1. Subsequent studies

on MINS management measures and the impact of GA vs RA in its incidence should also be carried on.

Conflict of interest statement:

None.

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ATTACHMENTS

TABLE

Table 1. Demographics and comorbidities of the patients

	No Troponin Elevation n = 132 N (%)	**MINS n = 24 P – Value N (%)**	**P - Value**
Age (years)	69.71 ± 9.260	70.18 ± 10.861	0.832
Sex (Male)	100 (79.37)	19 (86.36)	0.569* (0.445)
Hypertension	113 (88.28)	20 (90.90)	1.000* (0.719)
Smoking history	65 (50.78)	14 (63.64)	0.265
Diabetes	55 (43.30)	7 (31.82)	0.313
Dyslipidaemia	109 (85.16)	18 (81.82)	0.749* (0.688)
CKD	14 (11.11)	5 (22.73)	0.163* (0.133)
Obesity	15 (11.90)	2 (9.09)	1.000* (0.703)
PAD	34 (26.77)	9 (40.91)	0.177
CAD	44 (34.65)	13 (59.09)	0.029

PAD and CAD	18 (14.06)	6 (27.27)	0.065
COPD	17 (13.39)	1 (4.55)	0.475* (0.240)
	No Troponin Elevation n = 132 N (%)	**MINS n = 24 P – Value N (%)**	**P - Value**
CHF	20 (15.75)	10 (45.45)	0.003* (0.001)
ASA	2.87±0.479	3.00±0.309	0.093
Asymptomatic	68 (54.00)	18 (81.80)	0.157
Symptomatic	58 (46.03)	4 (18.18)	
TIA	11 (8.70)	3 (21.40)	0.966
Stroke	47 (37.30)	1 (4.50)	0.143
Preop Hb (g/L)	12.30 ± 36.80	11.54 ± 3.20	0.367
Post-clamping deficits	67 (50.38)	10 (41.67)	0.432
BB	90 (71.40)	16 (72.7)	0.399
CCB	40 (31.70)	12 (54.50)	0.039
ACEI	90 (71.40)	16 (72.70)	0.901
Diuretics	52 (41.30)	9 (40.90)	0.975

*Fisher's Exact Test

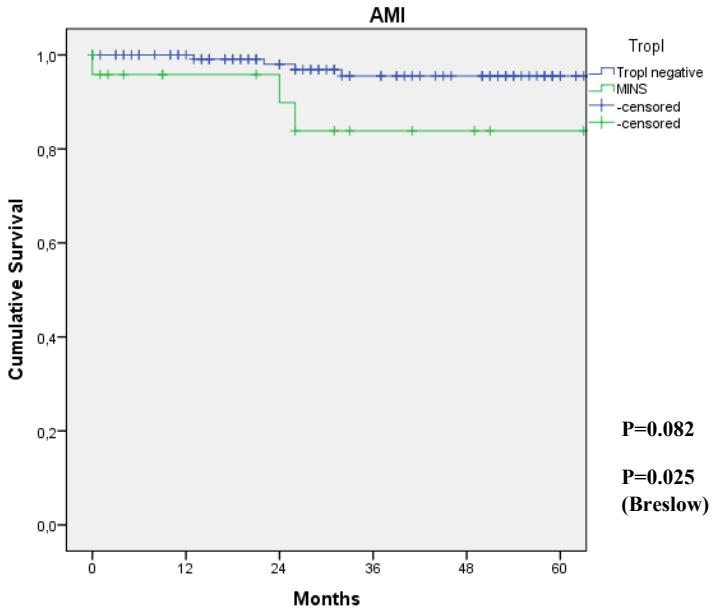
Legend: ACEI, Angiotensin-converting enzyme inhibitors; ASA, American Society of Anesthesiologists; BB, Beta-blockers; CAD, Coronary artery disease; CCB, Calcium channel blockers; CHF, Cardiac heart failure; CKD, Chronic kidney disease (creatinine = 0.1326 mmol/dl); COPD, Chronic obstructive pulmonary disease; PAD, Peripheral artery disease; Preop Hb, Preoperative hemoglobin; TIA, Transitory ischemic attack.

FIGURES

Figure 1: Survival plots. 60 months follow-up Kaplan Meier survival plots for different clinical events post-CEA, for groups with or without troponin I elevation. A – Myocardial Infarction; B –Stroke; C –MACE; D – All-cause Death.

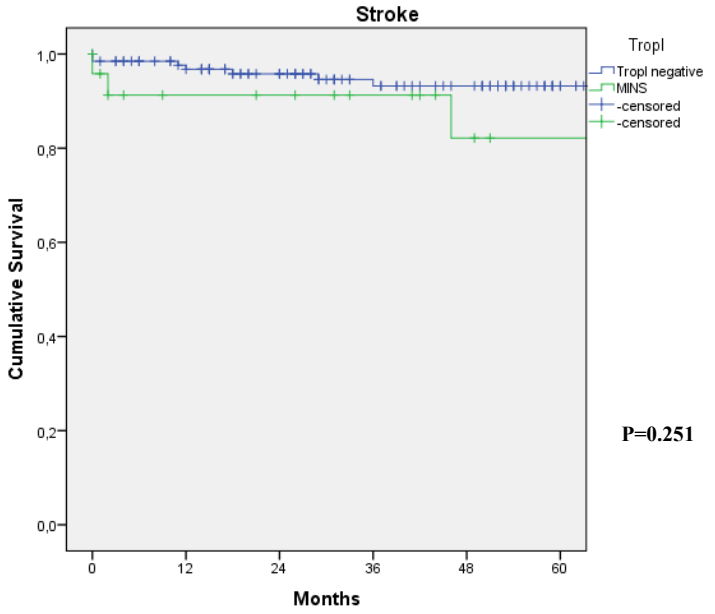
TropI, Troponin I; MINS, Myocardial Injury after non-cardiac surgery; SE: Standard Error

A



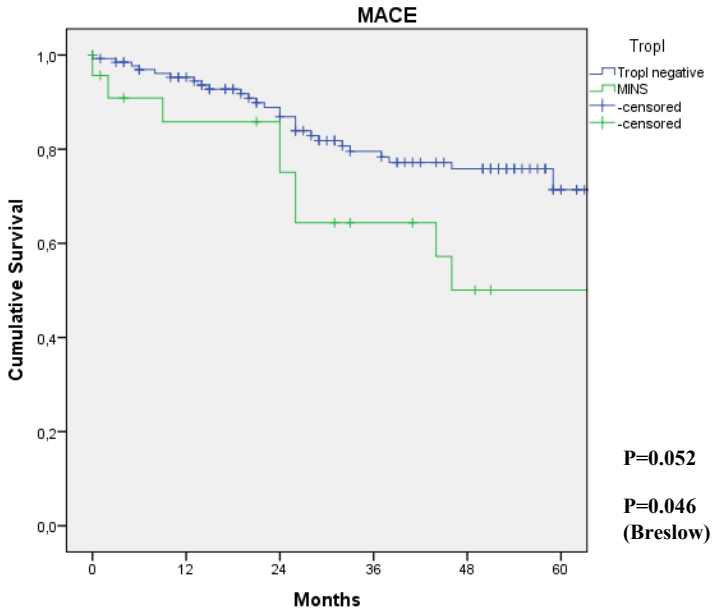
Time (months) (AMI)	1	12	24	36	48	60
TropI negative (132)	127 0	99.1% SE: 0.9% 112 0	98% SE: 1.4% 89 2	95.5% SE: 2.2% 68 4	95.5% SE: 2.2% 58 4	95.5% SE: 2.2% 30 4
MINS (24)	95.8% SE: 4.1% 23 1	95.8% SE: 4.1% 17 1	83.9% SE: 8.7% 15 2	83.9% SE: 8.7% 11 3	83.9% SE: 8.7% 10 3	83.9% SE: 8.7% 8 3

B



Time (months) (Stroke)	1	12	24	36	48	60
TropI negative (132)	98.5% SE: 1.1% 130 2	96.8% SE: 1.6% 113 4	95.8% SE: 1.8% 90 5	93.2% SE: 2.5% 68 7	93.2% SE: 2.5% 58 7	93.2% SE: 2.5% 29 7
MINS (24)	95.8% SE:4.1% 23 1	91.3% SE: 5.9% 17 2	91.3% SE: 5.9% 16 2	91.3% SE: 5.9% 13 2	82.1% SE: 10.2% 9 3	82.1% SE: 10.2% 7 3

C

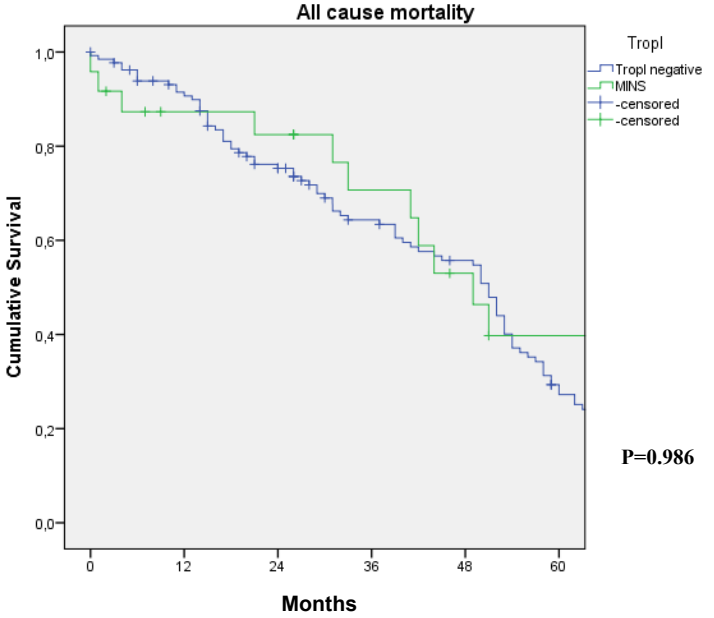


P=0.052

P=0.046 (Breslow)

Time (months) (MACE)	**1**	**12**	**24**	**36**	**48**	**60**
TropI - (132)	99.2% SE: 0.8% 131 1	95.3% SE: 1.9% 118 6	86.9% SE: 2.9% 89 13	79.5% SE: 4% 67 20	75.8% SE: 4.3% 57 23	71.4% SE: 5.1% 29 25
MINS (24)	95.7% SE: 4.3% 22 1	85.8% SE: 7.6% 17 3	85.8% SE: 7.6% 17 3	64.4% SE: 10.9% 10 7	50.1% SE: 12.3% 7 9	50.1% SE: 12.3% 7 9

D



P=0.986

Time (months) (All cause death)	**1**	**12**	**24**	**36**	**48**	**60**
TropI neg (132)	99.2% SE: 0.8% 131 1	90.7% SE: 2.6% 114 3	75.3% SE: 3.9% 90 7	64.3% SE: 4.4% 68 9	55.7% SE: 4.7% 57 14	27.2% SE: 4.4% 27 19
MINS (24)	95.8% SE:4.1% 23 1	87.3% SE: 6.9% 18 6	82.5% SE: 8% 17 9	70.7% SE: 10.3% 12 10	53% SE: 11.7% 9 11	39.8% SE: 12% 5 12

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