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Glycated Hemoglobin as a Long-Term Predictor of Cardiovascular Outcomes in Patients Undergoing Carotid Endarterectomy

Raquel Alexandra Carneiro Pinheiro Silva

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

Glycated Hemoglobin as a Long-term Predictor of Cardiovascular Outcomes in Patients Undergoing Carotid Endarterectomy

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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.	X
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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Raquel Alexandra Carneiro Pinheiro Silva, abaixo assinado, nº mecanográfico 201905398, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

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Raquel Alexandra Carneiro Pinheiro Silva

Agradecimentos

“O verdadeiro heroísmo consiste em persistir por mais um momento, quando tudo parece perdido.”

— W. F. Grenfell

Chegar até aqui foi um percurso desafiante, repleto de momentos de crescimento, dúvidas, conquistas e resiliência. No entanto, esta caminhada nunca foi solitária. Pelo contrário, foi marcada pelo apoio inestimável de pessoas que, de diferentes formas, deixaram a sua marca e tornaram este caminho mais rico e significativo.

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Este capítulo chega ao fim, mas cada fim traz consigo um novo começo, e que venham muitos mais desafios a superar!

Trabalho de acordo com as normas da revista “Acta Chirurgica Belgica”

Glycated Hemoglobin as a Long-Term Predictor of Cardiovascular Outcomes in Patients Undergoing Carotid Endarterectomy

Running title: Glycated Hemoglobin as a Long-Term Predictor in Carotid Surgery

Original research article

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Keywords:

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Abstract:

Background:

Several biomarkers are known to play a role in predicting long-term complications of non-cardiac surgeries, including major adverse cardiovascular events (MACE), myocardial infarction, or death. Carotid endarterectomy (CEA) is considered a low to medium-risk surgery for carotid stenosis aimed at preventing stroke events. Glycated hemoglobin (HbA1c) is a biomarker with potential prognostic value of MACE. This study aims to assess the potential role of HbA1c as a short and long-term predictor of all-cause mortality and MACE in patients undergoing CEA.

Methods:

A post hoc analysis was performed using data from a prospective database of patients who underwent carotid endarterectomy (CEA) under regional anesthesia (RA) at a tertiary referral center between January 2014 and December 2023. Patients with available HbA1c measurements taken up to three months before surgery were included and categorized into two groups based on an HbA1c threshold of 6.5%. Kaplan-Meier survival analysis and multivariable Cox regression models were used to assess the impact of HbA1c levels on time-dependent outcomes. The primary outcome was the incidence of long-term major adverse cardiovascular events (MACE) and all-cause mortality. Secondary outcomes included the incidence of stroke, acute myocardial infarction (AMI), acute heart failure (AHF), and major adverse limb events (MALE).

Results:

A total of 65 patients who underwent CEA were evaluated. The mean age was 71.4 ± 8.5 years, with 53 (81.5%) males, and the median follow-up period was 30 [13.5-46.4]

months. Patients with HbA1c ≥ 6.5% were significantly younger (68.8 ± 8.8 vs. 73.8 ± 7.9 years, p=0.015). Kaplan-Meier survival analysis revealed a significant association between HbA1c levels and stroke incidence (log-rank p=0.045), with a trend toward increased major adverse cardiovascular events (MACE) (log-rank p=0.038). Multivariable analysis confirmed that HbA1c was an independent predictor of major adverse limb events (MALE) (aHR: 3.387, CI: 1.078-10.643, p=0.037), while its association with stroke did not reach statistical significance (aHR: 3.205, CI: 0.959-10.716, p=0.059). No significant associations were found between HbA1c and myocardial infarction (p=0.415), acute heart failure (p=0.545), or all-cause mortality (p=0.246).

Conclusion:

HbA1c has been demonstrated to predict long-term MACE, stroke and MALE following CEA independently. While its role in predicting other major cardiovascular events remains inconclusive, HbA1c serves as a readily available and cost-effective biomarker for vascular risk stratification in this population.

Introduction

Carotid endarterectomy (CEA) is a surgical procedure aimed at removing atherosclerotic plaque from the carotid artery in order to prevent ischemic strokes (1). It is recommended for patients with moderate-to-severe symptomatic or asymptomatic carotid stenosis, as studies have demonstrated its efficacy in reducing the risk of recurrent cerebrovascular events (1-5). Current guidelines emphasize the importance of early intervention in symptomatic patients, recommending CEA for those with carotid stenosis ranging from 50% to 99% within 14 days of an ischemic event, as this significantly reduces the risk of recurrent stroke (6). In asymptomatic patients with stenosis of ≥ 60%, CEA may be considered if additional risk factors for disease progression are present, such as unstable plaques or evidence of stenosis progression (6).

While CEA effectively lowers stroke risk, it does not eliminate the broader cardiovascular burden these patients face. Carotid atherosclerosis is not only a risk factor for stroke but also a marker of systemic vascular disease, predisposing patients to long-term major cardiovascular events such as myocardial infarction, coronary interventions, and vascular complications (7-9). Despite the benefits of CEA, patients require ongoing medical management to mitigate their continued cardiovascular risk and improve long-term outcomes (7, 10).

Given the persistent cardiovascular risk in patients undergoing CEA, identifying reliable biomarkers for long-term prognosis is essential. Glycated hemoglobin (HbA1c) is widely used as an indicator of long-term glycemic control and has been increasingly recognized as a predictor of major adverse cardiovascular events (MACE) in both diabetic and non-diabetic populations (11, 12). Elevated HbA1c levels have been associated with an increased incidence of cardiovascular disease, all-cause mortality, and cerebrovascular

complications, independent of traditional cardiovascular risk factors (13, 14). However, its prognostic role specifically in patients undergoing CEA remains underexplored. Given that atherosclerosis is a systemic disease, HbA1c may serve as a valuable tool for identifying patients at heightened risk of long-term cardiovascular events after surgical intervention.

This study aims to evaluate the potential role of HbA1c as a long-term predictor of MACE, including acute myocardial infarction, acute heart failure, stroke, MALE and overall mortality, in patients undergoing CEA.

Methods

Study Sample and Data Source

Patients were recruited from a tertiary care and referral center, where they underwent CEA under regional anesthesia (RA) for the treatment of carotid stenosis. The study included consecutive patients admitted between January 2014 and December 2023, with corresponding data recorded from a prospective database. A post hoc analysis was subsequently performed for patients with HbA1c measurements taken up to three months before surgery. Two groups were established based on a predefined HbA1c threshold (6.5%) and were compared. The selected value of 6.5% was determined through optimal binning and fell within the described range. Patients who underwent concurrent cardiac surgery or were unwilling to undergo regional anesthesia were excluded.

Preoperatively, the patient's comorbidities and demographics were assessed. All patients received optimal medical treatment, including single antiplatelet therapy and statin. CEA procedure under RA is the standard treatment performed in this health care

center. The carotid endarterectomy surgery was performed using both patch and eversion techniques, as chosen by the surgeon based on their preference.

Patients were assessed in the first 30 days post-procedure and the subsequent long-term surveillance period. The outpatient clinic's clinical record was summarily reviewed for the reported outcomes, including patient-related events such as acute heart failure (AHF), acute myocardial infarction (AMI), stroke, major adverse limb events (MALE) and all-cause mortality.

This study adheres to the Strengthening the Reporting Of Cohort Studies in Surgery (STROCSS) criteria (15). The study protocol complies with the Declaration of Helsinki and is in accordance with the European Union General Data Protection Regulation (GDPR). The Center's Ethics Committee has assigned approval number identifier 248-18 to this study.

Definitions

Symptomatic carotid stenosis was defined according to the current guidelines of the European Society for Vascular Surgery and measured by duplex ultrasound or computed tomography angiogram (6, 16). MACE was considered the composite of AHF, ischemic cardiovascular events, and all-cause mortality (17). Mortality etiology was determined using the Death Certificate Information System (SICO™), the mortality information system in Portugal. Major Adverse Limb Event (MALE) was a composite outcome of major ischemic amputation, acute limb ischemia and need for peripheral revascularization (18).

Chronic kidney disease (CKD) was defined as serum creatinine ≥ 1.5 mg/dL. AHF is defined as a new onset of heart failure or as an acute decompensation of chronic heart failure, most often presented as systemic congestion.

Outcome assessment

Patients were assessed in the first and third month after surgical intervention and annually thereafter, resorting to clinical examination and duplex ultrasound in the outpatient setting. The primary outcome was the incidence of long-term MACE and all-cause mortality. Long-term period was defined as any event occurring after 30 postoperative days (19). Secondary outcomes included the occurrence of MALE, stroke, AMI and AHF.

Statistical Analysis

The sample size for a survival test was calculated using online Sample Size Calculators for Designing Clinical Research (https://sample-size.net/sample-size-survival-analysis/, March 2025), with a statistical power (β) of 80% and a significance level of 0.05. Despite reported diffuse differences in event rates, the sample was determined to be 23 events, assuming a hazard ratio 4 across groups (20, 21) . To account for an expected 5% loss to follow-up rate, the authors aimed to collect a total estimated sample of 65. Nonetheless, a larger sample size would be necessary to detect variations in outcome within a 30-day timeframe, given the low rate of 30-day events.

Data collection and analyses were conducted using IBM SPSS Statistics (IBM Corp., release 2023. IBM SPSS Statistics for Windows, version 29.0.2, Armonk, NY, USA). Normally distributed data were presented as mean and standard deviation (SD), while categorical variables were expressed as frequency and corresponding percentage. For univariable analysis, $\chi 2$ or Fisher's test were used for qualitative data, and Student's T-test for quantitative. A statistical significance threshold of less than 0.05 was considered.

Patients with a HbA1c level equal or superior to 6.5% (exposed group) were compared to patients with HbA1c levels below 6.5% (control group), based on baseline demographic and clinical comorbidities. To investigate the impact of preoperative HbA1c levels on time-dependent variables, a Kaplan-Meyer survival analysis with log-rank estimators was conducted. Adjusted Hazard Ratio (aHR) and 95% confidence intervals (CI) for the occurrence of outcomes were assessed through multivariable Cox regression analysis.

Results

Demographics and epidemiological data of patients

Data from all consecutive patients who underwent CEA between January 2014 and December 2023 was evaluated. A total of 65 patients had HbA1C measurements taken up to three months before surgery. The sensitivity analysis conducted revealed no significant differences between the group with and without HbA1c measurements, indicating consistent outcomes.

Mean age of the patients enrolled in this study was 71.4±8.5 years, with 53 (81.5%) males and 12 females (18.5%). The median [interquartile range; IQR] time of follow-up was 30 [13.5-46.4] months.

The HbA1C < 6.5% group had a mean age of 73.8± 7.9 years, whereas the HbA1C ≥ 6.5% group had a mean age of 68.8± 8.8 years (P=0.015).

Regarding cardiovascular risk factors, the majority of patients had a history of hypertension (86.2%) and dyslipidemia (86.2%). Smoking history (40.5% vs. 57.1%,

P=0.184) , dDiabetes (21.6% vs. 96.4%, P<0.001) and iInsulin therapy (2.8% vs. 25.9%, P<0.001) were more frequent in the HbA1c≥6.5% group (Table I).

The sensitivity analysis conducted revealed no significant differences between the group with and without HbA1c measurements, indicating consistent outcomes.

Survival analysis

During follow-up, Kaplan-Meier survival analysis revealed a significant association between HbA1c levels and stroke incidence, with patients with HbA1c ≥ 6.5% experiencing significantly higher rates of stroke compared to those with HbA1c < 6.5% (Log-rank P = 0.045). Similarly, a trend toward higher rates of major adverse cardiovascular events (MACE) was observed in patients with elevated HbA1c, although the association did not reach strong statistical significance (Log-rank P = 0.038, Tarone-Ware P = 0.113).

Conversely, long-term incidence of acute myocardial infarction (AMI) (Log-rank P = 0.415) and acute heart failure (AHF) (Log-rank P = 0.545) were comparable between the studied groups, suggesting no significant impact of HbA1c levels on these outcomes. The incidence of major adverse limb events (MALE) also showed a trend towards statistically significant difference between groups (Log-rank P = 0.057).

Regarding all-cause mortality, no significant difference was observed between patients with HbA1c ≥ 6.5% and those with lower HbA1c levels (Log-rank P = 0.246), indicating that long-term survival was not markedly influenced by glycemic status. (Figure 1).

On multivariable analysis, a statistically significant association was observed between HbA1c levels and major adverse limb events (MALE), with an adjusted hazard ratio (aHR) of 3.387 (95% CI: 1.078-10.643, P=0.037), indicating that elevated HbA1c may contribute to worse vascular outcomes. Additionally, peripheral artery disease (PAD) was a strong predictor of MALE, showing an aHR of 4.567 (95% CI: 1.697-12.295, P=0.003), reinforcing its role as a key risk factor for limb-threatening ischemia (Table II). Conversely, atrial fibrillation (AF) did not show a significant association with MALE (aHR: 0.043, 95% CI: 0.000-1445.526, P=0.553). Interestingly, age demonstrated a protective effect against MALE, with an HR of 0.915 (95% CI: 0.853-0.983, P=0.014), suggesting that younger patients may have a higher relative risk of adverse limb events.

Regarding stroke incidence, an elevated HbA1c level (≥ 6.5%) was associated with an increased risk of stroke, though it did not reach statistical significance (aHR: 3.205, 95% CI: 0.959-10.716, P=0.059). Similarly, atrial fibrillation (AF) (aHR: 2.116, 95% CI: 0.453-9.881, P=0.340) and age (aHR: 1.015, 95% CI: 0.955-1.079, P=0.636) did not show significant correlations with stroke occurrence in the adjusted model.

Discussion

This analysis revealed a significant association between HBA1C levels and the risk for long-term MALE in patients undergoing CEA under RA, with a 3.4-fold increased risk. Additionally, peripheral artery disease (PAD) was identified as a strong predictor of MALE, reinforcing its well-established role in peripheral vascular complications, as has been previously reported (22). Noteworthy, while HbA1c was independently associated with a higher risk of MALE, its impact on stroke outcomes was less pronounced. Additionally, age and AF did not demonstrate significant associations with either MALE

or stroke outcomes, suggesting that metabolic and vascular factors, particularly HbA1c and PAD, play a more central role in determining long-term adverse events in this population.

These findings align with previous literature emphasizing the role of glycemic control in vascular complications (23). Elevated HbA1c has been linked to increased systemic inflammation, endothelial dysfunction, and accelerated atherosclerosis progression, which can contribute to worse long-term outcomes in patients with cardiovascular disease (24). Prior studies have suggested that poor glycemic control is associated with a higher risk of stroke and limb ischemia, particularly in individuals with established vascular disease (25).

The fact that HbA1c did not show a significant impact on myocardial infarction (AMI), acute heart failure (AHF), or all-cause mortality in this study suggests that the mechanisms linking glucose dysregulation to vascular events may differ depending on the affected vascular territory (26).

One of the most unexpected findings was that older age appeared to have a protective effect against MALE (HR: 0.915, P=0.014). This result challenges the common assumption that older patients face higher vascular risk and suggests alternative explanations. One possibility is that younger patients may be subjected to more aggressive interventions or may present with more rapidly progressing disease due to genetic or metabolic factors (27). Another explanation is survivor bias, as older patients who remain eligible for CEA may represent a healthier subset, with better management of risk factors (28). Additionally, younger patients in the cohort may have been more exposed to risk factors such as smoking, which accelerates atherosclerosis progression and increases the likelihood of limb-related complications (29). Furthermore, differences

in treatment strategies may have played a role, as younger patients are more likely to undergo repeated revascularization attempts, which could impact outcomes (10).

Regarding HbA1c and stroke risk, although patients with HbA1c ≥ 6.5% had a higher incidence of stroke, the association did not reach statistical significance (aHR: 3.205, P=0.059). Several factors may explain this finding. First, the sample size may have been insufficient to achieve statistical significance due to a limited number of events. Additionally, other risk factors such as hypertension, dyslipidemia, and antithrombotic therapy may play a dominant role in stroke risk (30), overshadowing the effect of HbA1c. The pathophysiology of stroke is complex, involving both embolic and thrombotic mechanisms, and hyperglycemia may not have a direct effect in all cases. Despite the lack of statistical significance, the P-value of 0.059 suggests a trend toward an increased risk, which may become clearer with a larger cohort or longer follow-up duration.

AF, a well-known risk factor for stroke, did not show a significant association with stroke or MALE in this study. This may be due to effective anticoagulation therapy, which could have mitigated the risk of thromboembolic events in patients with AF (31). Another possible explanation is the small number of AF cases in the cohort, limiting the power to detect a statistically significant association. Additionally, if most strokes in this study were atherothrombotic rather than embolic, the role of AF in this population would be less relevant. These findings highlight the need to consider multiple stroke mechanisms when assessing risk in patients undergoing CEA, rather than relying solely on AF as a predictor.

Unlike MALE and stroke, HbA1c did not show a significant relationship with AMI or AHF. This may be explained by the aggressive management of cardiovascular risk factors in patients undergoing CEA, which could reduce the independent impact of

HbA1c on coronary events. Moreover, the mechanisms underlying coronary and carotid atherosclerosis, though related, are not identical (32). Coronary plaque instability and acute thrombosis may be more strongly influenced by lipid metabolism and hypertension than by glycemic control alone (33). Additionally, widespread use of cardioprotective medications, such as statins, ACE inhibitors, and beta-blockers, may have diminished any independent association between HbA1c and AMI/AHF(34).

Similarly, no significant difference in long-term survival was observed between groups with high and low HbA1c. Several factors may account for this. First, other prognostic factors such as age, renal function, and cardiovascular disease burden may have had a stronger influence on survival than HbA1c alone. Additionally, a longer follow-up period might be necessary to detect a potential impact of chronic hyperglycemia on mortality. Lastly, comorbidities not included in the analysis, such as chronic kidney disease, systemic inflammation, and sarcopenia, may have played a more significant role in determining mortality(35-37).

HbA1c has been proposed as a valuable biomarker for cardiovascular risk stratification, yet its role in preoperative risk assessment remains under debate. Given the strong association observed with MALE in this study, it may be beneficial to incorporate HbA1c screening into vascular risk assessment protocols, particularly in patients with PAD. However, its role as an independent predictor of stroke remains inconclusive, necessitating larger studies to further explore this relationship.

Preoperative HBA1C is a long-term predictor of cardiovascular events and mortality, underscoring its significance in the preoperative evaluation (11, 25). However, studies on prophylaxis and management strategies remain limited. The use of aspirin and statins has demonstrated a 25% reduction in myocardial infarction and mortality (38).

Additionally, a thorough review and optimization of patients' comorbidities before surgery can significantly enhance postoperative recovery.

This study has several strengths, including extended follow-up period along with prospective data collection, a well-characterized cohort, and standardized surgical protocols, ensuring high data quality and consistency in procedural execution. Additionally, the surgical interventions were performed in a single center, reducing variability in perioperative management. However, it is important to acknowledge its limitations. The limited sample size may have reduced statistical power, particularly for stroke, AMI, AHF and mortality outcomes, potentially impacting the ability to detect significant associations. The post-hoc nature of the study introduces a risk of selection bias, as patients who underwent HbA1c measurement may differ systematically from those who did not. Additionally, the study was conducted in a large academic teaching institution, which may limit the external validity of the results when extrapolated to community hospitals that perform a high volume of CEA procedures. Although sensitivity analysis was performed to mitigate bias, residual confounding cannot be entirely excluded, particularly regarding smoking history, medication use, and disease duration. Furthermore, the inclusion criteria for surgical candidacy may have introduced a selection bias, as individuals with more advanced cardiovascular disease manifestations may have been less likely to undergo surgery, influencing the overall risk profile of the study population. These factors should be considered when interpreting the findings and underscore the need for larger, multicenter studies to validate these results and improve generalizability.

Conclusion

HbA1c is an accessible and cost-effective biomarker that has shown a significant association with long-term vascular outcomes in patients undergoing CEA. In this study, elevated HbA1c levels were independently associated with an increased risk of major adverse limb events (MALE), reinforcing its potential role in postoperative risk stratification. While a trend toward a higher incidence of stroke was observed in patients with poor glycemic control, the association did not reach statistical significance, highlighting the need for further investigation.

Despite the well-established benefits of CEA in stroke prevention (30), these findings raise concerns regarding the long-term vascular risk in patients with elevated preoperative HbA1c levels. Given that hyperglycemia plays a central role in systemic inflammation, endothelial dysfunction, and atherosclerosis progression (24), these patients may benefit from a multidisciplinary approach, both before and after surgery. Optimization of cardiovascular risk factors, tighter metabolic control, and structured rehabilitation programs should be considered to mitigate long-term complications and improve overall patient outcomes.

To better define the clinical significance of HbA1c in this context, larger prospective studies with extended follow-up periods and consistent patient work-up are necessary. Future research should focus on delineating the best therapeutic strategies for medium- and high-risk patients undergoing CEA, particularly those with HbA1c $\geq$ 6.5%, to determine whether targeted interventions could lead to improved long-term vascular outcomes and overall survival.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Table I - General patient's characteristics and preoperative comorbidities.

	Population N =65	HbA1C<6.5 N= 37	HbA1C≥6.5 N= 28	P Value
Age (years) (mean±SD)	71.4 ± 8.5	73.8± 7.9	68.8 ± 8.8	0.015
Gender (Male), n (%)	53 (81.5)	28 (75.7)	25(89.3)	0.161
Gender (Female), n (%)	12 (18.5)	9 (24.3)	3 (10.7)	0.161
Hypertension n (%)	56 (86.2)	31 (83.8)	25 (89.3)	0.525
Smoking history, n (%)	31 (47.7)	15 (40.5)	16 (57.1)	0.184
Diabetes, n (%)	35 (53.8)	8 (21.6)	27 (96.4)	<0.001
Dyslipidemia, n (%)	56 (86.2)	31 (83.8)	25 (89.3)	0.525
CKD, n (%)	10 (15.4)	7 (18.9)	3 (10.0)	0.364
Obesity, n (%)	18 (27.7)	9 (24.3)	9 (32.1)	0.485
PAD, n (%)	13 (20.0)	7 (18.9)	6(21.4)	0.802
CAD, n (%)	28 (43.1)	18 (48.6)	10 (35.7)	0.297
COPD, n (%)	12 (18.5)	6 (16.2)	6 (21.4)	0.592
AF, n (%)	7 (10.8)	7 (18.9)	0	0.015
CABG, n (%)	11 (16.9)	6 (16.2)	5 (17.9)	0.861
Coronary Stent, n (%)	6 (9.5)	4 (11.1)	3(7.4)	0.620
Insulin dependent, n (%)	8 (12.7)	1(2.8)	7(25.9)	<0.001
Symptomatic, n (%)	33(51.6)	19(52.8)	14(50)	0.825
CI, n (%)	8 (12.1)	5 (13.5)	3 (10.3)	0.695
ASA, n (%) II III IV	 10(15.4) 51(78.5) 4(6.2)	 6 (16.2) 29 (78.4) 2(5.4)	 4 (14.3) 22 (78.6) 2 (7.1)	0.943

Legend Table I: SD – Standard Deviation.; CKD – Chronica kidney disease(creatinine ≥ 1.5 mg/dl); PAD – Peripheral artery disease; CAD – Coronary artery disease; COPD – Chronic obstructive pulmonary disease; AF – Atrial fibrillation; CABG – Coronary Artery Bypass Grafting; CI – Cardiac insufficiency; ASA – American Society of Anesthesiologists Physical Status Classification System.

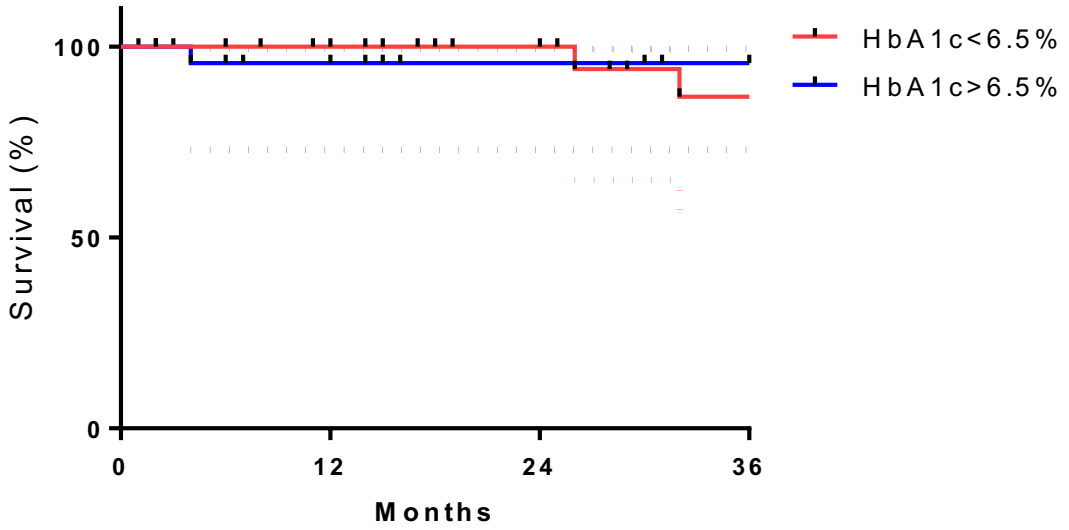
Table II – Multivariable analysis of Major Adverse Limb Events and Stroke

MALE	HR	(5-95% CI)	P Value	aHR	(5-95% CI)	P Value
Age	0.915	0.853-0.983	0.014	-	-	-
PAD	5.359	1.328-21.621	0.018	4.567	1.697-12.295	0.003
AF	0.043	0.000-1445.526	0.553	-	-	-
HbA1c≥ 6.5%	4.00	0.805-19.886	0.090	3.387	1.078-10.643	0.037
STROKE						
Age	1.015	0.955-1.079	0.636	-	-	-
AF	2.116	0.453-9.881	0.340	-	-	-
HbA1c≥ 6.5%	3.205	0.959-10.716	0.059	3.205	0.959-10.716	0.059

Legend Table II: CI- Confidence Interval; HR- Hazard Ratio; aHR- Adjusted hazard ratio; PAD – Peripheral artery disease; AF – Atrial fibrillation.

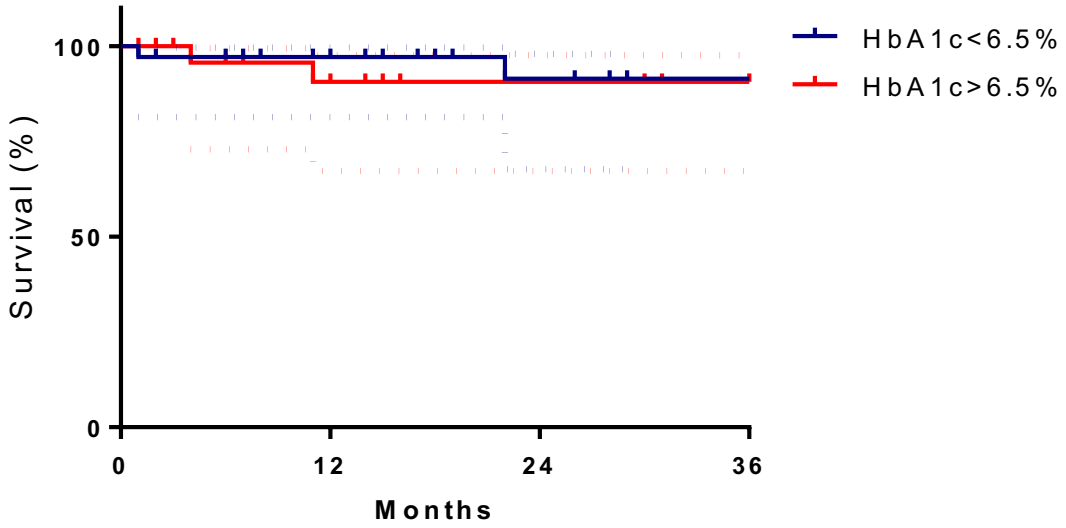
Figure 1 – Kaplan Meier survival plots for different clinical events post-CEA, for groups with and without HbA1c levels ≥ 6.5

A. AMI



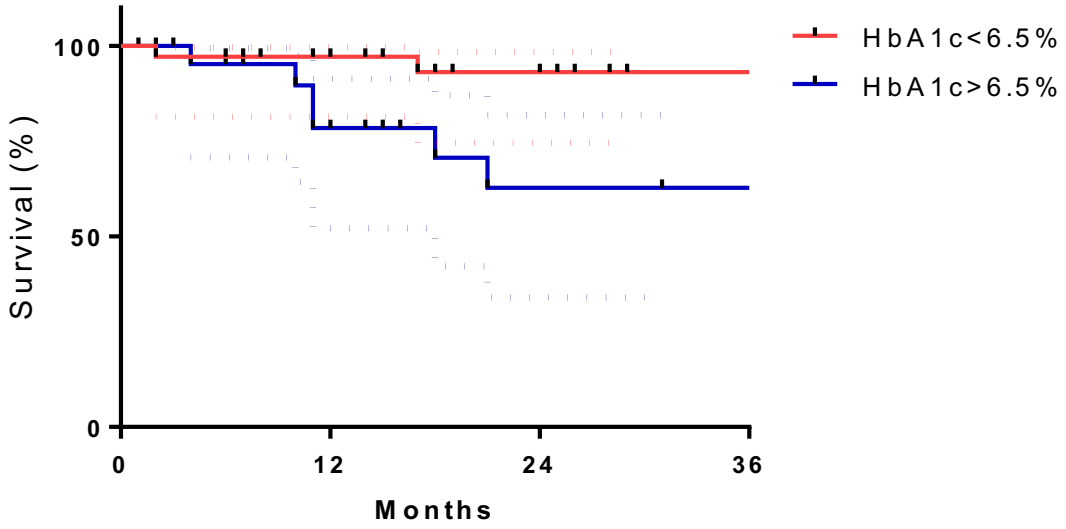
AMI Log rank p=0.415		30d	12	24	36
HbA1C < 6.5%	% SE (%) Cases Nº at risk	97.3 2.7 1 35	97.3 2.7 1 27	97.3 2.7 1 18	84.5 8.8 3 12
HbA1C ≥ 6.5%	% SE (%) Cases Nº at risk	100 0 0 26	95.7 4.3 1 18	95.7 4.3 1 15	95.7 4.3 1 11

1.B. AHF



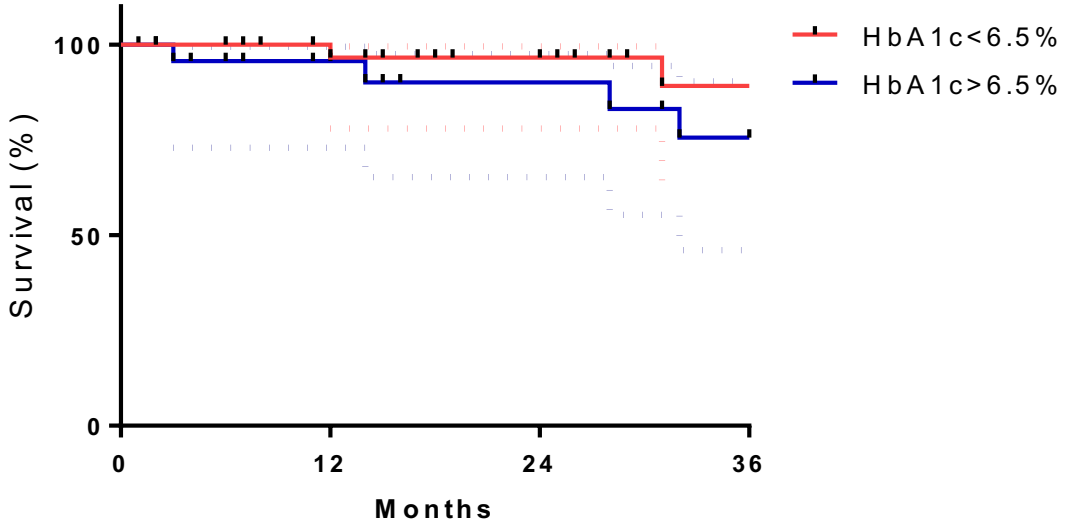
AHF Log rank p=0.545		30d	12	24	36
HbA1C < 6.5%	% SE (%) Cases Nº at risk	97.3 2.7 1 35	94.5 3.8 2 25	89 6.5 3 16	89 6.5 3 13
HbA1C ≥ 6.5%	% SE (%) Cases Nº at risk	100 0 0 26	90.6 6.3 2 17	90.6 6.3 2 14	90.6 6.3 2 11

1.C. Stroke



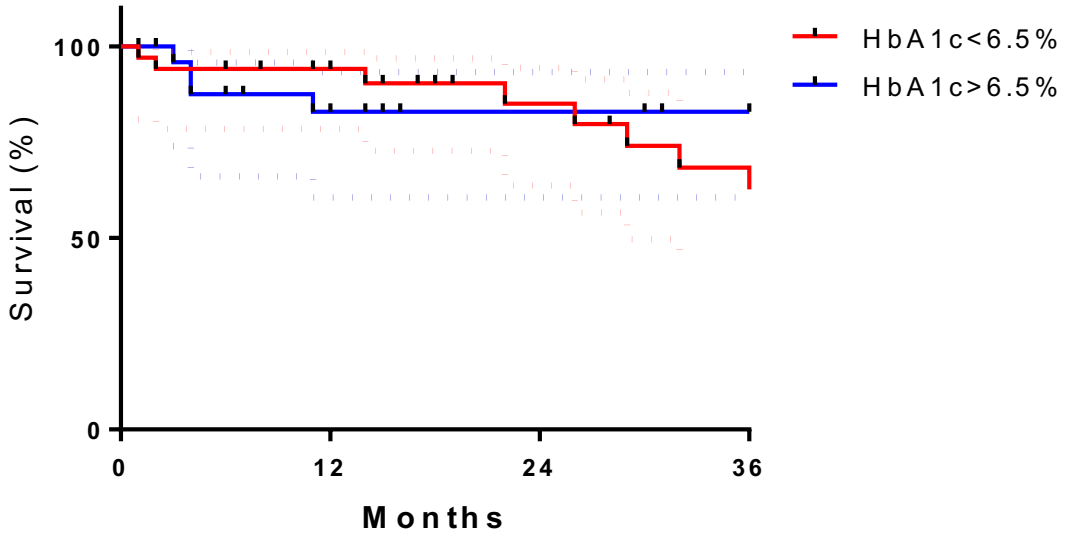
Stroke Log rank p=0.045		30d	12	24	36
HbA1C < 6.5%	% SE (%) Cases Nº at risk	97.3 2.7 1 35	94.5 3.8 2 26	90.6 5.3 3 17	90.6 5.3 3 12
HbA1C ≥ 6.5%	% SE (%) Cases Nº at risk	92.9 4.9 2 24	72.8 9.7 6 13	58.3 12 8 8	58.3 12 8 7

1.D. MALE



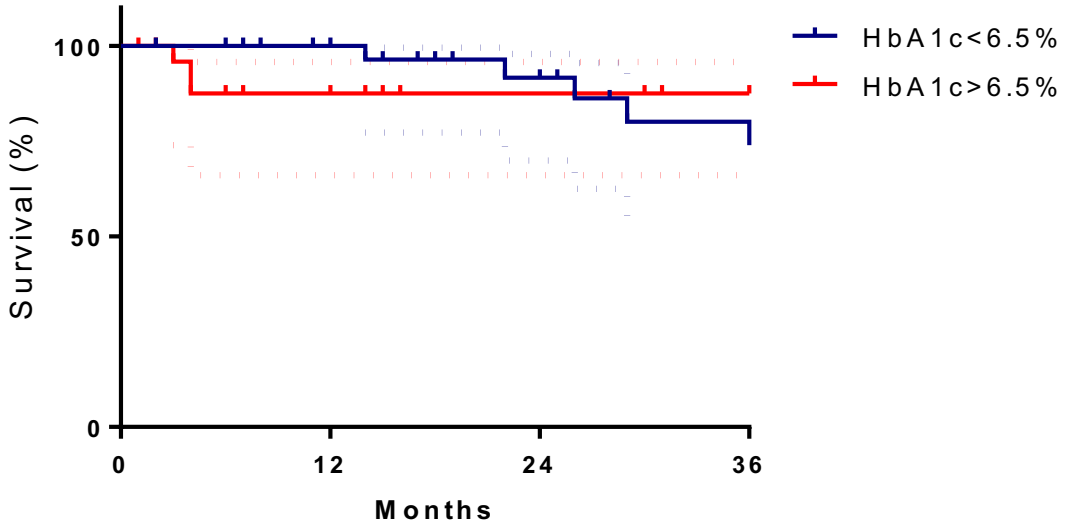
MALE Log rank p=0.057		30d	12	24	36
HbA1C < 6.5%	% SE (%) Cases Nº at risk	100 0 0 36	96.6 3.4 1 27	96.6 3.4 1 18	89.1 7.8 2 12
HbA1C ≥ 6.5%	% SE (%) Cases Nº at risk	96.4 3.5 1 25	92.2 5.3 2 17	86.8 7.3 3 13	72.8 10.9 5 9

1.E. MACE



MACE Log rank p=0.038 Tarone-Ware p=0.113		30d	12	24	36
HbA1C < 6.5%	% SE (%) Cases Nº at risk	94.6 3.7 2 34	89.0 5.2 4 25	80.4 7.5 6 16	64.6 10.2 9 12
HbA1C ≥ 6.5%	% SE (%) Cases Nº at risk	100 0 0 26	82.9 7.8 4 17	82.9 7.8 4 14	82.9 7.8 4 11

1.F. All-cause Mortality



All-Cause Mortality Log rank p=0.246		30d	12	24	36
HbA1C < 6.5%	% SE (%) Cases Nº at risk	100 0 0 36	100 0 0 28	91.6 5.8 2 18	80.1 9.2 4 13
HbA1C ≥ 6.5%	% SE (%) Cases Nº at risk	100 0 0 26	87.5 6.8 3 18	87.5 6.8 3 15	87.5 6.8 3 12

A – Acute myocardial Infarction (AMI); B – Acute Heart Failure (AHF); C- Stroke; D - Major Adverse Limb Event (MALE); E – Major Adverse Cardiovascular Event (MACE); F -All-cause Mortality.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	-
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7-8
		(*e*) Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10

		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The journal welcomes educational and illustrative images that highlight a clinically relevant aspect of surgical practice. Images may consist of medical iconography (CT scan, PET...), peroperative images, clinical photography, or pathology slides. Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for color, at the correct size). Figures should be saved as TIFF, PostScript or EPS files. Figures should be supplied as separate files and not embedded in Microsoft Word™ or similar software. When submitting medical images or patient photographs, patient anonymity should be guaranteed in the appropriate manner.

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1. Reporting of P values

- P values alone are not permitted. They should always be accompanied by a measure of the effect size, and of the precision of the measurement (95% confidence intervals)
- P values should always be reported as exact values, never as 'NS' (not significant) or using the > or < symbol, with the only exception of a P value <0.0001.
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2. Summarizing data

- Data should be checked for normality of distribution using an appropriate statistical test. Normally distributed data should be reported as mean (SD), and otherwise as median (range) or median (IQR).
- When generating graphs, limit the use of color. Bar charts should have error bars representing standard deviation or SEM. Non scientific graphs such as pie charts, 3D charts, etc are not acceptable.

3. Use of statistical tests

- Differences between groups with a non normal data distribution should be compared with non parametric tests
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- P values should be adjusted for multiple testing, when appropriate (Bonferroni)

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