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TITRE

INFLUENCE DE L'INCLUSION DANS UNE ETUDE CLINIQUE SUR LE PRONOSTIC DES PATIENTS AU DECOURS D'UN SYNDROME CORONAIRE AIGU

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Résumé

Introduction. Les études cliniques sont la pierre angulaire des recommandations internationales en cardiologie. Cependant, leurs résultats peuvent être influencés par la sélection des patients inclus et par les modifications comportementales des patients après l'inclusion (effet Hawthorne). Nous avons testé l'hypothèse que les patients inclus par notre équipe dans des études cliniques au décours d'un syndrome coronaire aigu ont un moindre risque cardiovasculaire de base et un meilleur pronostic à 1 an que les patients non inclus.

Méthode. Nous avons réalisé une étude rétrospective monocentrique sur l'ensemble des patients pris en charge en coronarographie pour un syndrome coronaire aigu (SCA) en 2017. Les patients inclus dans l'une des études actives ont été comparés aux patients non inclus, tant sur leurs caractéristiques de bases que sur les évènements cardiovasculaires majeurs et les décès survenant dans l'année suivant le SCA index.

Résultats. Au cours de l'année 2017, 690 patients ont eu une coronarographie pour SCA dans notre service. Parmi eux, 144 ont été inclus dans une étude (6 essais thérapeutiques et 1 cohorte). Les patients inclus avaient un profil de risque cardiovasculaire moins sévère, étant significativement plus jeunes (62,6 vs 68,9 ; $p < 0,001$), moins hypertendus (41,7 vs 56,2% ; $p = 0,003$) moins dyslipidémiques (33,6 vs 47,5% ; $p = 0,004$), avec moins d'antécédents d'angioplastie coronaire (8,3 vs 28,9% ; $p < 0,001$), de pontage aorto-coronaire (1,4 vs 6,6 ; $p = 0,003$) ou d'infarctus du myocarde (IDM) (4,9 vs 13,4% ; $p = 0,007$). A un an, la survenue d'évènements cardiovasculaires majeurs était plus faible dans le groupe des patients inclus (5,6 vs 12,7% ; $p = 0,02$). L'existence d'un diabète ($p = 0,04$) et une durée d'hospitalisation plus longue ($p = 0,02$) étaient indépendamment associés à la survenue du critère de jugement principal. L'inclusion dans une étude était associé à moins d'évenements cardiovasculaires en analyse univariée, cette association n'était plus statistiquement significative en analyse multivariée.

Conclusion. Les patients inclus dans une étude ont un profil de risque cardiovasculaire plus faible et un meilleur pronostic que les patients non inclus. Les déterminants de ces différences sont complexes, probablement sous l'influence des protocoles et de la sélection à l'inclusion réalisée par les investigateurs. L'effet Hawthorne joue probablement un rôle sur les évènements, même si nos résultats ne confirment pas l'inclusion dans une étude comme étant un facteur prédictif indépendant d'évènement. Ce constat devrait être pris en compte lors de l'extrapolation des résultats d'une étude clinique à la population générale dans le cadre des recommandations internationales.

IMPACT OF ENROLLEMENT IN A CLINICAL STUDY ON PATIENTS' PROGNOSIS AFTER AN ACUTE CORONARY SYNDROME

Mots-clefs

Etude clinique

Syndrome coronaire aigu

Biais de sélection

Effet de participation à la recherche

Pronostic

Keywords

Clinical study

Acute coronary syndrom

Selection bias

Research participation effect

Prognosis

Abstract

Introduction. Clinical studies are the cornerstone of international cardiology guidelines. Nonetheless, inclusion bias and patients' behavioural changes after inclusion can impact the results of clinical studies. The purpose of this study was to test the hypothesis that patients enrolled in clinical studies in our unit have a lower cardiovascular risk, and a better prognosis at one year than non-enrolled patients.

Methods. We included in this retrospective monocentric study all patients admitted for an acute coronary syndrom (ACS) and who underwent a coronary angiogram in 2017. Patients enrolled in clinical studies were compared to "not enrolled" patients on their baseline charasteristics and on one-year follow-up major cardiovascular events (MACE).

Results. During 2017, 690 patients underwent a coronary angiogram for an ACS in our center. Among these patients, 144 were enrolled in a clinical study (6 clinical trials, 1 cohort). Enrolled patients had a more favorable cardiovascular risk profile, being younger (62,6 vs 68,9 ; $p < 0,001$), with less hypertension (41,7 vs 56,2% ; $p = 0,003$), less dyslipidemia (33,6 vs 47,5% ; $p = 0,004$), less history of percutaneous coronary intervention (PCI) (8,3 vs 28,9% ; $p < 0,001$), of coronary artery bypass graft surgery (CABG) (1,4 vs 6,6% ; $p = 0,003$) or myocardial infarction (MI) (4,9 vs 13,4% ; $p = 0,007$). At 1-year follow-up, there was statistically fewer MACE in the "enrolled group" (5,6 vs 12,7% , $p = 0,02$). Diabetes ($p = 0,04$) and the length of stay ($p = 0.02$) were independently associated with the occurrence of the primary outcome. Enrollement in a clinical study was a protective factor against MACE occurence in univariate analysis ($p = 0.02$), this association was not statistically significant in mulvariate analysis.

Conclusion. Enrolled patients in our center had a lower cardiovascular risk profile and a better prognosis than non-enrolled patients. The selection made by investigators might be an important factor leading to these differences. Research participation effects probably contributes to improved outcomes, although our results do not confirm study enrollment as an independent predictive factor of events. Nonetheless, our results suggest that one may mitigate the extrapolation of study results to the overall population.

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En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

Table des matieres

Résumé **2**
Abstract **4**
Mots-clefs **4**
Liste des enseignants **6**
Serment d'Hippocrate **11**
Table des matieres **12**
Introduction **13**
Methods **17**
Population and data collection **17**
Groups. **18**
Follow up **18**
Ethical consideration **19**
Statistical analysis **19**
Results **20**
One-year follow up. **22**
Predictors of MACE. **22**
Discussion **24**
Hawthorne effect.. ..... **26**
Conclusion **28**
References **29**
Table and figures **31**

LIST OF ABBREVIATIONS

ACS : Acute coronary syndrome

ANDAMAN : Aspirin Twice a Day in Patients With Diabetes and Acute Coronary Syndrome

BARC : Bleeding academy research consortium

BMI : body mass index

CABG : Coronary artery bypass graft surgery

CARIM : CARdioprotection in Myocardial Infarction

COLCOT : Colchicine Cardiovascular Outcomes Trial

CRAC : Club régional des angioplasticiens du Centre

eGFR : estimated glomerular filtration rate (MDRD)

FLOWER-MI : FLOW Evaluation to Guide Revascularization in Multi-vessel ST-elevation Myocardial Infarction

HBP : High blood pressure

LFEV : Left ventricular ejection fraction

MACE : Major adverse cardiovascular and cerebrovascular events

MI : Myocardial infarction

NSTEMI : Non ST-segment elevation myocardial infarction

PARADISE-MI : Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI

PCI : Percutaneous coronary intervention

REALITY : Cost-effectiveness and Cost-utility of Liberal vs Restrictive Red Blood Cell Transfusion Strategies in Patients With Acute Myocardial Infarction and Anaemia

RCT : Randomized clinical trial

STEMI : ST-segment elevation myocardial infarction

UA : Unstable angina

Introduction

Medical knowledge is mainly based on evidence rather than empirical statements. Evidence based medicine largely uses randomized controlled trial (RCT), which is considered the strongest research design for evaluating interventions in health. As a consequence, cardiology guidelines such as the European Society of Cardiology and the American Heart Association/American college of Cardiology rank the highest level of evidence when data driving the guidelines are derived from multiple randomized clinical trials and/or systematic reviews and meta-analysis.

This high level of evidence is mainly due to randomization and the use of a control group, which enable to evaluate an intervention effect, as groups are similar in terms of both known and unknown prognostic factors (1). Randomization guarantees between-group comparability and ensures that groups only differ in outcomes because of the intervention being tested. A high-quality randomization has to be ensured by A) a truly random sequence generation, B) unpredictability of the allocation (2–4) that has to be concealed until the intervention is assigned, and C) masking (or blinding) of group allocation that has to be maintained whenever possible. Masking refers to a process that attempts to keep the group (e.g. active drug or placebo) to which the study subjects are assigned not known or easily ascertained by those who are “masked”. The goal of masking is to prevent ascertainment bias.

Results of RCT can nevertheless be weakened by selection bias (5–9). Enrolled patients’ profile is indeed highly dependent on RCT inclusion and exclusion criteria that may leave aside a significant subgroup of patients. One may also acknowledge that all screened

patients who meet the inclusion criteria and do not meet the exclusion criteria are not always enrolled or even proposed to, because physicians may not systematically screen all consecutive patients and/or may propose protocol inclusion because of various consideration such as distance from the investigating centre, frailty, patients ability to understand the protocol.

This concern has particularly emerged since the inclusion rate dropped during the last decades (10), thereby stressing the problem of generalizing statistical results to the overall population.

Moreover, behavioral studies have suggested that patients enrolled in interventional or observational studies may behave differently than not-enrolled patients, this being described as the "Hawthorne effect" (11) (12). The Hawthorne effect may lead to overestimate the effect of an intervention by improving outcomes of enrolled patients through a different behaviour.

A better prognosis of patients included in studies has already been suggested (13,14). For instance, participation in obstetrics and gynaecology clinical trials improved outcomes (particularly in high quality RCTs) in women's health in a recent meta-analysis (15) (NIJJAR), and the accrued benefit by women participating in RCTs was sustained irrespective of whether the RCT intervention was effective or not. Both Hawthorne effect and inclusion bias could partly explain this clinical trials participation related improved outcomes.

Therefore, one may question the global extrapolation of guidelines based on the results of RCT, since patients enrolled in these RCT may not accurately reflect the overall population.

Our research group has a specific interest in acute coronary syndromes and has been enrolling patients in several registries and RCT at the acute phase of myocardial infarction for many years. The European Society of Cardiology guidelines on STEMI and NSTEMI/Unstable angina (UA) are based on data from RCT in which we enrolled several of our patients. Despite our efforts, not all of our MI patients are screened and/or enrolled in these studies and we wondered whether our enrolled patients had a more favorable profile than our non-enrolled patients. The purpose of this study was to test the hypothesis that patients admitted for an acute coronary syndrom (ACS) and enrolled in clinical studies in our unit have a lower cardiovascular risk, and a better prognosis at one year than non-enrolled patients.

Methods

Population and data collection

This is a retrospective monocentric study, with prospectively collected data. The population was all consecutive patients admitted for an acute coronary syndrome (ACS) who underwent a coronary angiogram in Tours University hospital, from January the 1st to December the 31st 2017. The list of all ACS patients was extracted from our local database on CardioReport® (CardiovascularXchange®) through its specific research software AngioQuery®.

Administrative, clinical and procedural data were collected to feed the CRAC registry database (6) (PMID : 29685699): a multicentric, prospective and permanent cardiology registry in Centre Val-De-Loire French region, which includes all patients referred for coronary angiogram. A non-opposition written consent form was mandatory before inclusion and data collection in this registry.

Data were real-time recorded by the interventional cardiologists in the reporting software (CardioReport®) at the time of the procedure. Laboratory blood tests at the time of the ACS were retrospectively collected from our hospital digital files.

Data regarding baseline characteristics included: age, cardiovascular risk factors, distance between patient's home and our hospital (calculated with Google Maps ®), length of stay in our clinical unit, history of myocardial infarction (MI), history of percutaneous coronary intervention (PCI), history of coronary artery bypass graft surgery (CABG), preserved left ventricular ejection fraction (LVEF) status defined as LVEF > 40%, and presence of multivessel disease on the angiogram. For the prespecified subgroup of STEMI patients, the

delay from diagnosis ECG to culprit lesion guide wire passage and the use of fibrinolysis were also recorded.

Groups.

Patients were divided in two groups, depending whether they were enrolled in a clinical study, having signed a consent form during their stay. Active screening and enrollment in seven clinical studies were ongoing during this period: a prospective acutely reperfused STEMI cohort “CARIM” (NCT02967965), a myocardial infarction phase 3 RCT “COLCOT“ (NCT02551094), a STEMI phase 3 RCT “FLOWER-MI” (NCT02943954), an acute coronary syndrome phase 4 RCT “ANDAMAN” (NCT02520921), an acute coronary syndrome phase 4 RCT “AUGUSTUS” (NCT02415400), a myocardial infarction RCT “REALITY” (NCT02648113) and a myocardial infarction phase 3 RCT “PARADISE-MI” (NCT02924727). The description and objectives, inclusion and exclusion criteria of all clinical trials are summarized in *Table 1*.

Follow up

As required by the CRAC registry, an intra-hospital and one-year phone call follow up was performed by local investigators for all patients, whether or not they were included in a study. Information about current medication, major adverse cardiac and cerebrovascular events (MACE) including death, MI, unplanned revascularization and stroke were collected, as well as severe bleeding events (defined as BARC > 3 (Mehran). The primary outcome of our study was the event of MACE at the 1-year follow-up.

Ethical consideration

Our study being retrospectively performed in patients enrolled in the CRAC registry there was no need for additional ethic committee advice. All patients had signed a non-opposition form at the time of admission for acute coronary syndrome (ACS) that included future use of their data for research purpose.

Statistical analysis

Analyses were performed using the statistical software RStudio Desktop Open Source Edition (Rstudio Team, 2019, Version 1.2.1335), enhanced by the Epi package (Bendix Carstensen and Martyn Plummer, 2019, v2.38) and questionr package (Julien Barnier, 2018, V.0.7.0). Continuous variables were reported as means ± standard deviations. Discrete variables were described as counts and percentages. Groups were compared using Student t test after verifying equal standard deviation for continuous variables (otherwise using Welch test), and by the Pearson's $\chi 2$ test for discrete variables, with Yates continuity correction for small effectives. A p value < 0.05 was considered statistically significant. Relatives risks and odd ratios were given with 95% confidence intervals. Univariate and multivariate logistic regression was used to determine predictive factors of MACE at 1 year.

Results

In our center, 690 patients with ACS underwent a coronary angiogram in 2017. Patients who were admitted at least two times for an ACS in 2017 were not considered as a a new entry at each admission, but as a unique patient. The flow chart is presented in *Figure 1*. Among 144 (20.9%) were enrolled in a clinical study during this period. Patient's baseline characteristics are presented in table 1. Mean age was 67.56 ± 13.12 years. Patients in the « enrolled group » were younger than the "not enrolled" group (62.6 vs 68.9 years respectively, $p < 0.001$) and had a lower cardiovascular risk profile, with a significantly lower prevalence of hypertension (41.67 vs 56.15 %, $p = 0.0027$), dyslipidemia (33.57 vs 45.51 %, $p = 0.0038$), a lower BMI (26.45 vs 27.59 kg/m^2, $p = 0.025$) and a shorter length of stay (3.5 ± 2.16 vs 4.26 ± 7.6 days, $p = 0.042$). Diabetes mellitus was not statistically different between groups. Current smoking was however higher in the enrolled group (40.6 vs 27.9 %, $p = 0.005$).

Enrolled patients had significantly fewer past cardiovascular history and comorbidities than not enrolled patients. Past myocardial infarction was observed in 4.86 vs 13.39 % respectively ($p = 0.007$), past PCI in 8.33% versus 28.94 % ($p < 0.001$), and past CABG in 1.39 vs 6.60 % ($p = 0.026$). The enrolled group included more STEMI (68.75 vs 31.68 %, $p < 0.001$).

There was no statistical difference on heart rate and blood pressure at admission. Estimated glomerular filtration rate (GFR) by the MDRD formula was higher in the included group (94.2 vs 84.8 ml/min/1.73m^2, $p < 0.001$), so were the hemoglobin level (144 vs 140 g/dl, $p = 0.042$), the troponin peak level (3871 vs 2253 IU/l, $p < 0.001$) and the CPK peak level (2016 vs 1175 IU/l, $p < 0.001$).

Regarding the severity of coronary artery disease, coronary angiogram showed a non-significant trend of less multivessel disease in enrolled patients (54.17 vs 65.38%, p = 0.17).

In the overall population, there were few differences on medical treatments at discharge, with a significantly more frequent use of ticagrelor in enrolled patients (87.5 vs 64.67%, p < 0.001), and consequently a less frequent use of clopidogrel (11.11 vs 35.67, p < 0.001) in this group.

In the STEMI subgroup, enrolled patients remained significantly younger (61 vs 65.65 years, p = 0.002) than non enrolled patients, with a shorter length of stay (3.79 vs 5.85 days, p < 0.001). As in the overall analysis, enrolled patients were more often active smokers (47.96 vs 33.33 %, p= 0.025). Other risk factors did not significantly differ between groups. Non enrolled patients had significantly more past PCI (7.07 vs 16.76%, p = 0.037). The diagnostic ECG-to-wire delay, a surrogate marker of ischemia duration, was shorter in the enrolled group, with a mean delay of 1.75 vs 2.16 hours (p = 0.003).

In the ACS without ST elevation subgroup, enrolled patients were also significantly younger (66.04 vs 70.36 years, p= 0.0126) and had less history of PCI (11.11 vs 34.5%, p=0.0025), without any other statically significant differences regarding cardiovascular risk factors, clinical and paraclinical findings. As observed in the overall population, enrolled patients were more frequently treated with ticagrelor (84.4 vs 53.6 %, p < 0.001) rather than clopidogrel (15.6 vs 45.6%, p < 0.001) at discharge.

In-hospital outcomes were also analyzed: there was significantly less in-hospital death in enrolled patients (0 vs 3.48%, p= 0.047). This difference remained significant in the STEMI subgroup (0 vs 10.4 %, p = 0.002). In-hospital severe bleeding (i.e. BARC score ≥ 3) (16)

occurred in 0 vs 4.62% of patients in the STEMI subgroup, with a strong trend towards significance (p = 0.07).

One-year follow-up.

At 1 year, the primary composite outcome (including death, myocardial infarction, stroke, unplanned revascularization) was significantly less often met in enrolled patients (5.56 vs 12.67%, p = 0.024). There was no statistical difference in analyzing the events of the composite criterion individually: i.e. Death (1.39 vs 4.69%, p = 0.121), myocardial infarction (1.39 vs 2.74%, p = 0.536), stroke (no events reported), unplanned revascularization (4.17 vs 8.41%, p = 0.126). There was also no difference in the occurrence of major bleeding (0.69 vs 2.50%, p = 0.314). In the subgroup analysis, there was no significant difference in one-year follow up events.

Predictors of MACE.

In univariate analysis, inclusion in a clinical study was associated with a significantly lower MACE occurrence (OR = 0.405, [0.176 - 0.818], p = 0.020). Current smoking (OR = 0.502 [0.368 - 0.685], p = 0.027) and admission for STEMI (OR = 0.557 [0.421 - 0.737], p = 0.037) were also found to be associated with significantly less MACE during the one year follow up. The predictive factors of MACE were age (OR = 1.022 [1.004- 1.043], p = 0.020), length of stay (OR = 1.035 [1.008- 1.067], p = 0.011), diabetes (OR = 2.031 [1.197- 3.387], p = 0.007) and pluritroncular disease (OR = 2.1689 [1.243- 3.989], p = 0.009). Estimated GFR was non-significantly associated with less MACE (OR = 0.993 [0.983 - 1.004], p = 0.206), as well as

hemoglobin level (OR = 0.987 [0.972 - 1.003], p = 0.093) and LVEF over 40% (0.629 [0.352 - 1.179], p = 0.130).

All parameters significantly associated with MACE occurrence were tested in multivariate analysis. Remaining independent predictor factors of MACE were diabetes (OR = 1.748 [1.007 - 2.983], p = 0.043) and length of stay (OR = 1.035 [1.006 - 1.066], p = 0.017). In multivariate analysis, study inclusion did not reach the statistical significance as an independent predictor factor of MACE (OR = 0.542 [0.228 - 1.148], p = 0.133), neither did pluritroncular disease (OR = 1.717 [0.964 - 3.209], p = 0.076). A significant association was found between STEMI and diabetes and lead to an increased risk of MACE (Coefficient 1.19, p = 0.049).

Discussion

Our data showed a more favorable risk profile at inclusion in ACS patients undergoing coronary angiography enrolled in a clinical study as well as a better prognosis compared to non-enrolled patients, and thus confirmed our hypothesis.

The enrolled patients' better prognosis in univariate analysis might be explained by different reasons. The main difference to be mentioned is that enrolled patients had a lower risk profile than non-enrolled patients, with less hypertension, less dyslipidemia, less past history of cardiovascular diseases, and above all younger age. The first assumption to explain this age gap would be to incriminate an upper age limit as an exclusion criterion in studies. The AUGUSTUS study did not include patients over 95 years old, and the CARIM cohort did not include patients over 80. But included patients remained statistically younger when only comparing patients under the age of 80. Given that STEMI patients are known to be younger than NSTEMI patients (17,18), another rational assumption to explain younger included patients would be the higher proportion of STEMI, resulting from a large STEMI patients cohort conducted during this period (CARIM). But included patients were still statistically younger in the STEMI subgroup as well as in the non-ST elevation ACS subgroup. These two findings suggest an inclusion bias, leading to a younger population in ACS studies. A better prognosis is expected in younger patients: an analysis of the Global Registry of Acute Coronary Events (GRACE) showed a 6-month mortality increase of 1.8% (95% CI 1.64 – 1.91) by each decade of age (19,20). However, age was not an independent predictor of outcome in our study.

Inclusion protocols may also lead to inclusion bias, due to multiple exclusion criteria. Most of our ongoing studies could not include patients in cardiogenic shock, with a short life expectancy, severe kidney disease or with a history of cardiac surgery. Patients with preexisting heart failure could not be enrolled in our STEMI cohort “CARIM”, and the largest ongoing RCT “COLCOT” even mentioned an open exclusion criterion, if the investigator considered the patient “unsuitable for the study”.

A correlation between study participation and better overall medical care was also suspected. A 2017 study (21) including more than 592 000 patients with acute myocardial infarction in 766 US hospitals showed different prognosis depending on whether patients were treated in trial hospital. Patients admitted to hospitals that participated in clinical trials more often received guideline-adherent care and had better long-term outcomes with one-year MACE rates lower for trials hospitals (adjusted HR 0.96, 95 % CI 0.93-0.99). With very few patients participating in clinical trials among enrolling hospitals (less than 1 %), these results cannot be only explained by improved outcomes in enrolled patients. The given explanations for these improved outcomes in trial-hospitals is that clinician-investigators seeking to deliver cutting-edge care through participation in clinical trials may be more likely to keep up to date on the latest literature and guidelines. (22,23).

In addition to this difference in inter-hospital care, our study attempted to highlight an intra-hospital difference between enrolled and not enrolled patients. At this intra-hospital level, another plausible reason for the better prognosis could be a better post-ACS care for included patients, with a better drug adherence and a closer follow-up. Most studies indeed

involved at least 3 medical consultations during the first 12 months after the ACS, which is arguably higher than the average frequency of consultation observed in all ACS comers' patients. In this study we did not retrieve the number of consultations during the first year after ACS since some patients especially non-enrolled patients, were followed up outside of our institution. Because of the retrospective nature of our study, we could not retrieve patients adherence to precriptions.

Hawthorne effect.

Research participant's modified behavior in response to being observed, also known as the "Hawthorne Effect" (11,24), might also be involved in better outcomes. Awareness of being observed can engenders beliefs about researchers' expectations. Conformity then lead behavior to change in line with these expectations. Because of the retrospective nature of our work we could not specifically measure this effect through a questionnaire investigating behavioral changes. We can only speculate that according to previously published data, patients enrolled in clinical studies are likely to modify their behavior with more adherence to healthy lifestyle, prescribed drugs and doctor's appointments.

Active smoking appeared as a protective factor against MACE in univariate analysis and was a non-significant protective factor in multivariate analysis, while other usual cardiovascular risk factors were MACE predictors. This might be related to the "smoker's paradox", already reported in some studies as an apparent survival benefit of smokers in the setting of ACS (25–28). Different explanations of this phenomenon have been proposed, firstly because of

confounding factors: smokers are indeed younger, have fewer risk factors and comorbidities, and are more aggressively treated (29–31). Another explanation highlighted by studies from the thrombolytic period was the higher thrombotic burden, which could confer a heightened response to thrombolysis (32). An enhanced response to clopidogrel therapy in smokers has also been proposed (33,34). Moreover, we suggest that smoking is a highly preventable cardiovascular risk factor, and smoking patients might have better prognosis thanks to an easier eviction of risk factors, compared to elderly, diabetic and hypertensive patients. Despite this evidence, studies still show active smoking as an independent predictor of outcome, making this concept controversial.

As previously mentioned, our study has several limitations mostly related to its retrospective nature. We could not retrieve patient's prescription after discharge such as continuation of dual antiplatelet therapy during the year following the index ACS. We could not either investigate patients adherence to drug prescription and healthy lifestyle that may also be modified by enrollment in a clinical study.

Conclusion

Enrolled patients in our center had a lower cardiovascular risk profile and a better prognosis than non-enrolled patients. The selection made by investigators might be an important factor leading to these differences. Research participation effects probably contributes to improved outcomes, although our results do not confirm study enrollment as an independent predictive factor of events. Nonetheless, our results suggest that one may mitigate the extrapolation of study results to the overall population. Moreover, demonstrating a causal relationship between study inclusion and better outcomes may raise ethical issues of not enrolling or at least screening patients in clinical studies, if such participation would be beneficial to them.

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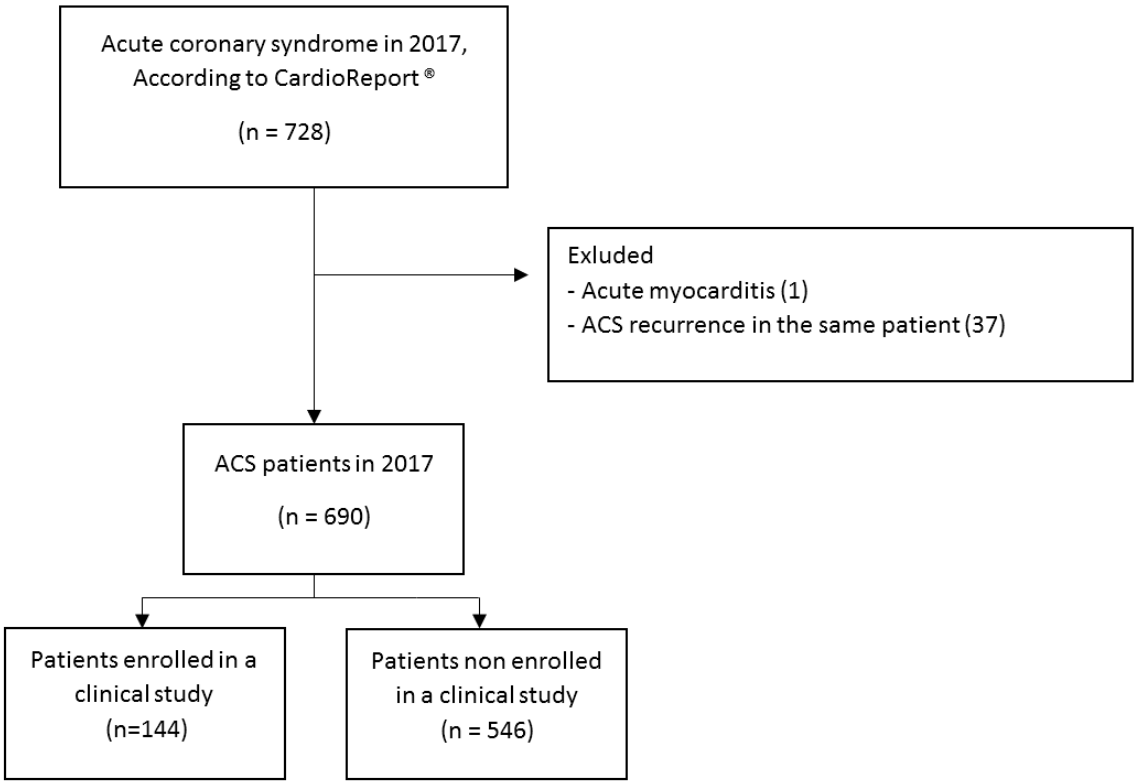
Tables et figures

Figure 1 : Flow chart



ACS : Acute coronary syndrome

Table 1 : Studies summary

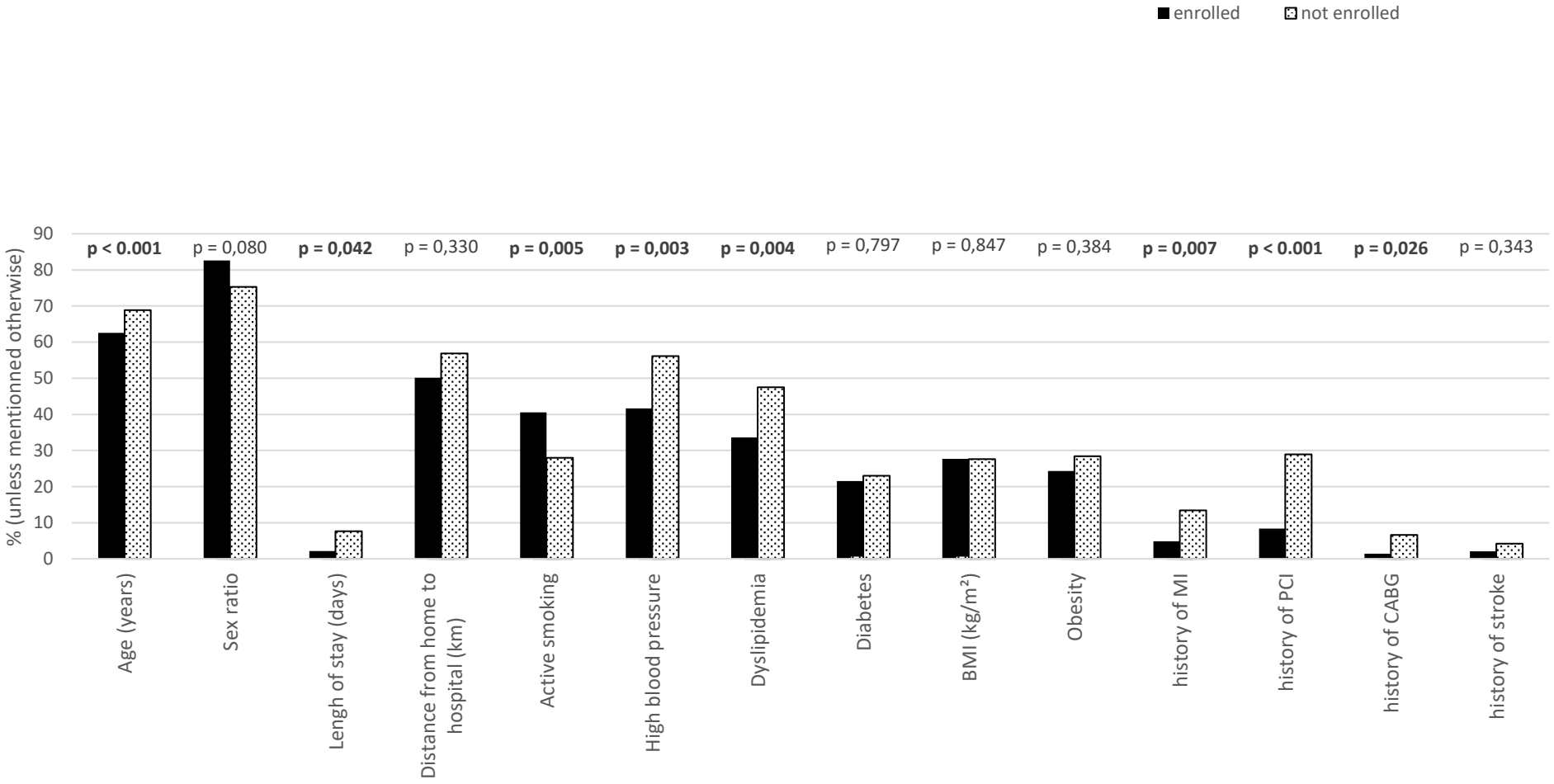
Study	Description	Type	Masking	STEMI/ NSTEMI/ NTE ACS	Number of patients (% of included patients)	Age limit	Follow-up frequency
FLOWER-MI	In STEMI patients with multi-vessel disease amenable to PCI, test the use of FFR in addition to angiography on cardiovascular outcomes, compared with the current practice of angiography- guided PCI, by improving the appropriateness of revascularization.	RCT	None	STEMI	10 (6.9%)	At least 18	M1, M6, M12
ANDAMAN	Compare treatment with enteric coated aspirin twice a day (100 mg in the morning and 100 mg in the evening) versus enteric coated aspirin 100 mg once per day on a composite end-point of ischemic events in diabetic patients with acute coronary syndrome.	Phase 4 RCT	None	STEMI / NSTEMI	12 (8.3%)	At least 18	M1, M6, M12
AUGUSTUS	Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention	Phase 4 RCT	None	STEMI NSTEMI NSTE ACS	5 (3.5%)	18-95	M1, M2, M3, M4, M5, M6
COLCOT	Evaluate whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after myocardial infarction.	Phase 3 RCT	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	STEMI / NSTEMI	61 (42.4%)	At least 18	M1, M3, M6, M9, M12
CARIM	Prospective cohort of 2,000 patients with a first myocardial infarction and undergoing reperfusion therapy in order to evaluate the impact of patient-related confounders on myocardial infarct size and LRI in order to further design a modeling of myocardial infarct size	Prospective cohort	-	STEMI	51 (35.4%)	18-80	Day 3, M6, M12.
PARADIZE	Evaluate the Efficacy and Safety of LCZ696 Compared to Ramipril on Morbidity and Mortality in High Risk Patients Following an AMI	Phase 3 RCT	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	STEMI / NSTEMI	4 (2.8%)	At least 18	W1, W2, M1, M2, M4, M8, M12, M16, M20, M24, M28, M32.
REALITY	Cost-effectiveness and Cost-utility of Liberal vs Restrictive Red Blood Cell Transfusion Strategies in Patients With Acute Myocardial Infarction and Anemia	RCT	None	STEMI / NSTEMI	1 (0.7%)	At least 18	M1

Table 2 : Baseline Characteristics, clinical and biological findings at admission, treatments at discharge in overall population

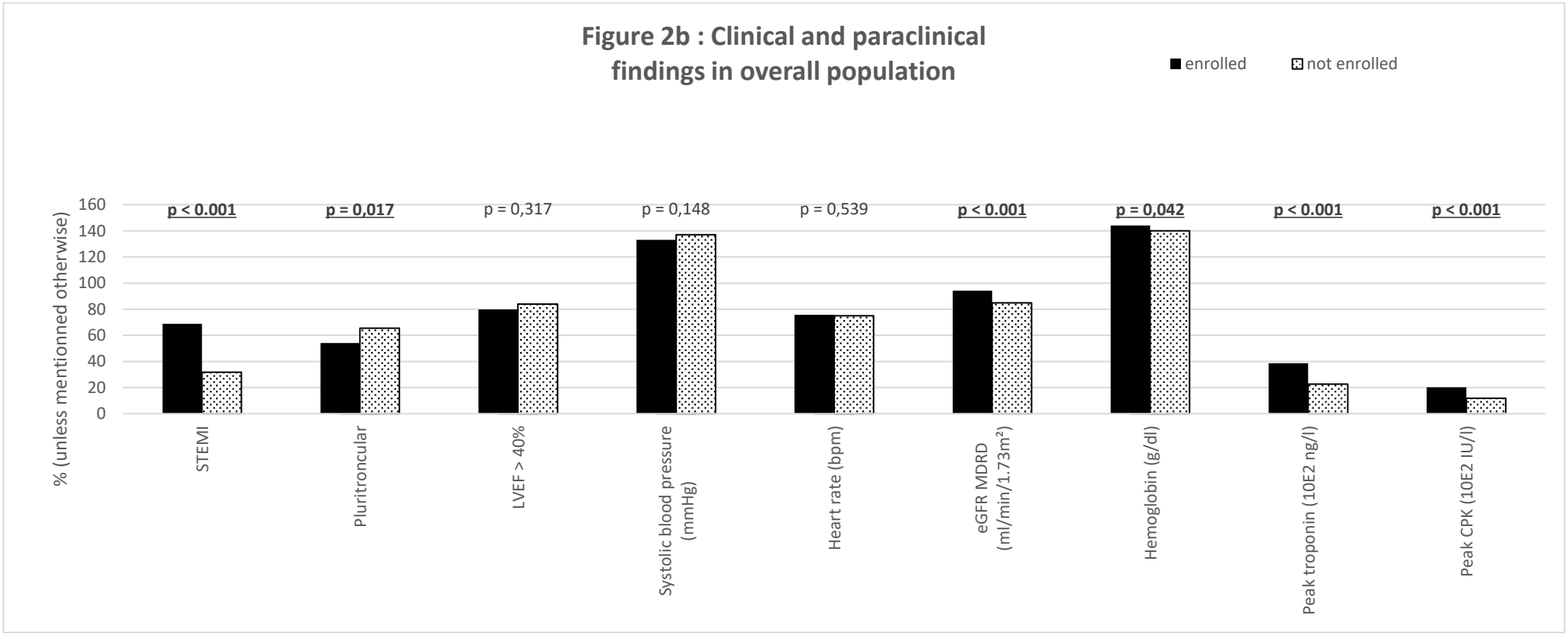
	Overall (n = 690)	*Enrolled patients (n = 144)*	*Not enrolled patients (n = 546)*	*p value*
Age	67,56 (13,12)	62,59 (10,96)	68,87 (13,35)	< 0,001
Male	530 (76,81)	119 (82,64)	411 (75,27)	0.080
Lengh of stay (days)	4,10 (6,84)	3,50 (2,16)	4,26 (7,60)	0.042
Distance from home to hospital (km)	55,45 (69,05)	50,13 (74,70)	56,85 (67,48)	0.330
Active smoking	210 (30,57)	58 (40,56)	152 (27,94)	0.005
High blood pressure	366 (53,12)	60 (41,67)	306 (56,15)	0.003
Dyslipidemia	306 (44,61)	48 (33,57)	258 (47,51)	0.004
Diabetes	156 (22,67)	31 (21,53)	125 (22,98)	0.797
BMI (kg/m²)	27,62 (4,79)	27,69 (4,53)	27,60 (4,86)	0.847
Obesity	190 (27,54)	35 (24,31)	155 (28,39)	0.384
history of myocardial infarction	80 (11,61)	7 (4,86)	73 (13,39)	0.007
history of PCI	170 (24,64)	12 (8,33)	158 (28,94)	< 0,001
history of CABG	38 (5,51)	2 (1,39)	36 (6,60)	0.026
history of stroke	26 (3,77)	3 (2,08)	23 (4,21)	0.343
STEMI	272 (39,42)	99 (68,75)	173 (31,68)	< 0,001
Pluritroncular disease	435 (63,04)	78 (54,17)	357 (65,38)	0.017
LVEF > 40%	561 (82,99)	115 (79,86)	446 (83,83)	0.317
Systolic blood pressure (mmHg)	136 (24,3)	133 (26,4)	136,6 (23,7)	0.148
Heart rate (bpm)	75 (16,2)	75,8 (16,4)	74,9 (16,1)	0.539
eGFR MDRD (ml/min/1.73m²)	86,9 (27,9)	94,2 (24,6)	84,8 (28,5)	< 0,001
Creatinin (µmol/l)	86,7 (38,3)	79,2 (23,27)	88,9 (41,4)	< 0,001
Hemoglobin (g/dl)	141 (17,4)	144 (15,8)	140 (17,9)	0.042
Peak troponin (ng/l)	2669 (3025)	3871 (3249)	2253 (2832)	< 0,001
Peak CPK (IU/l)	1374 (1950)	2016 (2123)	1175 (1851)	< 0,001
<u>Treatments at discharge</u>				
Aspirin	668 (99,55)	142 (98,61)	526 (99,81)	0.228
P2Y12 inhibitor	659 (98,21)	143 (99,31)	516 (97,91)	0.446
Ticagrelor	451 (67,21)	126 (87,5)	325 (61,67)	< 0,001
Clopidogrel	204 (43,68)	16(11,11)	188 (35,67)	< 0,001
Prasugrel	4 (0,60)	1 (0,69)	3 (0,57)	1
Anticoagulant	66 (9,84)	12 (8,33)	54 (10,25)	0.599
Apixaban	19 (2,83)	4 (2,78)	15 (2,85)	1
Vitamin K antagonist	26 (3,87)	6 (4,17)	20 (3,80)	1
Dabigatran	7 (1,04)	0 (0)	7 (1,33)	0.354
Rivaroxaban	14 (2,09)	2 (1,39)	12 (2,28)	0.740

BMI : Body mass index, PCI : percutaneous coronary intervention, STEMI : ST-segment elevation myocardial infarction, CABG : Coronary artery bypass graft surgery, LVEF : Left ventricular ejection fraction, eGFR : estimated glomerular filtration rate (MDRD)

Figure 2a : Baseline Characteristics and cardiovascular history in overall population



BMI : Body mass index, PCI : percutaneous coronary intervention, STEMI : ST-segment elevation myocardial infarction, CABG : Coronary artery bypass graft surgery, LVEF : Left ventricular ejection fraction, eGFR : estimated glomerular filtration rate (MDRD



STEMI : ST-segment elevation myocardial infarction, LVEF : left ventricular ejection fraction, eGFR :estimated glomerular filtration rate

Figure 2c : Antithrombotic treatment at discharge in overall population

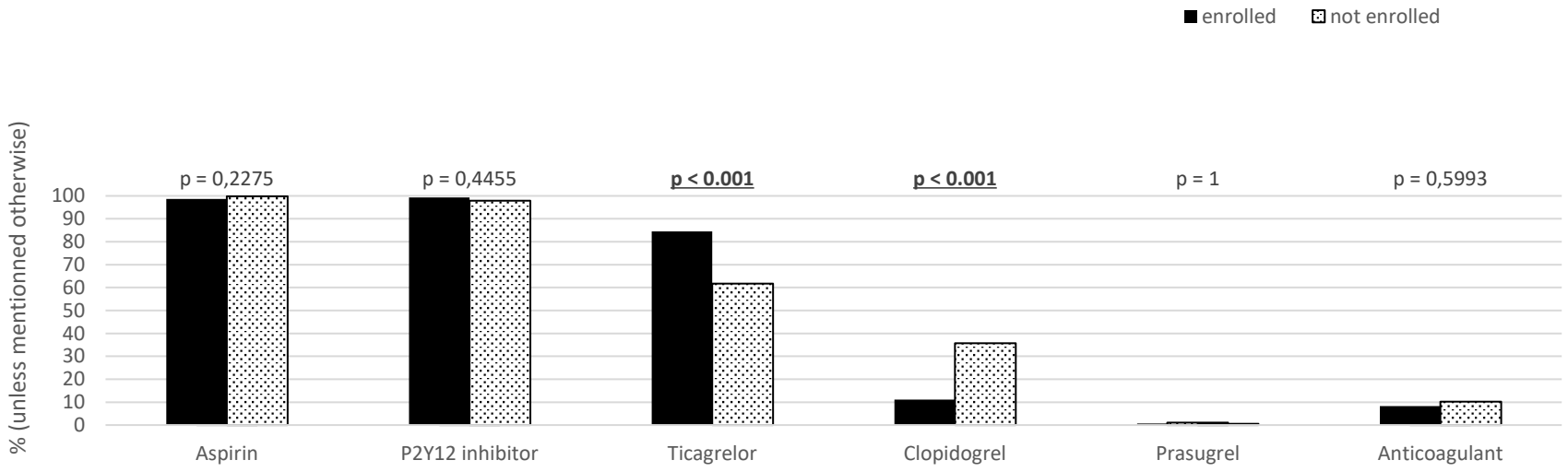
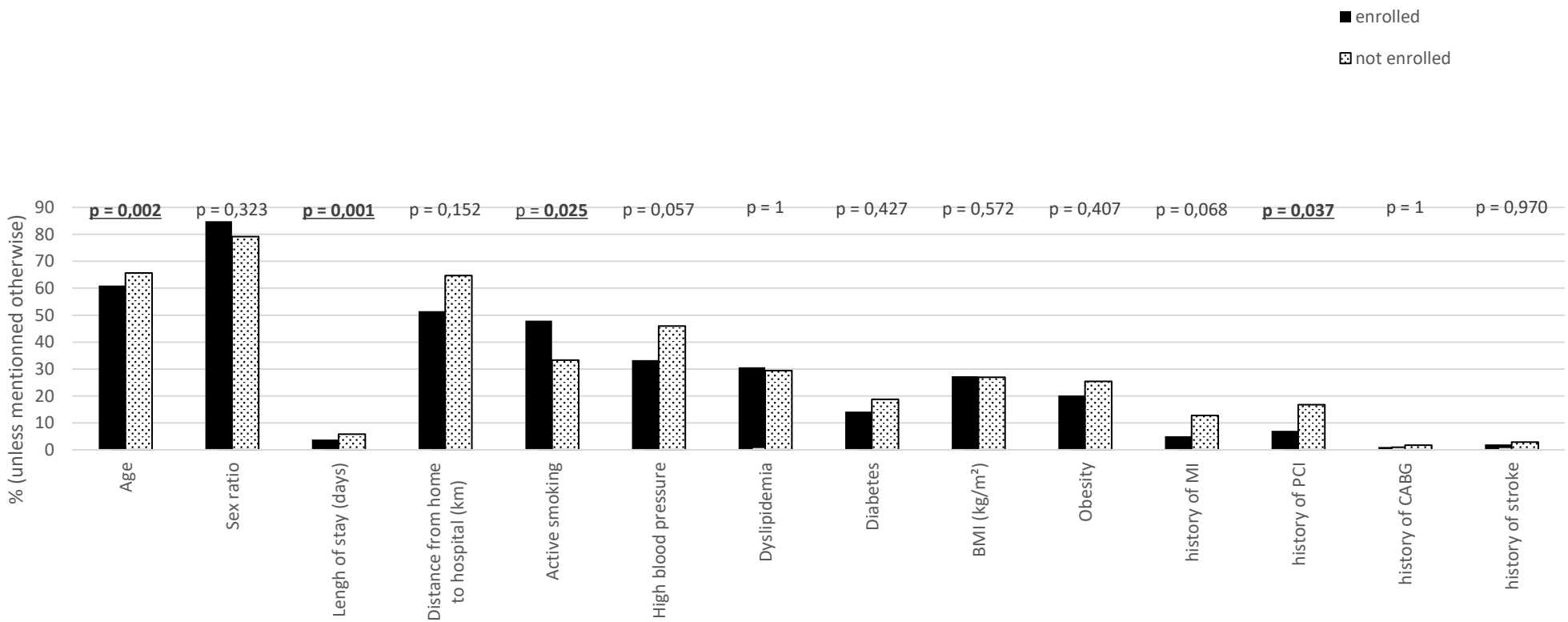


Table 3 : Baseline characteristics, clinical and biological findings at admission, treatments at discharge in STEMI patients

	Overall (n = 272)	*Enrolled patients (n = 99)*	*Not enrolled patients (n = 173)*	*p value*
Age	63,97 (12,90)	61,02 (10,92)	65,65 (13,65)	0.002
Male	221 (81,25)	84 (84,85)	137 (79,19)	0.323
Lengh of stay (days)	5,10 (6,20)	3,79 (1,60)	5,85 (7,59)	< 0.001
Distance from home to hospital (km)	59,82 (76,75)	51,44(67,14)	64,66 (81,59)	0.152
Active smoking	104 (38,66)	47 (47,96)	57(33,33)	0.025
High blood pressure	112 (41,33)	33 (33,33)	79 (45,93)	0.057
Dyslipidemia	80 (29,85)	30 (30,61)	50 (29,41)	1
Diabetes	46 (17,04)	14 (14,14)	32 (18,71)	0.427
BMI (kg/m²)	27,16 (4,60)	27,28 (4,64)	26,95 (4,54)	0.572
Obesity	64 (23,53)	20 (20,20)	44 (25,43)	0.407
history of myocardial infarction	27 (9,93)	5 (5,05)	22 (12,72)	0.068
history of PCI	36 (13,24)	7 (7,07)	29 (16,76)	0.037
history of CABG	4 (1,47)	1 (1,01)	3 (1,73)	1
history of stroke	7 (2,57)	2 (2,02)	5 (2,89)	0.970
ECG-guide wire delay (min)	2,00 (1,26)	1,75 (0,66)	2,16 (1,51)	0.003
Pluritroncular disease	152 (55,88)	49 (49,49)	103 (59,54)	0.380
Fibrinolysis	3 (1,10)	1 (1,01)	2 (1,16)	1
LVEF > 40%	77 (29,62)	25 (25,25)	52 (32,30)	0.285
Systolic blood pressure (mmHg)	125,6 (23)	126,8 (26,2)	124,9 (20,9)	0.252
Heart rate (bpm)	77,7 (16,7)	76,2 (16,2)	78,6 (17)	0.530
eGFR MDRD (ml/min/1.73m²)	89,8 (26,7)	94,3 (21,9)	87 (28,8)	0.023
Creatinin (µmol/l)	83,5 (29,4)	78 (19,4)	86,6 (33,5)	0.009
Hemoglobin (g/dl)	142 (18,5)	142,6 (16,9)	142 (19,5)	0.770
Peak troponin (ng/l)	4548 (3098)	5072 (3133)	4400 (3059)	0.089
Peak CPK (IU/l)	2639 (2296)	2664 (2209)	2625 (2352)	0.890
<u>Treatments at discharge</u>				
Aspirin	252 (99,60)	98 (98,99)	154 (100)	0.823
P2Y12 inhibitor	243 (96,05)	98 (98,99)	145 (94,16)	0.856
Ticagrelor	213 (84,19)	88 (88,89)	125 (81,17)	0.143
Clopidogrel	27 (10,67)	9 (9,09)	18 (11,69)	0.657
Prasugrel	3 (1,19)	1 (1,02)	2 (1,30)	1
Anticoagulant	21 (8,30)	8 (8,08)	13 (8,44)	1
Apixaban	6 (2,37)	3 (3,03)	3 (1,95)	0.898
Vitamin K antagonist	6 (2,37)	3 (3,03)	3 (1,95)	0.898
Dabigatran	2 (0,79)	0 (0)	2 (1,30)	0.681
Rivaroxaban	7 (2,77)	2 (2,02)	5 (3,25)	0.851

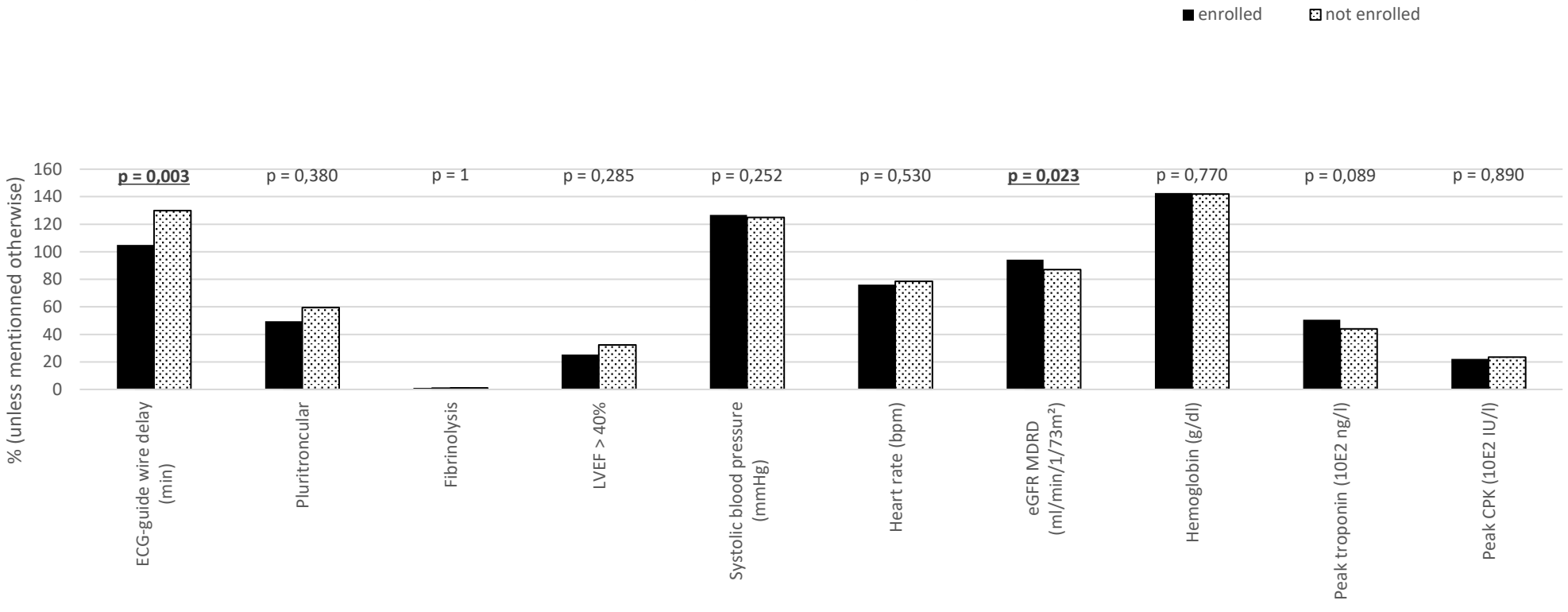
BMI : Body mass index, PCI : percutaneous coronary intervention, CABG : Coronary artery bypass graft surgery, LVEF : Left ventricular ejection fraction, eGFR : estimated glomerular filtration rate (MDRD)

Figure 3a : Baseline characteristics, cardiovascular history in STEMI patients



BMI : Body mass index, PCI : percutaneous coronary intervention, STEMI : ST-segment elevation myocardial infarction, CABG : Coronary artery bypass graft surgery, LVEF : Left ventricular ejection fraction, eGFR : estimated glomerular filtration rate (MDRD

Figure 3b : Clinical and paraclinical findings in STEMI patients



STEMI : ST-segment elevation myocardial infarction, LVEF : left ventricular ejection fraction, eGFR :estimated glomerular filtration rate

Figure 3c : antithrombotic treatment at discharge in STEMI patients

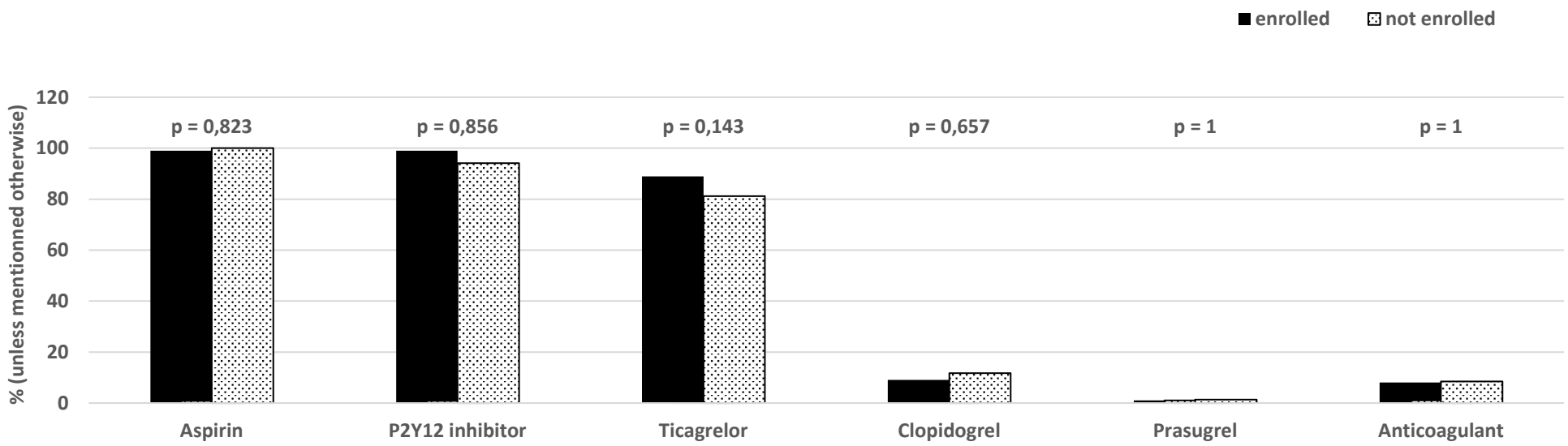
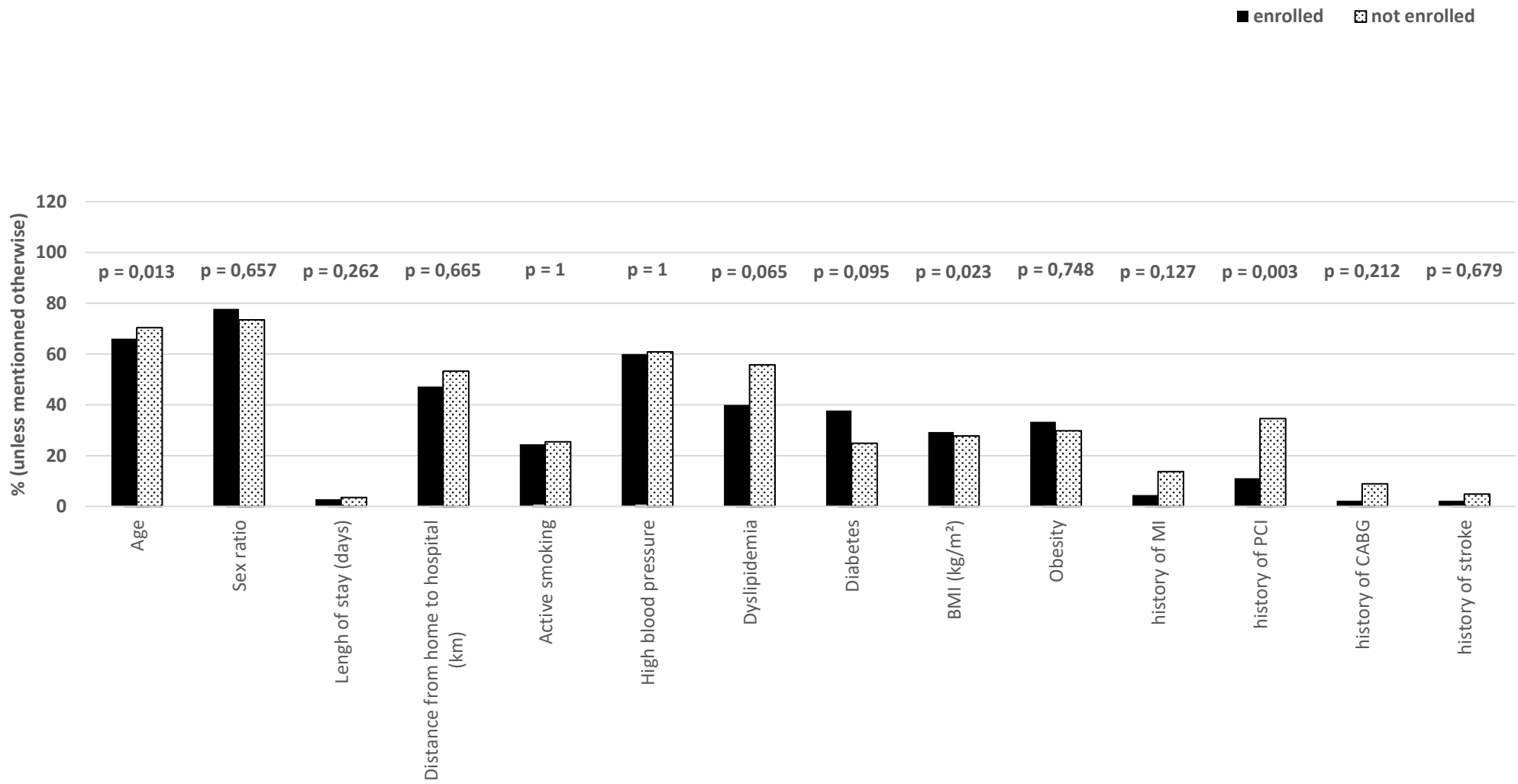


Table 4 : Baseline characteristics, clinical and biological findings at admission, treatments at discharge in non-ST-elevation ACS patients

	Overall (n = 418)	*Enrolled patients (n = 45)*	*Not enrolled patients (n = 373)*	*p value*
Age	69,90 (12,75)	66,04 (10,34)	70,36 (12,95)	0.013
Male	309 (73,92)	35 (77,78)	274 (73,46)	0.657
Lengh of stay (days)	3,45 (7,16)	2,86 (2,97)	3,53 (7,50)	0.262
Distance from home to hospital (km)	52,62 (63,49)	47,19 (90,24)	53,26 (59,68)	0.665
Active smoking	106 (25,36)	11 (24,44)	95 (25,47)	1
High blood pressure	254 (60,77)	27 (60,00)	227 (60,86)	1
Dyslipidemia	226 (54,07)	18 (40,00)	208 (55,76)	0.065
Diabetes	110 (26,32)	17 (37,78)	93 (24,93)	0.095
BMI (kg/m²)	27,92 (4,90)	29,31 (4,11)	27,75 (4,96)	0.023
Obesity	126 (30,14)	15 (33,33)	111 (29,76)	0.748
history of MI	53 (12,71)	2 (4,44)	51 (13,71)	0.127
history of PCI	134 (32,06)	5 (11,11)	129 (34,58)	0.003
history of CABG	34 (8,13)	1 (2,22)	33 (8,85)	0.212
history of stroke	19 (4,54)	1 (2,22)	18 (4,83)	0.679
Pluritroncular disease	283 (67,70)	29 (64,44)	254 (68,10)	0.744
LVEF > 40%	378 (90,87)	41 (91,11)	337 (90,84)	1
Systolic blood pressure (mmHg)	142,4 (22,9)	146,89 (21,5)	141,9 (23)	0.149
Heart rate (bpm)	73,4 (15,6)	75 (17)	73,2 (15,5)	0.490
eGFR MDRD (ml/min/1.73m²)	84,8 (28,6)	93,8 (29,9)	83,5 (28,3)	0.033
Creatinin (µmol/l)	89 (43,6)	81,4 (30,3)	90,1 (45,1)	0.093
Hemoglobin (g/dl)	141 (16,5)	147 (12)	140 (16,8)	0.001
Peak troponin (ng/l)	820 (1294)	1169 (1300)	758 (1284)	0.059
Peak CPK (IU/l)	357,9 (554)	556 (784)	327 (505)	0.066
<u>Treatments at discharge</u>				
Aspirin	370 (93,67)	40 (90,91)	330 (94,02)	0.639
$P2Y_{12}$ inhibitor	416 (99,52)	45 (100)	371 (99,46)	1
Ticagrelor	238 (56,94)	38 (84,44)	200 (53,62)	< 0.001
Clopidogrel	177 (42,34	7 (15,56)	170 (45,58)	< 0.001
Prasugrel	1 (0,24)	0 (0)	1 (0,27)	1
Anticoagulant	45 (10,77)	4 (8,89)	41 (10,99)	0.861
Apixaban	13 (3,11)	1 (2,22)	12 (3,22)	1
Vitamin K antagonist	20 (4,78)	3 (6,67)	17 (4,56)	0.798
Dabigatran	5 (1,20)	0 (0)	5 (1,34)	0.953
Rivaroxaban	7 (1,67)	0 (0)	7 (1,88)	0.755

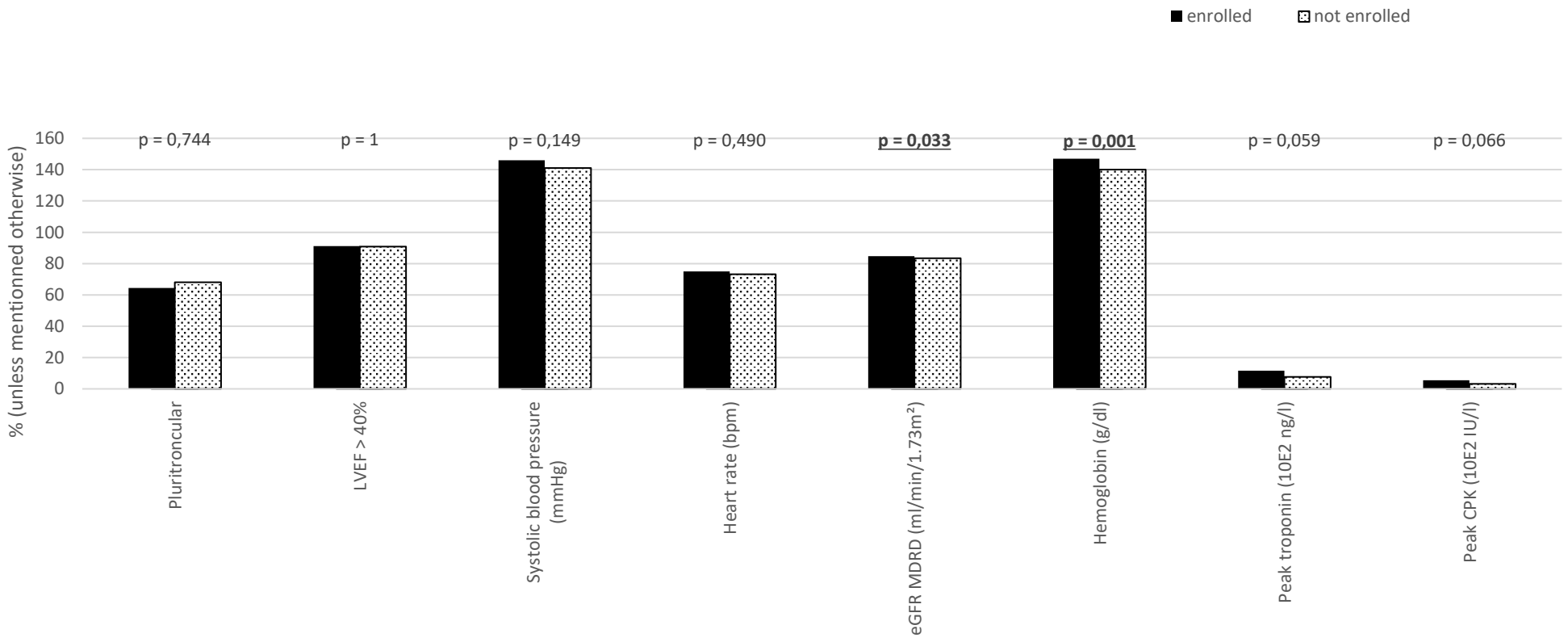
BMI : Body mass index, PCI : percutaneous coronary intervention, CABG : Coronary artery bypass graft surgery, LVEF : Left ventricular ejection fraction, eGFR : estimated glomerular filtration rate (MDRD)

Figure 4a : Baseline characteristics in non-ST-elevation ACS



BMI : Body mass index, PCI : percutaneous coronary intervention, STEMI : ST-segment elevation myocardial infarction, CABG : Coronary artery bypass graft surgery, LVEF : Left ventricular ejection fraction, eGFR : estimated glomerular filtration rate (MDRD

Figure 4b: Clinical and paraclinical findings in non-ST-elevation ACS



STEMI : ST-segment elevation myocardial infarction, LVEF : left ventricular ejection fraction, eGFR :estimated glomerular filtration rate

Figure 4c : Antithrombotic treatment at distcharge in non-ST-elevation ACS

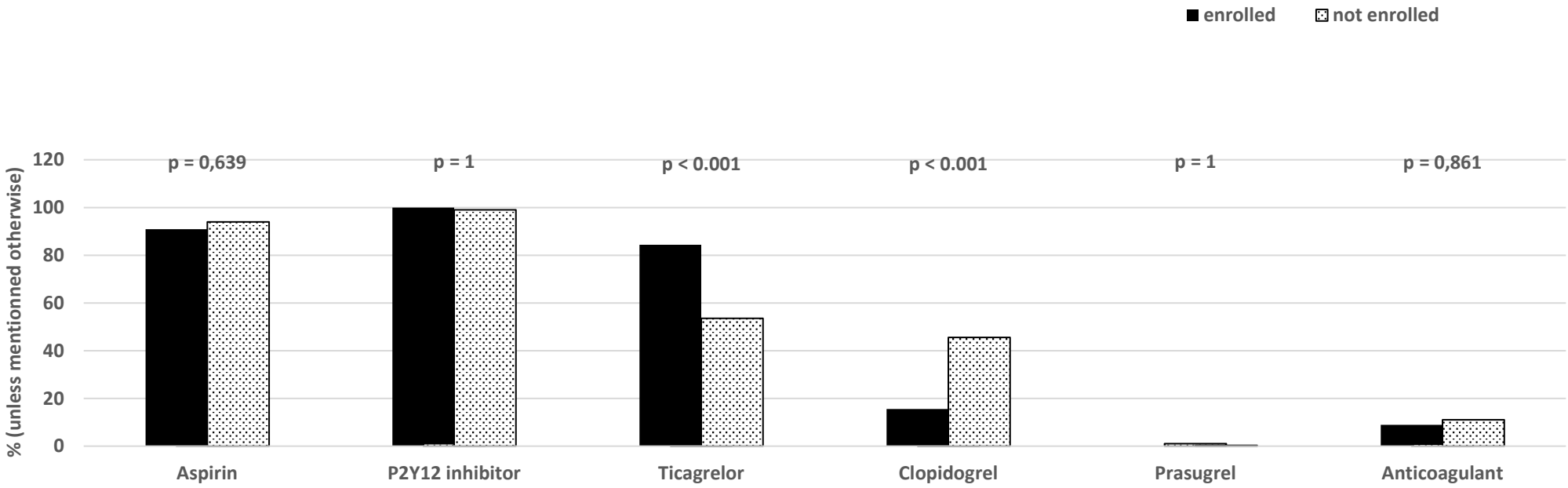


Table 5 : in-hospital events and follow-up in overall population

	Overall population (n = 690)	*Enrolled patients (n = 144)*	*Not enrolled patients (n = 546)*	*Relative risk [95% IC]*	*p value*
In-hospital events					
Death	19 (2,75)	0 (0)	19 (3,48)	0 [0 - NA]	0.047
Myocardial infarction	5 (0,72)	1 (0,69)	4 (0,73)	0.948 [0.107 - 8.416]	1
Stroke	0 (0)	0 (0)	0 (0)	-	1
BARC ≥ 3 bleeding	12 (1,74)	0 (0)	12 (2,20)	0 [0 - NA]	0.151
Unplanned PCI	3 (0,43)	1 (0,69)	2 (0,37)	1.896 [0.173 - 20.761]	1
One-year follow-up outcomes					
Composite primary endpoint (Death and/or stroke and/or myocardial infarction and/or unplanned revascularization)	73 (11,11)	8 (5,56)	65 (12,67)	0.439 [0.215 - 0.893]	0.024
Stroke	0 (0)	0 (0)	0 (0)	-	1
Death	26(3,96)	2 (1,39)	24 (4,69)	0.296 [0.071 - 1.239]	0.121
Myocardial infarction	16 (2,44)	2 (1,39)	14 (2,74)	0.507 [0.117 - 2.205]	0.534
BARC ≥ 3 bleeding	14 (2,11)	1 (0,69)	13 (2,50)	0.278 [0.037 - 2.106]	0.314
Unplanned revascularization	49 (7,48)	6 (4,17)	43 (8,41)	0.495 [0.215 - 1.14]	0.126
PCI	47 (7,18)	6 (4,17)	41 (8,02)	0.519 [0.225 - 1.199]	0.161
CABG	2 (0,31)	0 (0)	2 (0,39)	0 [0 - NA]	1

BARC : Bleeding academy research consortium, PCI : percutaneous coronary intervention, CABG : Coronary artery bypass graft surgery

Table 6 : in-hospital events and follow-up in STEMI patients

	Overall population (n=272)	*Enrolled patients (n = 99)*	*Not enrolled patients (n = 173)*	*Relative risk [95% IC]*	*p value*
In-hospital events					
Death	18 (6,62)	0 (0)	18 (10,40)	-	0.002
Myocardial infarction	5 (18,52)	1 (1,01)	4 (2,31)	-	0.764
Stroke	0 (0)	0 (0)	0 (0)	-	1
BARC ≥ 3 bleeding	8 (2,94)	0 (0)	8 (4,62)	-	0.072
Unplanned PCI	2 (0,74)	1 (1,01)	1 (0,58)	-	1
One-year follow-up events					
Composite primary endpoint (Death and/or stroke and/or myocardial infarction and/or unplanned revascularization)	19 (7,76)	4 (4,04)	15 (10,27)	0.393 [0.135 - 1.15]	0.122
Stroke	0 (0)	0 (0)	0 (0)	-	1
Death	9 (3,67)	1 (1,01)	8 (5,48)	0.184 [0.023 - 1.451]	0.139
Myocardial infarction	5 (2,05)	1 (1,01)	4 (2,76)	0.366 [0.042 - 3.227]	0.627
BARC ≥ 3 bleeding	7 (2,79)	1 (1,01)	6 (3,95)	0.256 [0.031 - 2.094]	0.323
Unplanned revascularization	11 (4,49)	3 (3,03)	8 (5,48)	0.553 [0.15 - 2.034]	0.553
PCI	11 (4,49)	3 (3,03)	8 (5,48)	0.553 [0.15 - 2.034]	0.553
CABG	0 (0)	0 (0)	0 (0)	-	1

BARC : Bleeding academy research consortium, PCI : percutaneous coronary intervention, CABG : Coronary artery bypass graft surgery

Table 7 : in-hospital events and follow-up in non-ST-elevation ACS patients

	Overall population (n = 418)	*Enrolled patients (n = 45)*	*Not enrolled patients (n = 373)*	*Relative risk [95% IC]*	*p value*
In-hospital events					
Death	1 (0,24	0 (0)	1 (0,27)		1
Myocardial infarction	0 (0)	0 (0)	0 (0)		1
Stroke	0 (0)	0 (0)	0 (0)		1
BARC ≥ 3 bleeding	4 (0,96)	0 (0)	4 (1,07)		1
Unplanned PCI	1 (0,24)	0 (0)	1 (0,27)		1
One-year follow-up events					
Composite primary endpoint (Death and/or stroke and/or myocardial infarction and/or unplanned revascularization)	54 (13,11)	4 (8,89)	50 (13,62)	0.652 [0.247 - 1.722]	0.513
Stroke	0 (0)	0 (0)	0 (0)	-	1
Death	17 (4,14)	1 (2,22)	16 (4,37)	0.508 [0.069 - 3.743]	0.774
Myocardial infarction	11 (2,68)	1 (2,22)	10 (2,73)	0.813 [0.107 - 6.206]	1
BARC ≥ 3 bleeding	7 (1,69)	0 (0)	7 (1,90)	0 [0 - NA]	0.748
Unplanned revascularization	38 (9,27)	3 (6,67)	35 (9,59)	0.695 [0.223 - 2.169]	0.715
PCI	36 (8,78)	3 (6,67)	33 (9,04)	0.737 [0.236 - 2.307]	0.801
CABG	2 (0,49)	0 (0)	2 (0,55)	0 [0 - NA]	1

BARC : Bleeding academy research consortium, PCI : percutaneous coronary intervention, CABG : Coronary artery bypass graft surgery

Table 8 : Predictors of primary outcome (MACE), logistic regression

	Univariate analysis					***Multivariate analysis***				
	coefficient	standard error	z value	odds ratio [95% IC]	p value	coefficient	standard error	z value	odds ratio [95% IC]	p value
(Intercept)						- 2.891	0.90	- 3.207	-	-
Study inclusion	- 0.903	0.387	- 2.331	0.405 [0.176 - 0.818]	0.020	- 0.612	0.41	-1.5	0.542 [0.228 - 1.148]	0.133
Age (years)	0.023	0.010	2.326	1.023 [1.004 - 1.043]	0.020	0.006	0.01	0.501	1.006 [0.983 - 1.03]	0.616
Male	- 0.390	0.274	- 1.426	0.677 [0.401 - 1.177]	0.154					
Lengh of stay	0.035	0.014	2.541	1.036 [1.008 - 1.067]	0.011	0.034	0.01	2.377	1.035 [1.006 - 1.066]	0.017
Distance from home to hospital	- 0.001	0.002	- 0.524	0.999 [0.994 - 1.002]	0.600					
Current smoking	- 0.688	0.310	- 2.218	0.502 [0.264 - 0.898]	0.027	- 0.307	0.36	- 0.849	0.736 [0.354 - 1.47]	0.396
Hypertension	0.124	0.250	0.498	1.132 [0.695 - 1.859]	0.619					
Dyslipidemia	-0.027	0.249	- 0.108	0.973 [0.594 - 1.585]	0.914					
Diabetes	0.709	0.264	2.680	2.031 [1.197 - 3.387]	0.007	0.558	0.28	2.023	1.748 [1.007 - 2.983]	0.043
BMI (kg/m²)	0.012	0.025	0.480	1.012 [0.962 - 1.063]	0.631					
Obesity	0.125	0.271	0.461	1.133 [0.655 - 1.906]	0.645					
history of MI	0.048	0.378	0.126	1.049 [0.469 - 2.104]	0.899					

history of PCI	0.403	0.267	1.510	1.497 [0.875 - 2.502]	0.131					
history of CABG	0.638	0.438	1.455	1.892 [0.741 - 4.238]	0.146					
history of stroke	0.139	0.630	0.220	1.149 [0.267 - 3.441]	0.826					
eGFR MDRD (ml/min/1.73m²)	- 0.007	0.005	- 1.265	0.993 [0.983 - 1.004]	0.206					
Peak troponin (10E2 ng/l)	- 0.00003	0.00005	- 0.585	1 [1 - 1]	0.558					
Hemoglobin (g/dl)	- 0.013	0.008	- 1.679	0.987 [0.972 - 1.003]	0.093					
STEMI	- 0.585	0.280	- 2.088	0.557 [0.315 - 0.949]	0.037	- 0.342	0.30	- 1.124	0.71 [0.382 - 1.27]	0.261
LVEF > 40%	- 0.463	0.307	- 1.512	0.629 [0.352 - 1.179]	0.130					
Pluritroncular disease	0.774	0.296	2.620	2.169 [1.243 - 3.989]	0.009	0.541	0.30	1.774	1.717 [0.964 - 3.209]	0.076

BARC : Bleeding academy research consortium, PCI : percutaneous coronary intervention, CABG : Coronary artery bypass graft surgery

Vu, le Directeur de Thèse

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académie d'Orléans-Tours | université de TOURS | Faculté de médecine

DEWAELE Jean

52 pages – 8 tableaux – 10 figures

Résumé **:**

Introduction. Les études cliniques sont la pierre angulaire des recommandations internationales en cardiologie. Cependant, leurs résultats peuvent être influencés par la sélection des patients inclus et par les modifications comportementales des patients après l'inclusion (effet Hawthorne). Nous avons testé l'hypothèse que les patients inclus par notre équipe dans des études cliniques au décours d'un syndrome coronaire aigu ont un moindre risque cardiovasculaire de base et un meilleur pronostic à 1 an que les patients non inclus.

Méthode. Nous avons réalisé une étude rétrospective monocentrique sur l'ensemble des patients pris en charge en coronarographie pour un syndrome coronaire aigu (SCA) en 2017. Les patients inclus dans l'une des études actives ont été comparés aux patients non inclus, tant sur leurs caractéristiques de bases que sur les évènements cardiovasculaires majeurs et les décès survenant dans l'année suivant le SCA index.

Résultats. Au cours de l'année 2017, 690 patients ont eu une coronarographie pour SCA dans notre service. Parmi eux, 144 ont été inclus dans une étude (6 essais thérapeutiques et 1 cohorte). Les patients inclus avaient un profil de risque cardiovasculaire moins sévère, étant significativement plus jeunes (62,6 vs 68,9 ; $p < 0,001$), moins hypertendus (41,7 vs 56,2% ; $p = 0,003$) moins dyslipidémiques (33,6 vs 47,5% ; $p = 0,004$), avec moins d'antécédents d'angioplastie coronaire (8,3 vs 28,9% ; $p < 0,001$), de pontage aorto-coronaire (1,4 vs 6,6 ; $p = 0,003$) ou d'infarctus du myocarde (IDM) (4,9 vs 13,4% ; $p = 0,007$). A un an, la survenue d'évènements cardiovasculaires majeurs était plus faible dans le groupe des patients inclus (5,6 vs 12,7% ; $p = 0,02$). L'existence d'un diabète ($p = 0,04$) et une durée d'hospitalisation plus longue ($p = 0,02$) étaient indépendamment associés à la survenue du critère de jugement principal. L'inclusion dans une étude était associé à moins d'évenements cardiovasculaires en analyse univariée, cette association n'était plus statistiquement significative en analyse multivariée.

Conclusion. Les patients inclus dans une étude ont un profil de risque cardiovasculaire plus faible et un meilleur pronostic que les patients non inclus. La sélection à l'inclusion contibuent probablement à cette différence. L'effet Hawthorne joue probablement un rôle sur les évènements, même si nos résultats ne confirment pas l'inclusion dans une étude comme étant un facteur prédictif indépendant d'évènement. Ce constat devrait être pris en compte lors de l'extrapolation des résultats d'une étude clinique à la population générale dans le cadre des recommandations internationales.

Mots clés : Etude clinique, syndrome coronaire aigu, biais de sélection, Effet de participation à la recherche, pronostic.

Jury :

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Directeur de thèse : Professeur Denis ANGOULVANT

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