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D.E.S de MEDECINE CARDIO-VASCULAIRE

Présentée et soutenue publiquement
Par
Léa JUENIN
Le 15 octobre 2021

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Avant-propos

La restauration précoce et complète du flux coronaire est l'objectif principal de la prise en charge du syndrome coronarien aigu avec sus décalage du segment ST (SCA ST+). En effet, la rapidité et la qualité de la reperfusion coronaire sont des facteurs pronostiques majeurs dans l'infarctus du myocarde, toutes deux associées à une diminution de la mortalité à court et moyen terme, comme cela a été démontré dans de nombreuses études [1-5].

L'angioplastie primaire est actuellement le traitement de référence du SCA ST+ en phase aigüe jusqu'à 48 heures du début des douleurs selon les recommandations [6-10]. En parallèle, le traitement pharmacologique à la phase pré-hospitalière est fondamental, il permet de préparer et d'améliorer les résultats de l'angioplastie avec stenting et fait partie intégrante des recommandations. Il se compose d'une dose de charge d'aspirine, d'une dose d'héparine adaptée au poids du patient ainsi que d'une dose de charge d'un inhibiteur du $P2Y_{12}$ [11]. Cette dernière molécule sera choisie parmi les trois disponibles actuellement, c'est à dire ticagrelor, prasugrel ou clopidogrel avec une préférence pour les deux premières, plus récentes et plus puissantes, ayant montré une meilleure efficacité en termes d'évènements ischémiques dans les syndromes coronariens aigus [12-13]. Une autre molécule de la même classe thérapeutique uniquement disponible par voie veineuse, le cangrelor, pourra être utilisée chez les patients qui ne peuvent avaler les comprimés comme chez les patients intubés selon les recommandations actuelles [14].

Des séries déjà anciennes montrent qu'à l'arrivée en salle de coronarographie une reperfusion coronaire complète avant tout geste endovasculaire est observée chez 15 à 30 % des patients [15,16]. La reperfusion coronaire complète est définie par la constatation à la coronarographie d'une recanalisation coronaire avec un flux TIMI 3 (opacification complète du lit distal sans retard) de l'artère coupable avant toute angioplastie ou geste endovasculaire (y compris thrombo-aspiration) et sans thrombolyse préalable.

De nombreuses études ont montré que la reperfusion coronaire complète à l'arrivée en salle de coronarographie constitue un facteur de bon pronostic indépendant mais aucune d'entre elle n'a été réalisée depuis l'utilisation des nouveaux inhibiteurs du $P2Y_{12}$ (ticagrelor et prasugrel) [17-25]. Une seule étude utilisant un nouvel inhibiteur du $P2Y_{12}$, le ticagrelor en l'occurrence, visant à comparer son administration pré ou intra hospitalière relève l'incidence des patients arrivant avec un flux TIMI 3 à la coronarographie. Cette dernière est

sensiblement la même quel que soit le mode d'administration du ticagrelor, à savoir 17,4% lorsque le ticagrelor est administré en pré-hospitalier et 16,9% lorsqu'il l'est en intra-hospitalier [26]. Une autre étude récente s'est intéressée aux caractéristiques cliniques et angiographiques des patients avec reperfusion spontanée mais parmi les inhibiteurs du $P2Y_{12}$ seul le clopidogrel était utilisé. Cette dernière montre ainsi que 26% des patients présentent une reperfusion coronaire spontanée [27].

Notre hypothèse est que la reperfusion coronaire spontanée survient plus fréquemment avec l'utilisation des nouveaux inhibiteurs du $P2Y_{12}$ actuellement le plus souvent utilisés dans les SCA ST+. Cet effet favorable sur la reperfusion coronaire précoce pourrait contribuer au bénéfice plus important de ces molécules constaté dans plusieurs études par rapport au clopidogrel dans le SCA ST+ [12-13]. Nous voudrions également évaluer si la reperfusion coronaire spontanée est plus fréquente chez certains patients, notamment ceux traités par anti agrégants plaquettaires et/ou anti coagulants au long cours et si elle est corrélée au délai entre l'administration du pré traitement et la coronarographie. Par ailleurs, nous nous intéresserons également à l'évolution de ces patients, que ce soit intra-hospitalière ou à plus long terme.

L'objectif principal de cette étude est donc d'évaluer l'incidence des patients admis pour SCA ST+ avec reperfusion coronaire spontanée constatée lors de la coronarographie en phase aigüe. Les caractéristiques cliniques et biologiques de ces patients recueillies pendant l'hospitalisation seront évaluées et comparées à ceux avec une artère occluse à l'admission. Nous évaluerons également le pronostic intra hospitalier et à un an de ces deux groupes de patients.

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Incidence, clinical characteristics, and prognosis of patients with ST-segment elevation myocardial infarction and spontaneous coronary reperfusion at admission in the modern antithrombotic strategy area.

Abbreviations

ACS = Acute coronary syndrome

BARC = bleeding academic research consensus

CK = creatine kinase

CRP = C-reactive protein

ECG = electrocardiogram

GFR = Glomerular filtration rate

GP = general practitioner

HF = heart failure

ICU = Intensive care unit

IQR = Interquartile range

LVEF = Left ventricular ejection fraction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = thrombolysis in myocardial infarction

Introduction

The rapid and complete restoration of coronary flow is a key issue in the management of ST-segment elevation myocardial infarction (STEMI) [1-5]. When possible, primary percutaneous coronary intervention (PCI) associated with antithrombotic drugs is the preferred reperfusion strategy [6-11]. In daily practice, some patients may achieve complete spontaneous reopening of the culprit artery at admission in the catheterization laboratory before undergoing any mechanical reperfusion therapy, which is called « spontaneous reperfusion » [12, 13]. The latter is defined as initial TIMI 3 flow (as classified by the Thrombolysis in Myocardial Infarction trial [14]) of the culprit coronary artery observed on diagnostic coronary angiography before PCI. Spontaneous reperfusion is associated with improved outcomes in several studies [15-25] but none of them was performed with the modern antithrombotic strategy including new $P2Y_{12}$ inhibitors (ticagrelor and prasugrel).

The objectives of this study was to report the incidence, clinical characteristics and prognostic impact of spontaneous coronary reperfusion of STEMI patients admitted for primary PCI using a modern medical antithrombotic strategy according to guidelines [11].

Methods

Study design and population

This single centre, observational and prospective study was conducted between June 1st and November 1st, 2020 in the cardiology department of Montpellier University Hospital. All consecutive patients referred to the catheterization laboratory for primary PCI during the study period were screened. We included all patients with STEMI defined by the European Society of Cardiology and receiving, according to guidelines, preloading dose of aspirin, heparin and $P2Y_{12}$ inhibitor [11, 27-29]. Inclusion criteria included patients in the early phase of STEMI (pain lasting less 12 hours) or with evolved STEMI (pain lasting between 12 and 48 hours) with ongoing symptoms suggestive of ischaemia, including haemodynamic instability, or life-threatening arrhythmias.

Exclusion criteria included patients referred for coronary angiography after thrombolysis and myocardial infarction outside of acute phase as previously defined.

The study was approved by the local ethics committee (IRB ID 202100821) and was conducted in accordance with the 1964 Helsinki declaration and subsequent revisions. The study was registered on the clinical trial website (NCT 04881552).

Pre-treatment

According to guidelines [11], clopidogrel was usually reserved to contraindications of others $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) related to bleeding risk including long-term anticoagulant therapy. Prasugrel wasn't used in our centre related to local prehospital emergency medical assistance service (*Service d'Aide Médicale Urgente*) protocol. Cangrelor was used when patients presenting vomiting after administration of ticagrelor or patients unable to absorb oral agents.

Regarding anticoagulation therapy, local habits were to use intravenous enoxaparin in first line, as allowed in guidelines [11].

Coronary angiography procedure

Coronary angiography was performed under local anaesthesia. Right radial approach was the default strategy, otherwise left radial or transfemoral access was used. Mechanical thrombectomy (ASAP aspiration catheter, Merit®) was performed for thrombotic burden lesions with indication left at the discretion of the interventional cardiologist. New generation drug-eluting stents (Orsiro, Biotronik®; Xience Sierra, Abbott®; Ultimaster Tansei, Terumo®; Resolute Onyx, Medtronic®) were implanted using a routine method.

Only the infarct-related artery (IRA) was treated during the initial intervention according to guidelines. In patients with multivessel disease, staged revascularization was performed usually before hospital discharge.

Data collection and follow up

In-hospital data were collected during the hospital stay for all patients. Data at one-year follow-up were obtained from medical records and by calling patient, general practitioner (GP) or cardiologist.

All the data were collected and analysed according to the CNIL MR-003 reference.

Study outcomes

The primary outcome was the incidence of initial spontaneous coronary TIMI flow grade 3 on emergency coronary angiography before primary PCI.

Secondary endpoints included:

- In-hospital clinical events including death, cardiogenic shock, cardiac arrest, ventricular arrhythmias, mechanical complications, heart failure (HF), myocardial reinfarction, stroke… and duration of hospitalization.
- In-hospital biological parameters related to infarct size including dosage of T-hs troponin, creatine kinase (CK), C-reactive protein (CRP).
- Echocardiographic evaluation before hospital discharge including at least left ventricular ejection fraction (LVEF).
- First year clinical events including death, re-hospitalization for cardiac reason (HF, ventricular arrhythmias, acute coronary syndrome), symptomatic angina, myocardial ischemia demonstrated on functional non-invasive tests, new coronary angiography or PCI, stroke and serious haemorrhagic event (BARC ≥ 3a).

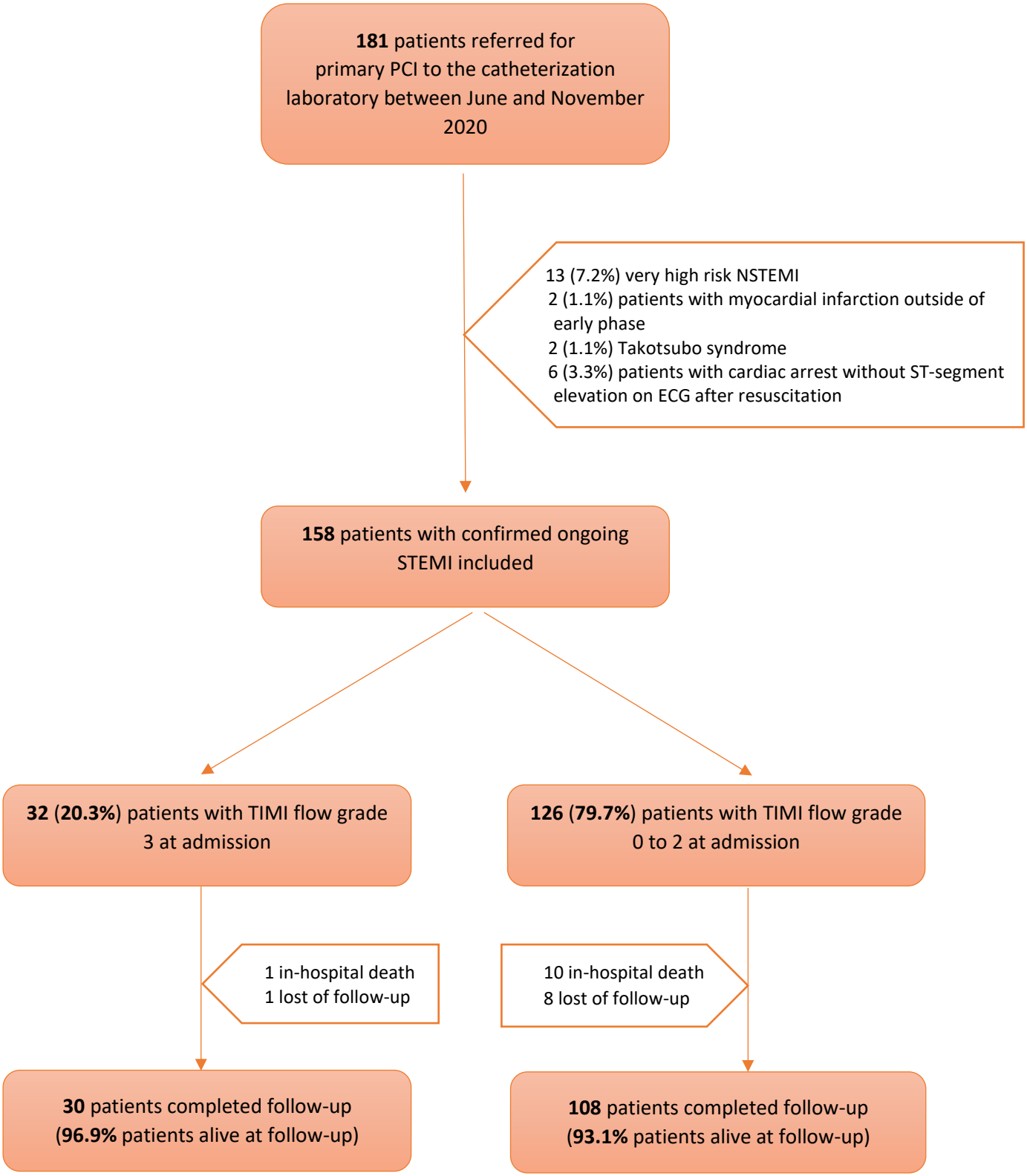
Statistical analysis

Categorical data are reported as counts and percentages. Continuous data are reported as mean ± standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed data. Comparisons used the chi-squared test or Fisher's exact test for categorical variables and Student's t test or the Mann-Whitney-Wilcoxon test, as appropriate, for continuous variables. A 2-tailed $p<0.05$ was considered statistically significant. Survival curves were constructed with the Kaplan-Meier method. All analyses were performed using SPSS statistics software, version 25 (IBM, Armonk, NY, USA).

Results

Study population

Figure 1 – Study flowchart



Among 181 STEMI patients referred in the catheterization laboratory for primary PCI during the study period, 158 (87.3%) patients with was confirmed to have ongoing STEMI and were included in the study ; 138 patients (93.9% of the living patients) completed 1-year follow-up (**Figure 1**). A total of 151 (95.6%) patients were admitted in the early-phase of STEMI and 7 (4.4%) patients presented evolved STEMI with ongoing symptoms suggestive of persistent ischaemia. Mean age was 64 ± 14 years old and 123 were male (77.8 %). Regarding cardiovascular risk factors we observed mainly hypertension (n=61; 38.6%), active smoking (n=60; 38.0%), dyslipidaemia (n=52; 32.9%) and diabetes (n=33; 20.9%). Initial presentation was cardiac arrest for 16 patients (10.1%) and 133 patients (84.2%) received a pre-hospital loading dose of ticagrelor. Median delay between chest pain and reperfusion therapy was 210 minutes (IQR 25-75: 150-345) (**Table 1**).

Primary endpoint

During the study period, 32 (20.3%) patients with confirmed ongoing STEMI presented angiographic evidence of spontaneous reperfusion (TIMI flow grade 3 on emergency coronary angiography before primary PCI). In this group, mean age was 66 ± 15 years old and 24 were male (75.0 %). At baseline (prior the ACS), 7 patients (21.9%) were treated with anti-platelet therapy, 4 (12.5%) with anticoagulation therapy and 8 (25.0%) with beta-blockers and statins. 24 patients (75.0%) received a loading dose of ticagrelor and 7 (21.9%) were pre-treated with clopidogrel (**Table 1**).

Secondary endpoints

- Baseline characteristics

Regarding population profile, there was significantly more patients with peripheral artery disease (p=0.03) and without family history of coronary artery disease (p=0.04) in the TIMI 3 group, diabetes (p=0.11) tended to be more frequent in the TIMI 3 group compared to TIMI 0-2 group. The opposite trend is observed with hypertension (p=0.17) which seems to be more frequent in the TIMI 0-2 group. Severe chronic kidney failure was significantly more frequent in the TIMI 3 population (p=0.04) but only two patients were observed with this pathology. Patients tended to be more frequently treated with anticoagulation therapy (p=0.24), clopidogrel (p=0.15) and beta-blockers (p=0.12) at baseline (prior the ACS) in the TIMI 3 group. Regarding STEMI characteristics, ST-elevation regression during transport was significantly more frequent in the TIMI 3 group (p<0.001) (**Table 1**).

Table 1 – Baseline characteristics of population and comparison between TIMI 3 and TIMI 0-2 at admission populations

	Overall population (n = 158)	**TIMI 0 to 2 at admission (n = 126)**	**TIMI 3 at admission (n = 32)**	***p***
Demographics				
Age (years), **mean**	64 (±14)	64 (± 14)	66 (± 15)	0.32
Male	123 (77.8%)	99 (78.6%)	24 (75.0%)	0.66
BMI (kg/m^2)**, median**	26 (24-29)	26 (24-29)	26 (23-30)	0.19
Cardiovascular risk factors				
Hypertension	61 (38.6%)	52 (41.3%)	9 (28.1%)	0.17
Diabetes	33 (20.9%)	23 (18.3%)	10 (31.3%)	0.11
Dyslipidaemia	52 (32.9%)	43 (34.1%)	9 (28.1%)	0.52
Active smoking	60 (38.0%)	48 (38.1%)	12 (37.5%)	0.95
Family history of CAD	31 (19.7%)	29 (23.2%)	2 (6.3%)	0.04
Comorbidities				
Previous CAD	25 (15.8%)	21 (16.7%)	4 (12.5%)	0.79
Previous myocardial infarction	9 (5.8%)	8 (6.5%)	1 (3.1%)	0.69
Peripheral artery disease	4 (2.5%)	1 (0.8%)	3 (9.4%)	0.03
Stroke	5 (3.2%)	3 (2.4%)	2 (6.3%)	0.27
Atrial fibrillation	9 (5.7%)	6 (4.8%)	3 (9.4%)	0.39
Chronic kidney failure				
GFR <60 mL/min/1.73m^2	11 (7.0%)	9 (7.1%)	2 (6.3%)	1.00
GFR ≤30 mL/min/1.73m^2	2 (1.3%)	0 (0.0%)	2 (6.3%)	0.04
Current treatment				
Anti-platelet therapy	31 (19.6%)	24 (19.0%)	7 (21.9%)	0.72
Aspirin	28 (17.8%)	22 (17.6%)	6 (18.8%)	0.88
Clopidogrel	7 (4.5%)	4 (3.2%)	3 (9.4%)	0.15
Both	4 (2.5%)	2 (1.6%)	2 (6.3%)	0.18
Anticoagulation therapy	11 (7.0%)	7 (5.6%)	4 (12.5%)	0.24
Vitamin K antagonist	2 (1.3%)	1 (0.8%)	1 (3.1%)	0.37
Non-vitamin K antagonist oral anticoagulants	9 (5.7%)	6 (4.8%)	3 (9.4%)	0.39
Beta-blockers	25 (16.0%)	17 (13.7%)	8 (25.0%)	0.12

Statins	29 (18.5%)	21 (16.8%)	8 (25.0%)	0.29
Presentation				
Preexisting angina pectoris	42 (26.6%)	33 (26.2%)	9 (28.1%)	0.83
Initial cardiac arrest	16 (10.1%)	12 (9.5%)	4 (12.5%)	0.74
Initial 3° atrioventricular block	9 (5.7%)	7 (5.6%)	2 (6.3%)	1.00
Initial ventricular tachycardia or fibrillation	13 (8.2%)	10 (7.9%)	3 (9.4%)	0.73
Localization of ST-segment elevation on ECG				
Extensive anterior	23 (14.6%)	19 (15.1%)	4 (12.5%)	1.0
Anterior	48 (30.4%)	37 (29.4%)	11 (34.4%)	0.59
Inferior	69 (43.7%)	56 (44.4%)	13 (40.6%)	0.70
Posterior	6 (3.8%)	5 (4.0%)	1 (3.1%)	1.00
Lateral	12 (7.6%)	9 (7.1%)	3 (9.4%)	0.71
ST-elevation regression during transport	18 (11.5%)	7 (5.6%)	11 (35.5%)	<0.001
Pre-treatment				
Loading dose of $P2Y_{12}$ inhibitor				
Clopidogrel	19 (12.0%)	12 (9.5%)	7 (21.9%)	0.06
Ticagrelor	133 (84.2%)	109 (86.5%)	24 (75.0%)	0.11
Cangrelor	9 (6.4%)	8 (6.4%)	1 (3.1%)	1.00
Enoxaparin	150 (94.9%)	122 (96.8%)	28 (87.5%)	0.05
Unfractionned heparin	8 (5.1%)	4 (3.2%)	4 (12.5%)	0.05
Delays (min)**, median**				
Symptoms onset to primary PCI	210 (150-345)	210 (150-346)	230 (148-338)	0.88
Loading dose of $P2Y_{12}$ inhibitor to primary PCI	95 (60-121)	98 (63-129)	90 (60-120)	0.63
Initial laboratory tests				
Creatinine at admission (µmol/L)**, median**	81 (66-96)	82 (66-101)	78 (66-91)	0.44
Hemoglobin at admission (g/dL)**, median**	14.4 (13.4-15.5)	14.4 (13.3-15.4)	14.5 (13.7-15.8)	0.37
LDL- cholesterol (g/L)	1.22 (0.97-1.46)	1.25 (1.0-1.5)	1.10 (0.90-1.57)	0.42
HbA1C (%)**, median**	5.8 (5.5-6.2)	5.8 (5.5-6.1)	5.6 (5.5-6.4)	**0.07**

Values are mean (± DS), median (interquartile range) or n (%)
BMI = body mass index, CAD = coronary artery disease, GFR = glomerular filtration rate, PCI = percutaneous coronary intervention, LDL = low density lipoprotein, HbA1C = glycosylated haemoglobin

- Pre-treatment

TIMI 3 flow at admission tended to be more frequent in patients receiving pre-treatment with clopidogrel than in patients receiving pre-treatment with ticagrelor (*p*=0.06) (**Table 2**).

Table 2 – TIMI at admission according to $P2Y_{12}$ inhibitor loading dose

	Loading dose of	Loading dose of ticagrelor	*p*
TIMI 0-2 at admission	12 (63.2%)	109 (82.0%)	0.06
TIMI 3 at admission	7 (36.8%)	24 (18.0%)	0.06

Delay between symptoms onset to primary PCI was similar in the two groups with respectively 210 minutes (IQR 150-346) in TIMI 0-2 group and 230 minutes (IQR 148-338) in TIMI 3 group (*p*=0.88). Delay between loading dose of P2Y12 to primary PCI was not significantly different with respectively 98 minutes (IQR 63-129) in TIMI 0-2 group and 90 minutes (IQR 60-120) in TIMI 3 group (*p*=0.63) (**Table 1**).

- Procedural characteristics

Thrombotic burden lesions tended to be more frequent in the TIMI 0-2 group (*p*=0.10). Mechanical thrombectomy was significantly less used in the TIMI 3 group (*p*=0.02). PCI with stent(s) was equally achieved in the two groups (*p*=0.88).

There was no difference about localisation of the culprit lesion between the two groups, the culprit artery was mainly the left anterior descending artery in both groups (n=55; 43.7% in TIMI 0-2 group and n=16; 50.0% in the TIMI 3 group).

Time of radioscopy tended to be shortened in TIMI 3 group than in TIMI 0-2 group (*p*=0.19). The same tendency was observed for X-ray dosimetry (*p*=0.20) (**Table 3**).

Table 3 – Procedural characteristics of population and comparison between TIMI 3 and TIMI 0 to 2 at admission populations

	Overall population (n = 158)	**TIMI 0 to 2 at admission (n = 126)**	**TIMI 3 at admission (n = 32)**	***p***
Culprit artery				
Left anterior descending artery	71 (44.9%)	55 (43.7%)	16 (50.0%)	0.52
Diagonal artery	9 (5.7%)	8 (6.3%)	1 (3.1%)	0.69
Circumflex artery	17 (10.8%)	14 (11.1%)	3 (9.4%)	1.00
Left obtuse marginal artery	6 (3.8%)	4 (3.2%)	2 (6.3%)	0.60
Right coronary artery	53 (33.5%)	43 (34.1%)	10 (31.3%)	0.76
Ramus intermedius artery	2 (1.3%)	2 (1.6%)	0 (0.0%)	1.00
High thrombus burden lesion	75 (47.5%)	64 (50.8%)	11 (34.4%)	0.10
Multivessel disease	90 (57.0%)	69 (54.8%)	21 (65.6%)	0.27
Treatment during angiography				
Mechanical thrombectomy	40 (25.5%)	37 (29.6%)	3 (9.4%)	0.02
Eptifibatide	49 (31.0%)	42 (33.3%)	7 (21.9%)	0.21
Isosorbide dinitrate	74 (47.4%)	61 (49.2%)	13 (40.6%)	0.43
Adenosine	9 (5.7%)	8 (6.4%)	1 (3.1%)	0.69
PCI with stent(s)	149 (94.3%)	119 (94.4%)	30 (93.8%)	0.88
TIMI flow grade at the end of the procedure				
TIMI 3	146 (92.4%)	115 (91.3%)	31 (96.9%)	0.46
TIMI 2	4 (2.5%)	4 (3.2%)	0 (0.0%)	0.58
TIMI 1	5 (3.2%)	4 (3.2%)	1 (3.1%)	1.00
TIMI 0	3 (1.9%)	3 (2.4%)	0 (0.0%)	1.00
Contrast product used (mL)**, median**	150 (113-175)	150 (110-180)	138 (119-170)	0.65
Time of radioscopy (min)**, median**	7.2 (5.9-11.6)	7.6 (6.0-12)	6.5 (4.0-10)	0.19
X-ray dosimetry (cGy/cm²)**, median**	4792 (2722-7568)	5087 (2911-7742)	3324 (2072-5614)	**0.**20

- In-hospital evolution

At admission in ICU, all patients with TIMI 3 flow on initial angiography were Killip class I with a trend in favour of this group compared to the TIMI 0-2 group (p=0.07). During hospitalisation, peaks of troponin and CK were significantly lower in the TIMI 3 (p<0.001). Despite a trend towards a higher CRP peak observed in the TIMI 0-2 group, no significant difference was highlighted (p=0.07).

In the TIMI 3 group, there was no ventricular arrhythmias, no conduction disorders and no cardiogenic shock during hospitalisation. Although there was no significant difference (p=0.46), there was about twice in-hospital death in the TIMI 0-2 group than in TIMI 3 group with respectively 10 (7.9%) and 1 (3.1%) death in each group. Duration of hospitalisation was similar between the two groups (**Table 4**).

Table 4 – In-hospital evolution of population and comparison between TIMI 3 and TIMI 0 to 2 at admission populations

	Overall population (n = 158)	**TIMI 0 to 2 at admission (n = 126)**	**TIMI 3 at admission (n = 32)**	***p***
At admission in ICU				
Chest pain	18 (11.4 %)	16 (12.7%)	2 (6.3%)	0.53
Killip class				
I	143 (90.5%)	111 (88.1%)	32 (100.0%)	0.07
II	5 (3.2%)	5 (4.0%)	0 (0.0%)	0.58
III	3 (1.9%)	3 (2.4%)	0 (0.0%)	1.00
IV	4 (2.5%)	4 (3.2%)	0 (0.0%)	0.58
Electrocardiogram				
Q wave	83 (53.9%)	69 (56.1%)	14 (45.2%)	0.28
Regression of ST-segment elevation	102 (66.2%)	80 (65.6%)	22 (68.8%)	0.74
Echocardiographic characteristics				
LVEF (%), median	50 (40-55)	50 (40-55)	50 (45-55)	0.36
Impaired LVEF	43 (27.2%)	36 (28.6%)	7 (21.9%)	0.42
Right ventricular dysfunction	16 (10.3%)	15 (12.1%)	1 (3.1%)	0.20
Laboratory test				
Peak of troponin (ng/L)	3063 (1541-6080)	3580 (1937-6320)	1498 (435-3061)	<0.001
Peak of CK (UI/L)	1144 (577-2381)	1438 (816-2646)	557 (259-1111)	<0.001
Peak of CRP (mg/L)	26.7 (8.8-73.4)	30.6 (10.7-83.5)	17 (5.2-55.4)	0.07
Complications during hospitalization				
Ventricular arrhythmias	5 (3.2%)	5 (4.0%)	0 (0.0%)	0.58
Conduction disorders	8 (5.1%)	8 (6.3%)	0 (0.0%)	0.36
Cardiac arrest	9 (5.7%)	8 (6.3%)	1 (3.1%)	0.69
Congestive heart failure	18 (11.4%)	13 (11.1%)	5 (15.6%)	0.37
Cardiogenic shock	7 (4.4%)	7 (5.6%)	0 (0.0%)	0.35
Stroke	2 (1.3%)	1 (0.8%)	1 (3.1%)	0.37
Intraventricular thrombus	2 (1.3%)	1 (0.8%)	1 (3.1%)	0.37

Mechanical complications	2 (1.3%)	1 (0.8%)	1 (3.1%)	0.37
Free wall rupture	2 (1.3%)	1 (0.8%)	1 (3.1%)	0.37
Ventricular septal defect	1 (0.6%)	0 (0.0%)	1 (3.1%)	0.20
Stent thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
All cause in-hospital death	11 (7.0%)	10 (7.9%)	1 (3.1%)	0.46
Duration of hospitalization (days)**, median**	5 (4-8)	5 (4-8)	5 (4-8)	0.84

- Follow-up

Median duration of the follow up was 12 months (IQR 25-75: 10-13) and the longest follow up was 14 months. There were 9 patients (6.1% of patients alive at follow up) lost of follow-up in equivalent proportion in each group: 8 (6.9%) patients in the TIMI 0-2 group and 1 (3.2%) patients in the TIMI 3 group (p = 0.69) (**Table 5**).

At one-year follow-up, a total of 16 (10.1%) patients died (**Figure 1**), respectively 13 (10.3%) patients in the TIMI 0-2 group and 3 (9.4%) in the TIMI 3 group with no significant difference between the two groups (p=1.00) (**Table 5**). Survival was not different according to TIMI flow grade at admission (**Figure 2**).

Regarding medical events, we observed 2 ACS (6.3%) and 1 stent thrombosis (3.1%) occurring in the TIMI 3 group during follow up period, while none of these events occurred in the TIMI 0-2 group. So, ACS and stent thrombosis during follow-up period tended to be more frequent in the TIMI 3 group (respectively, p=0.05 and 0.17) (**Table 5**).

Table 5 – Follow-up events of population and comparison between TIMI 3 and TIMI 0 to 2 at admission populations

	Overall population (n = 158)	**TIMI 0 to 2 at admission (n = 126)**	**TIMI 3 at admission (n = 32)**	***p***
Re-hospitalisation for cardiologic reason	20 (12.7%)	15 (11.9%)	5 (15.7%)	0.44
Angina pectoris	4 (2.5%)	3 (2.4%)	1 (3.1%)	0.74
Heart failure	3 (1.9%)	3 (2.4%)	0 (0.0%)	0.48
Acute coronary syndrome	2 (1.3%)	0 (0.0%)	2 (6.3%)	0.05
Myocardial ischemia demonstrated on functional non-invasive tests	5 (3.2%)	4 (3.2%)	1 (3.1%)	1.00
Coronary angiography	11 (7.0%)	8 (6.3%)	3 (9.4%)	0.38
Angioplasty	4 (2.5%)	3 (2.4%)	1 (3.1%)	0.74
Same artery angioplasty	3 (1.9%)	2 (1.6%)	1 (3.1%)	0.69
Stent thrombosis	1 (0.6%)	0 (0.0%)	1 (3.1%)	0.17
In-stent restenosis	1 (0.6%)	1 (0.8%)	0 (0.0%)	0.66
Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Serious haemorrhagic event	2 (1.3%)	2 (1.6%)	0 (0.0%)	0.35
All cause death at one year follow up (excluding in-hospital death)	5 (3.2%)	3 (2.4%)	2 (6.3%)	0.40
All cause death at one year follow up (including in hospital death)	16 (10.1%)	13 (10.3%)	3 (9.4%)	1.00
Follow up duration (months)	12 (10-13)	12 (10-13)	12 (11-13)	0.37
Lost of follow up (% of patients alive at follow up)	9 (6.1%)	8 (6.9%)	1 (3.2%)	0.69

Figure 2 – Survival curve of the total study population

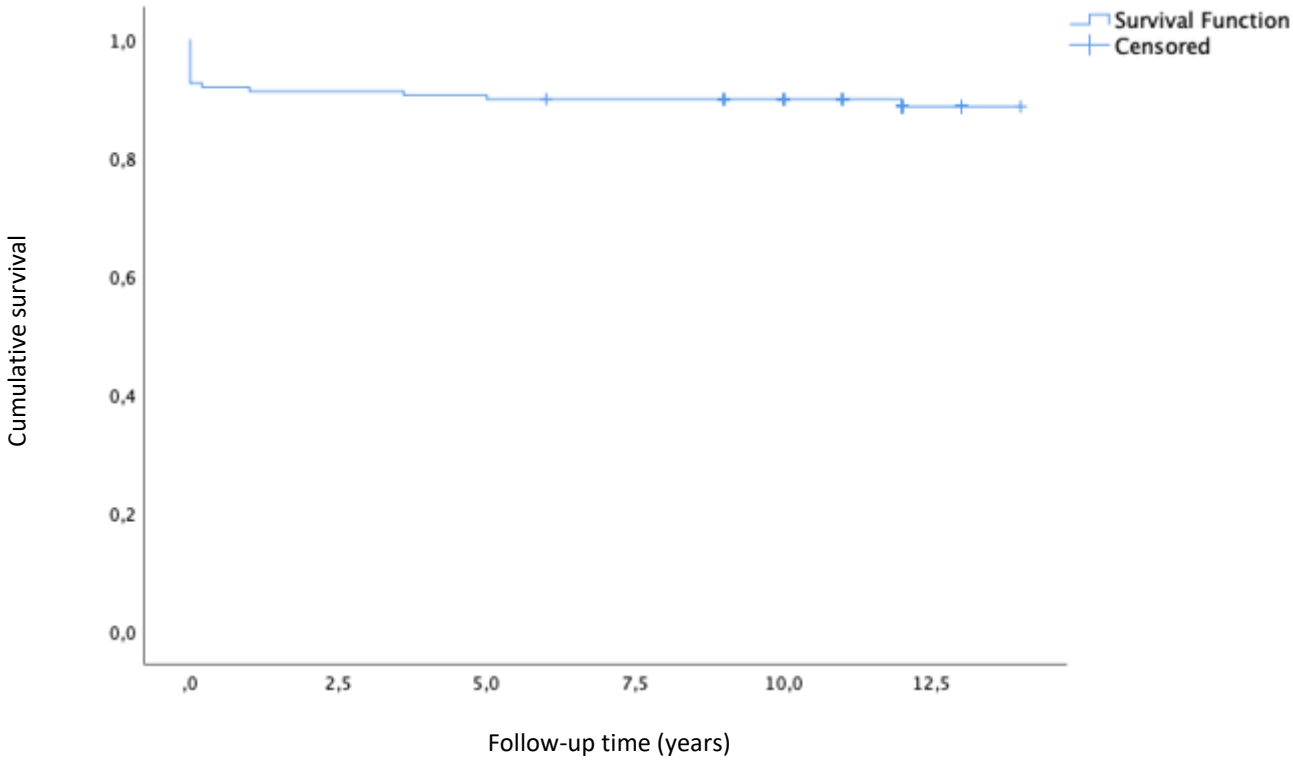
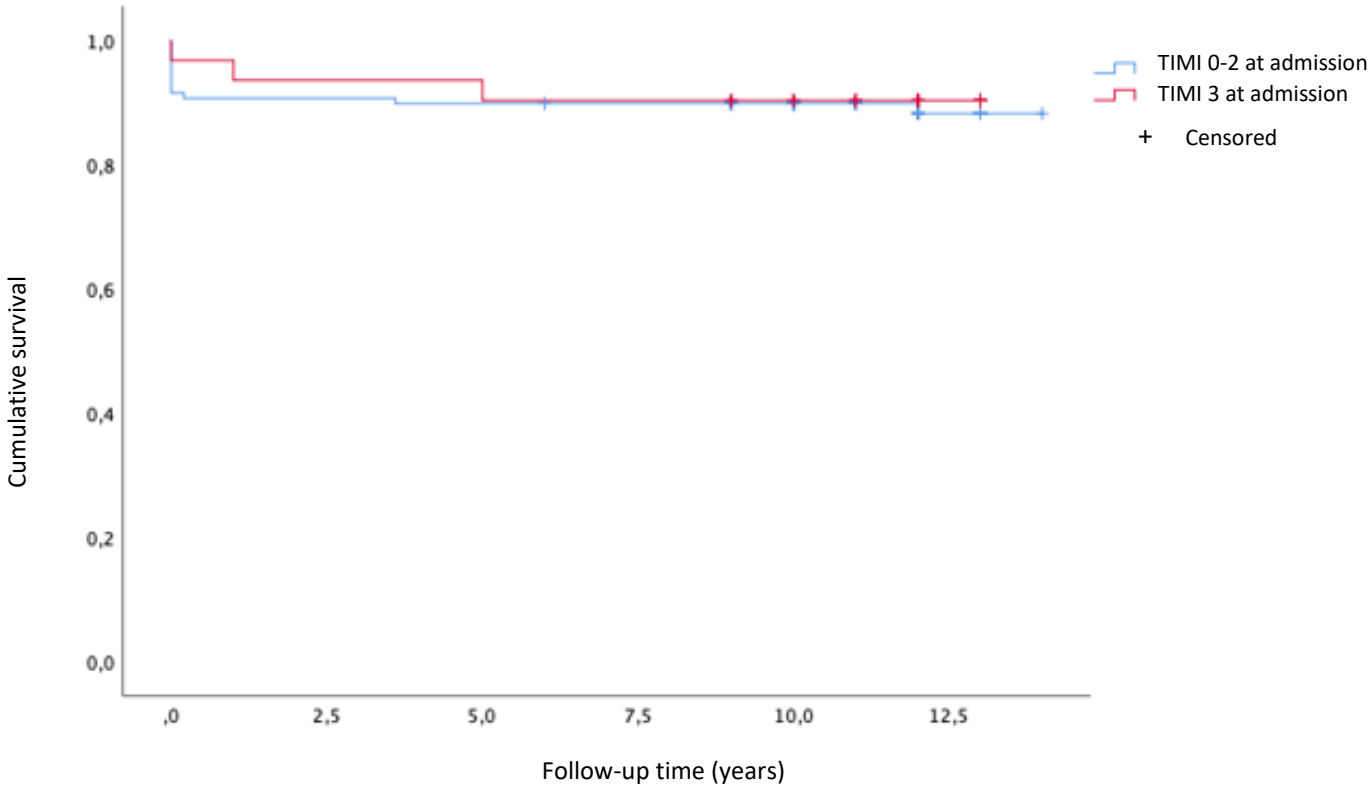


Figure 3 – Survival curve according to TIMI flow grade at admission



Discussion

This study shows that about 20% of STEMI patients admitted for primary PCI after prehospital antithrombotic therapy have angiographic evidence of spontaneous reperfusion at admission in the catheterization laboratory.

No identified predictive factors of spontaneous reperfusion were highlighted including the use of new generation $P2Y_{12}$ inhibitors.

TIMI 3 flow at admission seems to be related to lower risk profile of STEMI regarding infarct size and in hospitals events.

<u>TIMI 3 flow incidence at baseline angiography</u>

Previous old studies have shown that the incidence of spontaneous reperfusion of STEMI admitted in the cath lab was about 15 to 30% [12-13, 15-26]. Only two studies evaluated this parameter were undergoing with use of $P2Y_{12}$ inhibitors: Wang et al. [25], using clopidogrel as pre-treatment, observed 26% of TIMI 3 flow at admission in a retrospective study including 519 patients. Montalescot et al. [26], in the prospective and randomized study ATLANTIC, compared as a secondary endpoint, the incidence of TIMI flow grade 3 at admission when ticagrelor was used in a pre- or in an in-hospital strategy. The study showed similar results in the two groups (17.4% VS 16.9%, p=0.82). Our result regarding incidence of TIMI 3 flow, is consistent with these reports as with older studies that do not use loading dose of $P2Y_{12}$ inhibitors [12-13, 15-24]. No improvement of this important parameter is questionable if we consider improvement of the pre-treatment strategy of STEMI in the last twenty years. These results, even non-randomized, argue against beneficial effect of antithrombotic pre-treatment loading dose, even with new $P2Y_{12}$ inhibitors, on coronary reperfusion before PCI.

<u>Predictive factors of TIMI 3 flow at baseline angiography</u>

- Patients characteristics

In our study, only peripheral artery disease or severe kidney disease were significantly associated with TIMI 3 flow at admission. These results would suggest that vascular history or previous antithrombotic therapy (all patients suffering of severe kidney disease and 75% of patients suffering of peripheral artery disease were treated by anti-platelet therapy at baseline), may impact TIMI 3 flow at admission. However, regarding low incidence of patients in this group, interpretation with caution is required. Wang et al. [25] showed that patients with spontaneous reperfusion were younger in age, with culprit lesions mostly

located in the distant left anterior descending artery. Younger age was also observed in another study [23] but another one [21] showed that patients with spontaneous reperfusion were slightly older. So, the relation between age and spontaneous reperfusion remains unclear. Two old studies [18, 21] found that pre infarction angina was associated with the occurrence of spontaneous reperfusion but we did not highlight a difference about this criterion in our study.

- Pre-treatment

Surprisingly in our study, pre-treatment with clopidogrel tends to be more frequently associated with TIMI 3 flow than ticagrelor. No study has compared clopidogrel and ticagrelor regarding TIMI 3 flow at admission in the cathlab in STEMI. In the clopidogrel group, more patients have anticoagulation therapy at baseline, this may have impact the TIMI 3 flow at admission but this association was not significant. This results, even non-randomized, support the hypothesis that the benefit of pre-hospital administration of new generation $P2Y_{12}$ inhibitors in STEMI is no related to improvement of coronary reperfusion before PCI.

- Coronary angiography

Two studies [23, 25] showed that culprit distal lesions or left anterior descending branch were independently associated with spontaneous reperfusion. In the present analysis, there was no difference about localisation of the culprit lesion between the two groups.
As previously observed in old studies [18, 38], our study showed no significant difference between TIMI 3 flow at admission and the time interval between onset of pain and angiography. These results argue against an incidence of TIMI 3 flow that could be artificially increase with late delay of admission.

<u>Prognosis impact of spontaneous coronary reperfusion</u>

Most of the reports [15-25], performed before coming up of new $P2Y_{12}$ inhibitors, showed that patients with spontaneous reperfusion tended to have all the surrogates of improved myocardial salvage: less cardiac enzyme release, a higher left ventricular ejection fraction, fewer complications, and a better outcome than patients without spontaneous reperfusion. In our study, using mainly a modern strategy of pre-hospital treatment of new $P2Y_{12}$ inhibitors, this trend is confirmed: TIMI 3 flow at baseline angiography is clearly related with lower risk profile of STEMI. Thereby peaks of troponin and CK are significantly lower in the TIMI 3 group and we know that prognosis after acute myocardial infarction is strongly

determined by the extent of myocardial injury [30-32]. Several studies have evaluated troponin as a marker for infarct size and left ventricular dysfunction [33-37]. Of the same way, we observed a trend of less patients with impaired LVEF and right ventricular dysfunction in the TIMI 3 group. Interestingly we observed no ventricular arrhythmias, no conduction disorders and no cardiogenic shock during hospitalisation in the TIMI 3 group and, even no significant, there was about half as many in-hospital deaths in this group. Lastly, Killip class at admission was lower in the TIMI 3 group in accordance with previous studies [18, 19, 21].
In our study, delays between symptom onset to primary PCI and between loading dose of $P2Y_{12}$ inhibitors to primary PCI were not significantly different between the two groups so the differences about in-hospital evolution identified are really due to spontaneous reperfusion and not to difference in delays of admission or delays of therapy.

Regarding one-year follow-up, no difference were highlighted in prognosis but we observed a trend to more ACS and stent thrombosis in the TIMI 3 group but the low number of events does not allow to interpret these results. The lack of difference in one-year mortality between the two groups is in accordance with previous study [21], which showed that although spontaneous reperfusion was independently associated with improved survival at 30 days the association between spontaneous reperfusion and survival decreased at one year. But this is also to interpret with caution regarding low incidence of events in each group.

Study limitations

Our study has some limitations. Firstly, regarding the relatively small number of patients and events, the study lacks of power and interpretation of secondary endpoints must be done with caution. Secondly, the single centre design of study could also appear as a limitation. Considering the well-defined guidelines of STEMI pre-hospital therapy, excepted for prasugrel not usually used in our centre, no difference can be anticipated in the strategy of therapy in a multicentre study. However, our objective is to continue the study by using a multicentre design and a longer follow-up to better evaluate the profile of patients associated with TIMI 3 flow at admission and prognosis.

Conclusion

This prospective study shows an incidence of about 20% of STEMI patients admitted for primary PCI, with angiographic evidence of spontaneous reperfusion. This incidence is the same as that observed in old studies despite the use of a modern medical pre-hospital antithrombotic strategy using loading dose of anti-platelet therapy and mainly new generation $P2Y_{12}$ inhibitors.

There is no identified baseline demographic characteristics clearly predicting spontaneous reperfusion, but TIMI 3 flow at admission is associated with lower risk profile of STEMI regarding clinical and biological parameters. While in-hospital outcome seems to be better in patients with spontaneous reperfusion, there is no difference regarding medical events between the two groups at one-year follow-up. Multicentre study with longer follow-up is planned to better evaluate prognostic impact and predictive factors of TIMI 3 flow at admission with the modern antithrombotic strategy.

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Appendix

Appendix 1 – TIMI (Thrombolysis in Myocardial Infarction) classification

TIMI 0 refers to the absence of any antegrade flow beyond a coronary occlusion.

TIMI 1 flow is faint antegrade coronary flow beyond the occlusion, although filling of the distal coronary bed is incomplete.

TIMI 2 flow is delayed or sluggish antegrade flow with complete filling of the distal territory.

TIMI 3 flow is normal flow, which fills the distal coronary bed completely.

Appendix 2 – BARC (Bleeding Academic Research Consensus) classification

Type	Definition of BARC Bleeding (Primary Endpoint)
0	No evidence of bleeding.
1	Bleeding that is not actionable.
2	Any clinically overt sign of hemorrhage that is actionable, but does not meet criteria for type 3, 4, or 5 bleeding. It must meet at least one of the following criteria: • Requiring medical or percutaneous intervention guided by a healthcare professional • Leading to hospitalization or an increased level of care • Prompting evaluation (laboratory or imaging)
3	Clinical, laboratory, and/or imaging evidence of bleeding with healthcare responses, as listed below:
3a	• Any transfusion with overt bleeding • Overt bleeding plus hemoglobin (Hb) drop ≥3 to <5 g/dl (provided Hb drop is related to bleeding)
3b	Overt bleeding plus Hb drop ≥5 g/dl Cardiac tamponade Bleeding requiring surgical intervention for control Bleeding requiring intravenous vasoactive drugs
3c	Intracranial hemorrhage Intraocular bleed compromising vision
4	CABG-related bleeding • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period • Chest tube output ≥2 l within a 24-hour period
5	Fatal bleeding. Bleeding directly causes death with no other explainable cause. Categorized further as either definite or probable:
5a	Probable fatal bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed
5b	Definite fatal bleeding that is directly observed.

Annexes

Annexe 1 – Classification TIMI du flux coronaire

Type	Caractéristiques du flux
TIMI 0	Absence complète de flux au-delà de l'obstruction.
TIMI 1	Passage du produit de contraste au-delà de la sténose sans opacification complète du lit d'aval.
TIMI 2	Passage du produit de contraste au-delà de la sténose. Opacification complète du lit d'aval. Vitesse de lavage ralentie.
TIMI 3	Passage du produit de contraste au-delà de la sténose. Opacification complète du lit d'aval. Vitesse de lavage non ralentie.

Annexe 2 – Classification BARC (Bleeding Academic Research Consensus)

BARC 0	pas de saignement.
BARC 1	saignement qui ne modifie pas la prise en charge médicale et sur lequel aucune action médicale n'est entreprise ; peut induire des épisodes d'arrêts de la thérapie par le patient sans consultation d'un professionnel de santé.
BARC 2	saignement extériorisé qui a l'une des trois caractéristiques suivantes : il entraîne un traitement non chirurgical, il conduit à une hospitalisation ou à une évaluation médicale.
BARC 3	saignements plus sévères. Il existe trois sous catégories de BARC 3
Type 3a	saignement extériorisé avec chute de l'hémoglobine de 3 à 5 points (g/dL) ou une transfusion accompagnée d'un saignement extériorisé quel que soit le degré et l'importance de la transfusion.
Type 3b :	saignement extériorisé avec une chute de l'hémoglobine d'au moins 5 points, ou une tamponnade ou un saignement qui nécessite une hémostase chirurgicale (exclue les dents, la peau, le nez, les hémorroïdes), ou un saignement qui nécessite l'utilisation d'amine vasoconstrictrice intraveineuse.
Type 3c	hémorragie intracrânienne ou intraoculaire qui affecte la vision.
BARC 4	saignements péripontage aorto-coronaires. Saignement intracrânien dans les 48 heures, ré-intervention dans le but de contrôler l'hémorragie, transfusion d'au moins 5 unités de sang total ou de concentré de globules rouges dans les 48 heures, drainage thoracique d'au moins 2 litres dans les 24 heures.
BARC 5	saignements mortels.
Type 5a	saignement mortel probable, absence d'autopsie ou de confirmation par imagerie mais suspicion clinique
Type 5b	saignement mortel confirmé par autopsie ou imagerie

Annexe 3 – Protocole du SAMU 34 concernant les SCA ST+

SAMU 34 - SMUR MONTPELLIER - LUNEL

SCA ST+, ANGIOPLASTIE PRIMAIRE

Délai ECG qualifiant - Transport < 120 minutes

① **HBPM** (Enoxaparine = Lovenox® : 0,5 mg/kg IV)
ou **HNF** : 5000 UI IV
+ ② **Aspirine** 250 mg IV

***Si absence de contre-indication* (*)**
+ ③ **Ticagrelor**
BRILIQUE®180 mg
2 comprimés 90 mg ORO dispersibles
sur la langue ou dilués dans SNG

(*) Contre-indications Ticagrelor

- **Traitement par AVK**
- **Traitement par NACO (Dabigatran = Pradaxa®, Rivaroxaban=Xarelto®, Apixaban=Eliquis®)**
- **Risque hémorragique élevé**
- **ATCD Hémorragie intracrânienne / AVC ischémique**
- **Insuffisance Hépatique sévère**
- **Hémodialysé**
- **Allergie Ticagrelor**

Si contre-indications Ticagrelor
+ ③ Clopidogrel
PLAVIX ® 600 mg
2 comprimés 300 mg PO

THÉRAPEUTIQUES ASSOCIÉES
④ Morphine titrée si EN ≥ 6
⑤ Oxygénothérapie si SpO2 < 90 %

JANVIER 2018

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Etre suprême, 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 (e) 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 (se) et reconnaissant (e) 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 (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.

RESUME

Introduction : La restauration précoce du flux coronaire est l'objectif principal de la prise en charge du syndrome coronarien aigu avec sus décalage du segment ST (SCA ST+). En parallèle du traitement pharmacologique administré en pré hospitalier, l'angioplastie primaire est actuellement le traitement de référence à la phase aigüe. Dans les études à notre disposition, dont une seule réalisée depuis l'avènement des nouveaux inhibiteurs du $P2Y_{12}$, une reperfusion coronaire complète avant tout geste endovasculaire est observée chez 15 à 30 % des patients. De nombreuses études ont montré que cette dernière constitue un facteur de bon pronostic indépendant, cependant aucune d'entre elle n'a été réalisée avec l'utilisation des nouvelles molécules anti thrombotiques.

Objectifs : Déterminer l'incidence des patients se présentant pour un SCA ST+ avec reperfusion coronaire spontanée à l'arrivée en salle de coronarographie à l'ère des nouvelles stratégies anti thrombotiques (objectif principal). Définir les caractéristiques des patients qui présentent une reperfusion coronaire spontanée et déterminer l'impact de cette dernière sur le pronostic intra-hospitalier puis à un an (objectifs secondaires).

Matériel et méthodes : Etude monocentrique, prospective incluant tous les patients admis pour SCA ST+ en salle de coronarographie au CHU de Montpellier du 1er juin au 1er novembre 2020. Le critère de jugement principal était la constatation d'un flux TIMI 3 lors de la coronarographie réalisée en urgence.

Résultats : 158 patients ont été inclus. Parmi eux, 32 (20,3%) présentaient une reperfusion coronaire complète à l'arrivée en salle de coronarographie. Les délais de revascularisation étaient identiques dans les deux groupes (TIMI 0-2 VS TIMI 3 à l'admission). Les pics de troponine et de CK étaient significativement plus bas dans le groupe TIMI 3 (p<0,001). Les patients du groupe TIMI 3 présentaient moins d'insuffisance cardiaque (p=0,37) et aucun d'entre eux n'a présenté de choc cardiogénique (p=0,35). Deux fois moins de décès ont eu lieu durant l'hospitalisation dans le groupe TIMI 3 (p=0,46). La durée médiane de suivi était de 12 mois. La mortalité à un an était comparable dans les deux groupes (p=1,00).

Conclusion : L'incidence de la reperfusion coronaire spontanée de 20% dans notre étude est stable par rapport aux données plus anciennes, malgré l'avènement de nouvelles molécules anti-thrombotiques. Aucun facteur prédictif de reperfusion spontanée n'a été mis en avant dans cette étude notamment l'utilisation du ticagrelor comparé au clopidogrel. Ce paramètre apparait comme un facteur pronostique intra hospitalier à délai de reperfusion identique. En revanche à un an, aucune différence pronostique entre les deux groupes n'a été mise en évidence. Un suivi à plus long terme et l'inclusion d'un plus grand nombre de patients sont envisagés.

Mots-clefs : Syndrome coronarien aigu, reperfusion spontanée, coronarographie, TIMI, incidence, pronostic, ticagrelor, clopidogrel