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Épidémiologie, facteurs de risque et stratégie diagnostique en imagerie multimodale des thrombi intra ventriculaires gauches après infarctus du myocarde avec élévation du segment ST ; suivi monocentrique d'un an.

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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.

Épidémiologie, facteurs de risque et stratégie diagnostique en imagerie multimodale des thrombi intra ventriculaires gauches après infarctus du myocarde avec élévation du segment ST ; suivi monocentrique d'un an.

Résumé :

Objectifs- Évaluer la prévalence de thrombus intra Ventriculaire Gauche (VG) après un syndrome coronarien aigu avec élévation du segment ST (SCA ST+) par Echographie TransThoracique (ETT) et Imagerie par Résonnance Magnétique (IRM), identifier les patients à risque et la meilleure stratégie diagnostique.

Méthode et Résultats- 330 patients ont été inclus dans trois études prospectives nécessitant ETT et IRM après un SCA ST+. 136 patients ont eu ces deux examens, 12 (8.8%) ont présenté un thrombus VG dont 5 détectés uniquement par IRM et un uniquement par ETT. En analyse univariée, les facteurs de risque identifiés sont : un SCA ST+ antérieur (100% vs 47% ; p<0.001), intéressant l'Interventriculaire Antérieure (100% vs 46% ; p<0.001), FEVG plus basse à l'admission (35% vs 46% ; p<0.001) et après revascularisation (45% vs 52% ; p<0.001), akinésie antérieure (75% vs 20% ; p<0.001), apicale (92% vs 31% ; p<0.001), anévrisme VG (42% vs 2% ; p<0.001), volumes télédiastolique et télésystolique VG plus élevés (65 vs 55 ml/m² ; p=0.04 et 38 vs 27 mL/m² ; p<0.01), ITV sous-aortique plus basse (17 vs 19 cm/s ; p<0.01), Strain Global Longitudinal plus bas (-10 vs -14% ; p=0.02), présence de fièvre (33% vs 12% ; p=0.04), débit de filtration glomérulaire plus élevé (110 vs 95 ml/min/m² ; p=0.01), taux de créatinine plus bas (65 vs 76 µmol/L ; p=0.04), pic de Créatine Phospho Kinase plus élevé (5773 vs 2776 UI/L ; p<0.001).

Conclusion– Le thrombus VG reste fréquent en post SCA ST+, surtout si infarctus antérieur, avec FEVG altérée et/ou VG dilaté. L'IRM est plus sensible que l'ETT mais

du fait de sa disponibilité limitée, les examens à proposer et leur temporalité restent à mieux définir.

<u>Mots clés</u> :

Syndrome coronarien aigu – thrombus intraventriculaire gauche – anticoagulation – Echocardiographie transthoracique – Imagerie par résonance magnétique cardiaque

Incidence, risk factors and multimodality imaging of post STEMI left ventricular thrombus, a monocentric one year follow-up study.

Abstract:

Objectives- Evaluate the prevalence of Left Ventricular Thrombus (LVT) after ST-segment elevated myocardial Infarction (STEMI) by Trans Thoracic Echocardiography (TTE) and Cardiac Magnetic Resonnance (CMR), identify risk factors and better screening strategy.

Methods and results- 330 patients were included in three prospective studies requiring TTE and CMR in the aftermath of a STEMI. 136 patients underwent both of these exams; 12 LVT were detected (8.8%) including 5 only by CMR and one only by TTE

With an univariate analysis, we observed more LVT in patients with a left anterior descending (LAD) involved (100% vs 46% ; p<0.001), EKG anterior STEMI (100% vs 47% ; p<0.001), lower Left Ventricular Ejection Fraction (LVEF) at baseline (35% vs 46% ; p<0.001) and after revascularization (45% vs 52% ; p<0.001), LV aneurysm (42% vs 2% ; p<0.001), anterior akinesia (75% vs 20% ; p<0.001), apical akinesia (92% vs 31% ; p<0.001), higher indexed LV end-diastolic and end-systolic volumes (65 vs 55ml/m² ; p = 0.04, 38 vs 27mL/m² p<0.01), lower Left Ventricular Outflow Tract Velocity Time Integral (LVOT VTI) (17 vs 19cm/s ; p<0.01) and Global Longitudinal Strain (-10 vs -14% ; p = 0.02), fever (33% vs 12% p = 0.04), lower creatinine level (65 vs 76µmol/L ; p = 0.04), higher glomerular filtration rate (110 vs 95ml/min/m² ; p = 0.01) and Creatin Kinase peak (5773 vs 2776UI/L ; p<0.001).

Conclusion- LVT remains common after STEMI, even more in certain subgroups of patients like anteriors ones, those with altered LVEF and/or dilated LV.

CMR allows better diagnosis than TTE, but, because of its availability, the nature of the examinations to carry out and their timing remains to be defined.

Key Words:

Anticoagulation – Cardiac Magnetic Resonance – Left Ventricular thrombus –

ST Elevated Myocardial Infarction – Transthoracic Echocardiography

Abbreviations:

AF: Atrial Fibrillation

BMI: Body Mass Index

CK: Creatin Kinase

CMR: Cardiac Magnetic Resonance

GLS: Global Longitudinal Strain

ICD: Implantable Cardioverter-Defibrillator

INR: International Normalized Ratio

LAD: Left Anterior Descending artery

LV: Left Ventricular

LVOT: Left Ventricular Outflow Tract

LVT: Left Ventricular Thrombus

LVEF: Left Ventricular Ejection Fraction

MACE: Major Adverse Cardiovascular Events

PCI: Percutaneous Coronary Intervention

STEMI: ST Elevated Myocardial Infarction

TIA: Transient Ischemic Attack

TTE: Transthoracic Echocardiography

VKA: Vitamin K Antagonists

VTI: Velocity Time Integral

Table of Contents:

1. Introduction……17

2. Methods……..18

2.1. Study population……18

Fig 1

2.2. Demographic, clinical and biological datas……20

2.3. TTE Imaging Protocol……20

2.4. CMR acquisition and analysis……..22

2.5. Follow-up and late clinical outcomes……..23

2.6. Statistical analysis……..……..23

3. Results……..……24

3.1. Population……24

3.2. Thrombus detection……..……24

Fig 2

3.3. Univariate analysis of risk factors……26

Table 1, Table 2

3.4. Treatment and follow up……...30

4. Discussion……..31

4.1. Left Ventricular Thrombus incidence……..31

4.2. Detection of Left Ventricular Thrombus……..……32

4.3. Risk factors identified in patients with Left Ventricular Thrombus….33

4.4. Exams and follow up……34

4.5. Treatments…….……35

4.6. Limitations…….……..36

4.7. Clinical Perspectives……37

Fig 3

5. Conclusion…….……..40

6. Bibliography……..41

1. Introduction

Left ventricular thrombus (LVT) is a serious post myocardial infarction complication which increases length of hospital stay and cost of hospitalization but above all, leads to severe consequences when responsible for systemic embolization or cerebral stroke (up to 15% of patients with LVT)(1–12). Patients with LVT have high risks of Major Adverse Cardiovascular Events (MACE) (up to 37%), mortality (up to 19%) (13), short-term cerebrovascular events (7 to 11.8%) (10–12) and systemic thromboembolisms (LVT increases embolic events by 4) (14). Furthermore, it was showed that LVT regression is associated with reduced mortality (13).

Early coronary revascularization has dramatically decreased LVT occurrence (from 19-21% confirmed by echocardiography 40 years ago (2,3) to 3.5-12% confirmed by cardiac magnetic resonance (CMR) nowadays (1–4)), mainly due to less kinetic disorders.

Latest 2018 ESC guidelines for myocardial infarction management recommend repeated TransThoracic Echocardiography (TTE) to guide duration for curative anticoagulation (5) but don't clearly define diagnosis strategies, despite notifying several references with heavy use of CMR after ST-elevation myocardial infarction (1,6–8). TTE should be performed systematically during hospitalization and can be repeated at 6-12 weeks if LVEF is <40% in order to assess the need for an Implantable Cardioverter-Defibrillator (ICD); CMR can be performed in the event of an "inconclusive TTE". However, no details are given considering the indication and the time limit for carrying out these examinations for LVT screening.

Over ten years, CMR showed great diagnosis performances for LVT (15–18). For example, transthoracic echocardiography (TTE) has a sensitivity of 40% compared to 88% for CMR (19), but it is still proposed to a minority of patients (15–17).

CMR availability and economic considerations, especially in France, do not allow to perform it for every patient after ST Elevated Myocardial Infarction (STEMI). Incidence of LVT and medical consequences render it essential to define patient's risk factors to select those who would benefit from CMR.

Therefore, we hypothesized that a multimodality imaging strategy will perform better to detect LVT.

The aim of our study was to assess the prevalence of LVT by TTE and CMR, to identify main risk factors allowing to define a population at risk and assess better screening strategy and the occurrence of ischemic and hemorrhagic clinical events at one year.

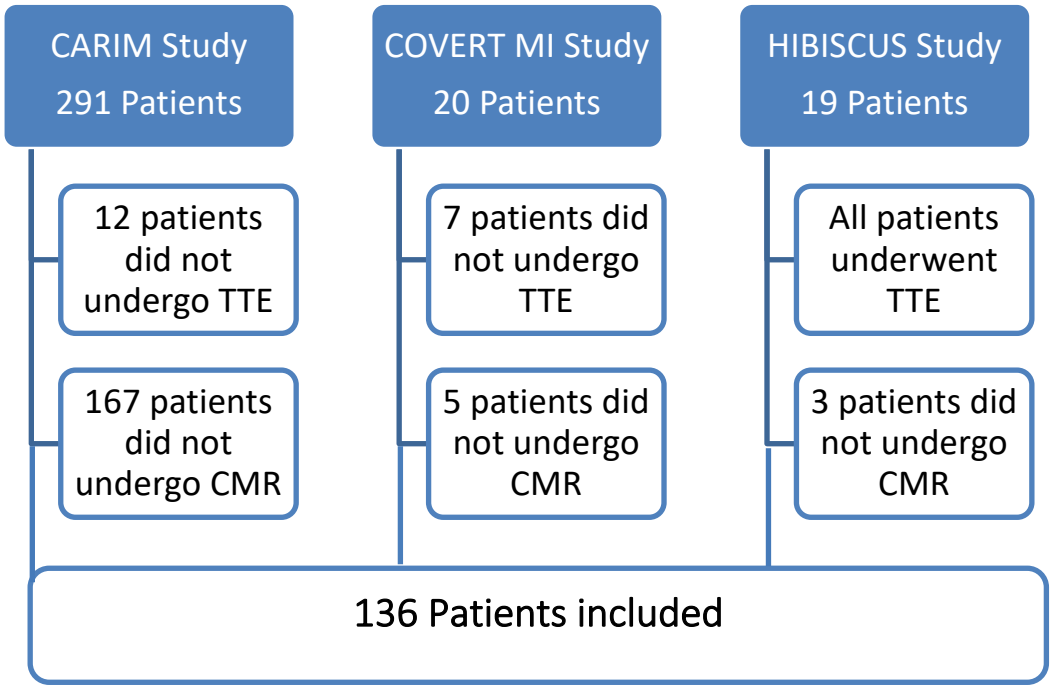
2. Methods

2.1. Study population

Our study population included patients with acute STEMI enrolled in three prospective cohorts: CARIM study (CARdioprotection in Myocardial Infarction) (291 patients), COVERT-MI protocol(20) (COlchicine for left VEntricular Remodeling Treatment in acute Myocardial Infarction) (20 patients) and HIBISCUS study (CoHort of patients to Identify Biological and Imaging markerS of CardiovascUlar outcomes in ST elevation myocardial infarction) (19 patients) between March 2015 and December 2020 in our center (University Hospital of Tours). For the three protocols, imaging protocol included both a TTE and a CMR in the immediate aftermath of STEMI in a systematic way, without distinguishing any of patients'characteristics. TTE and CMR were performed in a time delay of 7 days after Myocardial Infarction (MI) in CARIM study and COVERT MI Study. In HIBISCUS study, TTE was performed at 2 days and CMR in the month following MI.

Among the 330 patients, 136 patients finally underwent TTE (6 ± 4 days) and CMR (15 ± 12 days) after STEMI, due to local access (Fig 1)

Fig 1



Diagnosis of acute STEMI required ST elevation ≥1.0mm in at least 2 contiguous ECG leads in context of ischemic symptoms lasting longer than 20 min, and troponin rise(21).

Exclusion criteria of these three cohorts were: patient with diagnosis of previous MI, hypertrophic or dilated cardiomyopathy, significant valvular heart disease, chronic atrial fibrillation, pace maker or any permanent implanted device susceptible to interfere with LV remodeling, patient with preexisting heart failure, any previous cardiac surgery, previous chemotherapy susceptible to induce LV remodeling (anthracyclines), cardiogenic shock, an associated short-time life-threatening disease, pregnant or breast-feeding patient, contra-indication to CMR (claustrophobia, pacemaker or any other metallic implants, creatinine clearance <30mL/min/1.73m^2 MDRD) in the CARIM Cohort; history of prior myocardial infarction, cardiogenic shock, chronic treatment with

colchicine (Mediterranean familial fever mainly), patient with known history of severe drug intolerance to colchicine, patients treated by macrolides or pristinamycin, severe liver or known renal dysfunction (known GFR ≤30 ml/min), patients with any obvious contraindication to CMR (claustrophobia, pacemaker, defibrillator, history of hypersensitivity to gadoteric acid or to gadolinium contrast agents or to meglumine), lactose intolerance, swallowing disorders, patients without any health coverage or with any legal protection measure, patients with loss of consciousness or confused, female patients currently pregnant or women of childbearing age not using contraception in the COVERT-MI Protocol; and patients without any health coverage, any legal protection measure or contra-indication to CMR (claustrophobia, pacemaker or any other metallic implants, creatinin clearance < 30mL/min/1.73m^2 MDRD) in the HIBISCUS Cohort.

2.2. Demographic, clinical and biological datas

Demographic datas were recorded for each patient including age, gender, medical background and cardiovascular risk factors at admission.

Serial high sensitivity troponin T and Creatin Kinase (CK) levels were sampled at admission and every 8 hours until the peak. All other biological samples were taken upon admission.

2.3. TTE Imaging Protocol

Two-dimensional echocardiographic studies using standard views (parasternal, apical, and subcostal) were performed post-myocardial infarction by experienced

sonographers using commercial equipment (Vivid-S70, Vivid E9, and Vivid E95 R3, General Electric, Norway).

Image quality was assessed according to the following scale: 1 = poor echogenicity, 2 = average, 3 = good, 4 = excellent.

LVT was defined on TTE as an echogenic mass in the Left Ventricular (LV) cavity with well-defined margins, distinct from the endocardial border, visible in both systole and diastole in at least two views and located adjacent to a hypokinetic or akinetic area of the LV wall (22). LV aneurysm was defined as a dyskinetic bulge interrupting the LV contour in diastole and systole.

Regional wall motion was defined using the ASE/EACVI 17-segment model. with, for each segment, a quotation from 1 (dyskinetic) to 4 (normal), allowing to calculate the WMSI score of segment kinetics(23).
LV fractional shortening (FR), systolic and diastolic wall thickness, % wall shortening, end-systolic and end-diastolic LV diameters, ejection fraction, LV end-systolic and end-diastolic volumes (LVESV and LVEDV) according to the biplane Simpson method, LV filling pressures, tricuspid regurgitation fluxes, Left Ventricular Outflow Tract (LVOT) Velocity Time integral (VTI), Global Longitudinal Strain (GLS) and valvular function were assessed.

Contrast TTE (6,19,24) may be used to detect LVT early and is used in daily practice when echogenicity is not sufficient (2 or more segments not visualized (23)). SonoVue® (Sulfur hexafluoride gas, Bracco, Milan, Italy) is approved in France but there is a warning regarding its use in patients with a recent acute coronary syndrome (Haute Autorité de Santé, 2018, may) (25), because it might be responsible for anaphylactic shock (26), which could be dramatic in these unstable patients. So,

expected benefit of a contrast TTE was precisely assessed for each patient and not systematically performed.

2.4. CMR acquisition and analysis

From 2015 to 2018, CMR was performed in a 1.5-T scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) and then in a 1.5 T scanner (INGENIA Philips).

LVT on CMR was defined as LV cavity defects, most often adhering to regions of abnormal myocardial kinetics (hypokinesia but especially akinesia or dyskinesia) on cine sequences and should be confirmed by late gadolinium enhancement (confirming that the tissue is avascular).

In the CARIM Study, a standard multi-sequence protocol was used, with a stack of contiguous breath-hold cine images covering the heart and using a segmented k-space steady-state-free-precession (SSFP) sequence in short axis view; additional images were performed using spatial modulation of magnetization (CSPAMM) technique in a sub selection of planes with basal, mid-ventricular and apical locations. T2- and T2*-mapping sequences were done on the same short axis location as used for cine imaging. Then, first-pass perfusion images using a saturation-recovery gradient echo sequence again on the same slices were done. Contrast agent (0.2 mmol/kg body weight gadolinium-diethylenetriamine- pentaacetic acid) was injected into an antecubital vein by a power injector at a rate of 3 mL/s. After gadolinium bolus injection (2-3 min and 10 min), a 3D-inversion recovery gradient echo sequence was acquired to cover the whole left ventricle in short-axis and long-axis, and to assess early and late post-gadolinium enhancement.

In the HIBISCUS Study, a standard multi-sequence protocol was used, with a stack of contiguous breath-hold cine images and late post-gadolinium enhancement.

In the COVERT MI Study, scout imaging, coronal, sagittal and transaxial set of steady state free precession (SSFP) or fast spin echo images through the chest were done, with also cine sequences, standard first pass perfusion imaging, late enhanced post-contrast sequences with inversion recovery 10 minutes after gadolinium injection and TFL 3D sequences in short axis view covering the whole ventricle. The same acquisition was performed in the vertical and horizontal long axis views. Were also done late enhanced PSIR 3D post-contrast sequences in short axis view covering the whole ventricle, with the same acquisition performed in the vertical and horizontal long axis views. Eventually, T2 mapping sequence, T2 star mapping sequence and native T1 mapping sequence could be done.

2.5. Follow-up and late clinical outcomes

At one year after STEMI, patients underwent a medical visit at the University Hospital of Tours. Clinical status and adverse events were recorded: systemic embolization or cerebral stroke, ischemic or hemorrhagic complication or any Major Adverse Cardiovascular Events (MACE). All clinical outcomes were based upon review of hospitalization records and one-year medical visit report.

2.6. Statistical analysis

Continuous data with normal distribution are presented as mean and standard deviation. Categorical variables are presented as frequency with percentage. Statistical comparison of differences between groups was performed using Chi-

squared test, Fisher's exact test for categorical variables and Mann-Whitney's test for non-normally distribution continuous datas. All statistical tests were 2-tailed, and a value of $p < 0.05$ was considered statistically significant.

Calculations were generated by Medistica*,* pvalue.io, a graphic user interface to the R statistical analysis software for scientific medical publications.

3. Results

3.1. Population

Between March 2015 and December 2020, 291 patients were included in the CARIM study, 20 in the COVERT MI study and 19 in the HIBISCUS study. Due to local accessibility, 175 could not undergo CMR and 19 could not undergo TTE.

Our cohort consisted of 136 patients, mean age was 59 ± 10 years, 49% were tobacco users, 81% were men, 51% had anterior and/or anterolateral MI, LVEF at admission (before PCI) was 45 ± 9% and chest pain to revascularization time delay was 3.6 ± 2 hours.

3.2. Thrombus detection

TTE was performed on average 6 ±4 days and CMR 15 ±12 days after STEMI.

A LVT was detected in 12 of 136 patients at baseline (8.8%). 6 patients had LVT detected both on TTE and CMR. 5 patients had LVT on CMR but not on TTE. One patient did not have LVT in early CMR but developed it in TTE performed 20 days after. 124 patients didn't develop any LVT.

Considering image modality, CMR detected LVT in 11 out of 136 (8%) patients. TTE detected in 7 out of 136 (5%). TTE had 54% sensitivity and 99% specificity for detecting LVT confirmed by CMR.

Considering time delay, patients with a LVT detected had CMR 5 ± 13 days after TTE, those without LVT detected had CMR 9 ± 13 days after TTE (p = 0.27).

Contrast TTE was performed in 5 patients for whom LVT was suspected in TTE. All of them finally concluded that there was no thrombus; 2 of these 5 patients actually had a LVT on CMR. One had CMR 3 days after contrast TTE, the other one 33 days after.

Among the 3 other patients with LVT on CMR but not on TTE, these two examinations were performed the same day for one patient and for the two remainings, CMR was performed 7 days after TTE.

Among the 6 patients with LVT detected both on TTE and CMR, the two examinations were both performed the same day in 4 patients, CMR was performed the day after TTE in 1 patient and 25 days later in. So, in patients with LVT, time delay between the 2 examinations was 5 ± 9 days for LVT diagnosed by TTE and CMR vs 10 ±13 days for LVT only diagnosed by CMR p = 0.31.

Among the 5 patients with LVT only detected on CMR, one had excellent, one had good, three had medium, and none had poor image quality.

Fig 2 shows two patients with LVT detected on CMR. Both had a TTE concluding in the absence of thrombus, one on the same day and one 7 days before.

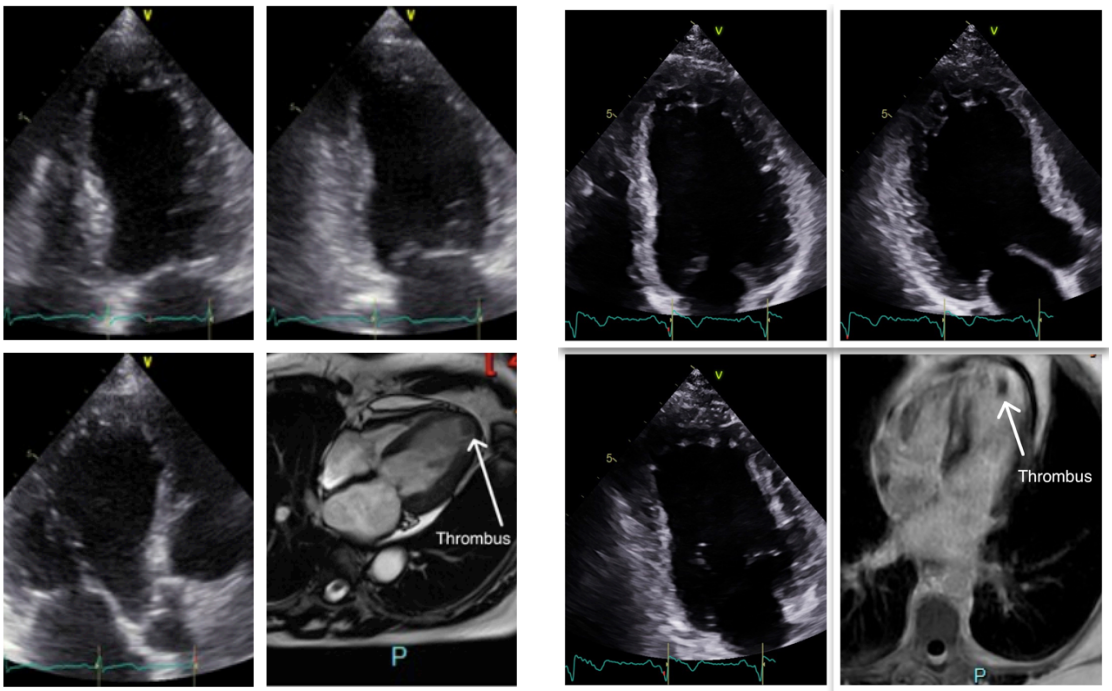


Fig 2

3.3. Univariate analysis of risk factors

All LVT occurred in STEMI with left anterior descending (LAD) as the culprit artery and with EKG anterior territory ($p < 0.001$ and $p < 0.001$).

LVT was found in 17% of patients with anterior STEMI (12/70) and in 62% (5/8) of patients presenting with apical aneurysm ($p < 0.001$).

Patients with and without LVT did not differ with respect to gender, cardiovascular risk factors or medical background (all p = NS as shown in Table 1).

Table 1 : Patients' characteristics

	Overall (n=136)	LVT - (n=124)	LVT + (n=12)	p
Patients characteristics				
Age (years)	59 ±10	59 ±10	60 ±14	0,6
Male Gender, %(n)	81% (109)	81% (101)	75% (9)	0,7
Body Mass Index (kg/m²)	26.4 ±4,4	26,5 ±4,4	25,4 ±4,7	0,3
Diabete mellitus, %(n)	5% (7)	6% (7)	0% (0)	1
Excessive alcohol consumption, %(n)	5% (7)	6% (7)	0% (0)	1
Hypercholestérolemia, %(n)	33% (45)	34% (42)	25% (3)	0,7
Hypertension, %, (n)	32% (43)	31% (39)	33% (4)	1
Tobacco Use, % (n)	49% (66)	50% (62)	33% (4)	0,3
Known vascular disease, %(n)	6% (8)	5% (6)	17% (2)	0,1
Atrial Fibrilation, %(n)	1% (1)	1% (1)	0% (0)	1
Personal history of deep venous thrombosis or pulmonary embolism, %,	4% (6)	5% (6)	0% (0)	1
Known heart desease, %(n)	4% (6)	4% (5)	0% (0)	1

As shown in Table 2, patients with LVT had lower baseline LVEF (35 ± 6% vs 46 ± 9%, p <0.001) but also lower LVEF after revascularization (45 ± 8% vs 52 ± 9%, p<0.01).

75% of patients with LVT (9/12) had anterior akinesia vs 20% of patients with no LVT (25/124; p = 0.001) and 92% (11/12) had apical akinesia vs 31% of patients with no LVT (38/124; p <0.001)

Inferior STEMI concerned 49% of patients without LVT (61/124) vs 0% (0/12) of patients with LVT (p <0,01).

Considering echo parameters, compared to the rest of the population, patients with LVT had higher indexed LV end-diastolic volume (EDV) (65 ± 16 ml vs. 55 ml ± 13 ml; p = 0.04), higher indexed LV end systolic volume (ESV) (37 ± 10 ml vs 26 ± 10 ml p <0.01) compared to patients with no LVT. LVOT VTI was significantly lower (17 ± 3 cm/s vs 19 ± 4 cm/s; p = 0.03) and global longitudinal strain (GLS) was also lower (-10 ± 2 % vs -15 ± 3 %; p = 0.02).

Patients with LVT were more likely to have fever during hospitalization compared to those with no LVT, (temperature >38°C: 33% (4/12) vs 12% (13/126); p = 0.04).

Biologically, kidney function appears better in patients with LVT: glomerular filtration rate was higher: 110 ± 18 ml/min/m² vs 95 ± 20 ml/min/m² (p <0.01) and creatinine level was significantly lower (66 ± 11 µmol/L vs 76 ± 15 µmol/L; p = 0.044). Creatin Kinase peak was also higher in patients with LVT (5773 ± 3176 UI/L vs 2776 ± 2073 UI/L; p <0.001) although Creatin Kinase rate at admission did not differ significantly (496 ± 756 UI/L in patients without LVT vs 516 ± 385 UI/L in patients with LVT; p = 0,1). Levels of C Reactiv Protein are not significantly different either between patients with LVT (6 ± 9 mg/L) than those without (9 ± 20 mg/L) (p = 0.3).

Time from pain to reperfusion did not appear to differ significantly between patients with and without LVT (3.6 ± 2 h in patients without LVT vs 3.8 ± 3 h in patients with LVT; p = 0.5).

Table 2:	Overall (n = 136)	LVT - (n=124)	LVT + (n=12)	p
EKG territory				
Anterior / Anterolateral (n)	51% (70)	47% (58)	100% (12)	<0,001
AVR (n)	1% (2)	2% (2)	0% (0)	1
Inferior / Inferolateral (n)	45% (61)	49% (61)	0% (0)	<0,01
Isolated Posterior (n)	2% (3)	2% (3)	0% (0)	1
LV infarction				
Chest Pain to revascularization interval (hours)	3,6 ±2	3,6 ±2	3,8 ±3	0,5
Primary PCI (n)	100% (136)	100% (124)	100% (12)	1
Stenosed / Occlude artery				
Diagonal branch of Left Anterior Descending (n)	2% (3)	2% (3)	0% (0)	1
Left Anterior Descending (n)	51% (69)	46% (57)	100% (12)	<0,001
Left Circumflex (n)	11% (15)	12% (15)	0% (0)	0,6
Left Marginal (n)	4% (6)	5% (6)	0% (0)	1
Posterior descending (n)	1% (1)	1% (1)	0% (0)	1
Right coronary (n)	38% (52)	41% (51)	8,3% (1)	0,03
TTE characteristics				
Apical aneurysm (n)	6% (8)	2% (3)	42% (5)	<0,001
Anterior akinésia (n)	25% (34)	20% (25)	75% (9)	<0,001
Apical akinesia (n)	36% (49)	31% (38)	92% (11)	<0,001
E/A	1,1 ±0,5	1,1 ±0,5	1,3 ±0,5	0,3
E/E'	8,2 ±2.9	8,1 ±2,9	8,8 ±2,6	0,3
LVOT VTI (cm/s)	19 ±4	19 ±4	17 ±3	0,03
Global longitudinal strain (%)	-14 ±3	-14 ±3	-10 ±2	0,02
Indexed left atrium volume (mL/m²)	30 ±9	30 ±9	36 ±12	0,1
Indexed Left Ventricular End Diastolic Volume (mL/m²)	56 ±14	55 ±13	65 ±16	0,04
Indexed Left Ventricular End Systolic Volume (mL/m²)	28 ±10	27 ±10	38 ±10	<0,01
LVEF at baseline (%)	45 ±10	46 ±10	35 ±6	<0,001
LVEF after revascularisation (%)	52 ±10	52 ±9	45 ±8	<0,01
Delta LVEF (baseline vs post revascularisation) (%)	6 ±9	6 ±9	9 ±5	0,1
Biology				
C Reactiv Protein (mg/L)	9 ±19	9 ±20	6 ±9	0,3
Creatine Kinase at baseline (UI/L)	498 ±732	496 ±756	516 ±385	0,1
Creatine Kinase Peak (UI/L)	3042 ±2340	2776 ±2073	5773 ±3176	<0,001
Creatinin (µmol/L)	75 ±15	75 ±15	66±11	0,04
Fibrinogen (g/L)	3,7 ±1,4	3,7 ±1,4	3,1 ±0,8	0,1
Glomerular Filtration Rate (mL/min/m²)	96 ±20	95 ±20	110 ±18	<0,01
Haemoglobin (g/L)	145 ±13	145 ±13	144 ±14	0,8
Mean corpuscular volume (fL)	91 ±4	91 ±4	91 ±5	0,9
Mean Patelet Volum (fL)	8,9 ±1	9 ±1	8,6 ±0,8	0,2
Patelet Count (G/L)	242 ±59	241 ±60	261 ±45	0,1
Body temperature during hospitalization				
Temperature >38°C during hospitalization (n)	12% (17)	10% (13)	33% (4)	0.04
Temperature >38.5°C during hospitalization (n)	1% (1)	0% (0)	8% (1)	0.09
Thombus detection:				
STEMI to TTE (Days)	6 ±4	6 ±4	6 ±2	0,9
STEMI to CMR (Days)	15 ±13	15 ±13	14 ±11	0,6
Delay TTE / CMR (Days)	9 ±13	9 ± 13	5 ±13	0,3
Adverse events				
Ischemic events	6% (8)	6% (7)	8% (1)	0,6
Ischemic or hemorrhagic events	7% (10)	7% (8)	17% (2)	0,3

Abbreviations: CMR: Cardiac Magnetic Resonnance, LVEF: Left Ventricular Ejection Fraction, LVOT VTI : Left Ventricular Outflow Tract Velocity Time Integral, PCI: Percutaneous Coronary Intervention, STEMI: ST Elevated

3.4. Treatment and follow up

In 11 of the 12 patients with LVT, a triple antithrombotic therapy was started using vitamin K antagonist (VKA) on top of Aspirin and Clopidogrel. One of them had his treatment changed at 6 months for Apixaban + Clopidogrel following a digestive hemorrhage. The last one was treated with Apixaban on top of Aspirin and Clopidogrel.

During the first year, two patients were lost of follow-up: one with a LVT and one without.

At one-year follow-up, an ischemic adverse event occurred in 8 patients (6%). In the 124 LVT patients with no LVT, 7 had an ischemic event: 3 strokes, 1 cardiac arrest due to early stent thrombosis, 2 others early stent thrombosis, 1 transient ischemic attack (TIA). In the 12 patients with LVT, 1 had a TIA.

Two hemorrhagic complications occurred at one year follow up: one in a patient with no LVT (Gastrointestinal bleeding from duodenal ulcer) and one in a patient with LVT (rectal bleeding in a context of VKA overdose, after LVT diagnosis).

And finally, a rhythmic complication occurred in a patient with LVT (cardiac arrest on ventricular tachycardia).

There was no difference between patients with or without LVT about having an ischemic adverse event during the first year (6% vs 8% in patients with LVT p = 0,6) neither an ischemic and/or hemorrhagic event (7% vs 17%; p = 0,3).

Among the 12 patients with LVT, only one still had thrombus at one year (treated at baseline with VKA + Aspirin + Clopidogrel).

Of note, a patient had LVT discovered at 3 months (systematic CMR), without any sign of thrombus on previous examinations (TTE day 8 and CMR day 9).

11 patients had MI after September 2020 and the one-year follow up is not over yet. All of them were free from events at 6 months follow-up.

4. Discussion

Our study showed an incidence of 8.8% of LVT among a population of patients with STEMI treated by primary PCI. Anterior STEMI, revascularized LAD as culprit artery, lower LVEF at admission and after revascularization, anterior or apical akinesia, LV aneurysm, higher ESV and EDV, lower LVOT VTI and GLS, better renal function, greater peak of creatin kinase and fever during hospitalization are univariate risk factors associated with occurrence of LVT after myocardial infarction.

4.1. Left Ventricular Thrombus incidence

The incidence of LVT in this study is comparable to the recently reported rates of 3.5-12%(1,4) and significantly lower than studies from the pre-early coronary revascularization era (up to 19-21%)(2,3).

Almost 1 out 5 patients with anterior STEMI had LVT; 1 out 4 if there's apical akinesia. Among patients presenting with apical akinesia, dilated LV (defined by LVEDV >74 mL/m² in men and >61 mL/m² in women(23)), and altered LVEF <45%, 50% had LVT.

The time to onset of these LVT is not precisely known but TTE was performed on average 6 days and CMR 15 days after STEMI, which is relatively early. Of note, a patient had a LVT discovered at 3 months (systematic CMR), without any sign of LVT on the examinations carried out previously.

4.2. Detection of Left Ventricular Thrombus

In our study, LVT appears to be more often detected by CMR than by TTE. LVT diagnosis was performed on CMR for 11 patients whereas TTE missed LVT in 5 patients.

CMR also diagnosed two LVT while contrast TTE concluded to no LVT.

As reported in previous studies (1,4–6), TTE seems to be inferior to CMR in LVT detection, even with contrast in the acute phase of MI. Srichai and al. (19) and Roifman and al. (27) highlighted that contrast-enhanced CMR showed the highest sensitivity and specificity for LVT detection (88% and 99% respectively) followed by cine-CMR imaging (sensitivity 58%-79%, specificity 99%), contrast TTE (sensitivity 23%-61%, specificity 96%-99), TTE (23-33% and 94-96% respectively) and TEE (40% and 96% respectively) for thrombus detection (19,27).

According to current recommendations, TTE must be systematic in the aftermath of STEMI. If echogenicity is not sufficient, TTE with contrast (although contraindicated in the early aftermath of STEMI) may be used with care and use of CMR may be helpful in case of non-contributory previous examinations. However, there are no clear recommendation as to the nature of the examination to be performed for the purpose of screening LVT in the aftermath of STEMI, or as to its timing. Accessibility and availability of CMRs varies widely locally, but in most centers it is not possible to perform CMR in all patients in a short delay after STEMI. So, there is a need to identify patients at risk in order to offer them screening strategy by CMR or at least repeated TTE.

4.3. Risk factors identified in patients with Left Ventricular Thrombus

Anterior akinesia, low LVEF, anterior territory, increased LV dimensions, aneurysm are well known risk factors (4,28). However, our study was interested in broader criteria, such as those integrated in the CHA_2DS_2VASc score (risk factors for developing intra-cardiac (left atrial) thrombi in Atrial Fibrillation (AF)). In our study, none of them ultimately emerges linked to the presence of LVT.

Many TTE criteria were analyzed, some of them had never been cited in this context, such as the LVOT VTI which was lower in our study in patients with LVT. Mansencal et al. previously demonstrated (24) that lower GLS was associated in patients with LVT.

Biologically, we studied the values of CK and not those of troponin due to change in troponin assay method in our center during the study (towards dosing of troponin I ultrasensitive), modifying threshold values and compromising the comparability of the results but it did not change our conclusions because CK is known to be as accurate in estimating the size of myocardial infarction as troponin (29,30). Creatin Kinase peak was higher in patients with LVT although Creatin Kinase rate at admission didn't differ significantly which reflects a higher infarct size in patients with LVT even if time to reperfusion did not appear to differ significantly.

Fever during hospitalization over 38°C is more frequent in patients with LVT in our study. Inflammation is known to be important in patients with large infarct size. It might promote thrombus formation. It is a clinical factor, simple to analyze, reproducible and easily available. However, unlike Shacham and al. (31), values of CRP and fibrinogen do not appear to be higher in patients with LVT while we expected an increase. We can possibly explain this by the short delay between chest pain to PCI and by the fact

that these values were only measured at patient's admission. Secondary inflammatory reaction was therefore not evaluated.

We didn't observe LVT in patients with inferior STEMI or right coronary occlusion. The only one patient with LVT who had a right coronary stenosis also had a LAD occlusion and an anterior STEMI. Yet we know that it is possible (although rare) to develop LVT in the aftermath of inferior STEMI.

Few studies studied renal function in patients with LVT after STEMI. It seems here, rather unexpectedly, that patients with LVT have a better kidney function. One could hypothesize that a better renal function leads to a faster clearance of the anticoagulant loading dose administered to patients at admission which favors the formation of a possible clot. Another explanation may be the fact that patients with chronic renal failure are more often patients with multiple cardiovascular risk factors and older, which favors the progressive development of underlying coronary lesions and of progressive collaterality. Thus, patients with this multivascular status and this collaterality are less at risk of having significant kinetic disturbances such as significant anterior or apical akinesias. Indeed, in our study, the multivascular status is more often found in patients with higher creatinine (mean creatinine 72 ± 13 µmol/L in patients with only one vessel vs 77 ± 14 µmol/L for multivascular patients; $p = 0.03$) and with a lower GFR (100 ± 21 mL/min vs 93 ± 18 mL/min; $p = 0.046$); which may reflect a patient profile with a more developed coronary collaterality and therefore less at risk of developing LVT.

4.4. Examinations and follow-up

ESC 2017 guidelines recommend to repeat TTE at 6/12 weeks in patients with LVEF ≤ 40% to assess the need for implantation of an ICD (5). It is also known that repeating CMR examinations following STEMI increases the number of LVT detected (4). In our

study, most patients with LVT detected both on TTE and CMR had these two examinations the same day. Patients with LVT detected on CMR but not by TTE carried out before had the CMR on average 10 days after TTE.

Sensitivity of TTE is lower than that of CMR (32), partly explained by its poorer spatial resolution. If LVT was most often diagnosed by CMR, it is also possible that we would screen more LVT by repeating TTEs for patients at risk, at least at 6 weeks as advised for patients with decreased LVEF. Perhaps TTE carried out systematically during hospitalization after a STEMI is too early.

According to 2011 AHA guidelines (33), risk of stroke is higher during the first two weeks after STEMI. However, the time to onset of LVT after STEMI isn't well known. This study of Visser and al. (3) with serial echographic studies post STEMI showed that about 90% of thrombi appeared in a delay of maximum two weeks after STEMI(3). However, this study was published in 1984, before the current early coronary revascularization era and antipatelet therapy strategy. The risk of stroke is estimated at 22.6 / 1000 within 30 days of STEMI and remains 2 to 3 times higher in the following 3 years (34). Most studies assess the presence of LVT one month after STEMI but we don't exactly know when it preferentially appears. Would it therefore be the right strategy to screen for these LVT during hospitalization and then again at a reasonable distance by TTE at least and by CMR in those at highest risk?

4.5. LVT treatment

Early detection of LVT therefore appears to be essential, especially when it is known that appropriate anticoagulation therapy may decrease embolic events incidence without increasing incidence of bleeding events (35).

Even if latest 2018 ESC guidelines for myocardial infarction management recommend VKA for curative anticoagulation (5), as proposed by Kajy (36), the use of Direct Oral Anticoagulants (DOACs) seems to be a reasonable alternative to VKA in the management of LVT. In our study, Apixaban was used in 2 patients without ischemic or hemorrhagic complications; one in first intention and one in the aftermath of a hemorrhagic complication with VKA and labile INR (International Normalized Ratio).

However, indication for triple therapy must be carefully assessed because although antithrombotic treatment is necessary and makes it possible to reduce peripheral ischemic events when LVT is identified; according to the prospective study of Bourezg and al. (37) indication for oral anticoagulation is independently associated with an increased risk of MACE and bleeding at one year.

No patient had prophylaxis triple therapy. It has been demonstrated that triple therapy with Warfarine against LVT formation following an anterior STEMI appears to result in no mortality benefit or reduction in stroke rates, but may increase the frequency of major bleeding (38).

Of note, the 12 patients in whom LVT was diagnosed, we found only one bleeding complication due to triple therapy (following an overdose of VKA) and no ischemic event after the introduction of an appropriate treatment (the patient who had a TIA had TTE and CMR the next day and therefore, the triple therapy began after his cerebral ischemic event).

4.6. Limitations

This is a single center study using datas from three different studies with their own limitations and characteristics. On the other hand, its strength is that a great variety of data was collected (standardized biological, clinical and echocardiographic data's).

The main limitation of this study concerns the size of our sample (and so, the low number of LVT detected) which does not allow us to perform a multivariate analysis.

Atrial fibrillation is a known factor of LVT development, like left heart valvular disease(28). Only few patients of this study had AF or LV valvular disease because it was part of the exclusion criteria of the CARIM study, as previous MI, or hypertrophic or dilated cardiomyopathy, patients with preexisting heart failure and patients with any previous cardiac surgery.

Our study did not demonstrate an increased risk of ischemic events, which can be explained by the size of our sample, the relatively low number of LVT detected but also by the short timeframe for carrying out screening examinations allowing patients with LVT to be treated quickly and thus prevent embolic complications.

Many patients did not undergo the planned examinations (194 out of the 330 patients at baseline). However, our results were in complete agreement with the prevalence of post-MI LVT found in previous studies (8.8% in our study vs 8 to 8.8% in previous studies (6,15)).

4.7. Clinical Perspectives

At present, very few CMRs are performed in the aftermath of a STEMI. Thus, a large number of LVT are probably underdiagnosed.

With a proportion of 8.8% of LVT in patients after STEMI and a TTE sensitivity of 54% as in our study, we can extrapolate that 4% of patients with recent STEMI could have an undiagnosed LVT if the CMR is not carried out. However, according to the retrospective study from Merkler et al.(10) the presence of LVT may be associated with the occurrence of 15% short-term stroke.

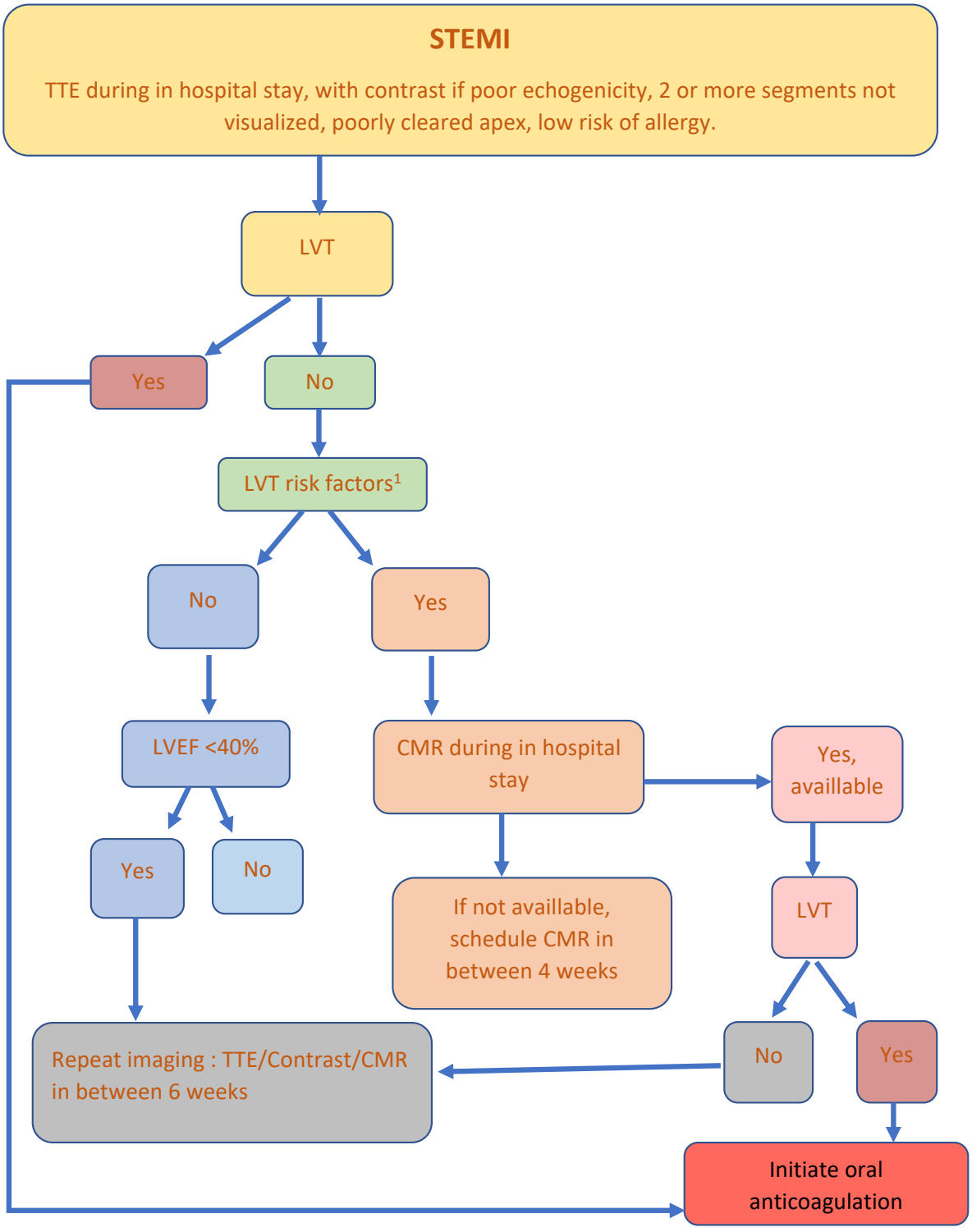
So, according to these datas, 0.6% of post-STEMI patients (15% of 4%) could have a preventable stroke by performing a CMR leading to introduce the right treatment.

To compare with, the absolute reduction in the risk of stroke recurrence after percutaneous closure of a patent foramen ovale (PFO) is approximately 1% per year (39–41) with in this case the need for a percutaneous intervention and the implantation of an intra-cardiac prosthesis.

We therefore have here a simple, non-invasive, safe imaging method that could avoid a severe complication with high potential for sequelae and loss of autonomy.

With about 100.000 STEMI each year in France according to the latest epidemiological records, it represents 600 patients/year in France with a severe pathology that could be easily prevented; 1970 to 6359 patients per year in Europe (746.4 million Europeans with the evaluation of incidence of 44 to 142 STEMI per 100.000 population per year) (42).

In view of these results, we propose an algorithm to aid the diagnosis of LVT, in order to optimize their detection and early management. (Fig 3)



[1] Anterior STEMI, revascularized LAD, lower LVEF on arrival and after revascularization, anterior or apical akinesia, LV aneurysm, higher end-systolic and end-diastolic LV volumes, lower LVOT VTI and GLS, better renal function, greater peak of creatin kinase and fever during hospitalization

Fig 3

5.Conclusion

Presence of LVT after STEMI is not rare (8.8%), even common among anterior STEMI (almost 1 in 5). Patients at highest risk had anterior STEMI, revascularized LAD, low LVEF at admission and after revascularization, anterior or apical akinesia, LV aneurysm, higher end-systolic and end-diastolic LV volumes, lower LVOT VTI and GLS, better renal function, greater peak of creatin kinase and fever during hospitalization. Even if CMR proves once again its superiority in LVT diagnosis, nature of the examinations to be carried out in post STEMI and their timing remain to be defined.

Reduced accessibility to CMR is pushing towards a strategy of screening patients at risk by TTE, which repetition at 4-6 weeks in association with CMR would seem to benefit patients greatly.

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42 pages – 2 tableaux – 2 figures – 1 illustration

Résumé :

Objectifs- Évaluer la prévalence de thrombus intra Ventriculaire Gauche (VG) après un syndrome coronarien aigu avec élévation du segment ST (SCA ST+) par Echographie TransThoracique (ETT) et Imagerie par Résonnance Magnétique (IRM), identifier les patients à risque et la meilleure stratégie diagnostique.

Méthode et Résultats- 330 patients ont été inclus dans trois études prospectives nécessitant ETT et IRM après un SCA ST+. 136 patients ont eu ces deux examens, 12 (8.8%) ont présenté un thrombus VG dont 5 détectés uniquement par IRM et un uniquement par ETT. En analyse univariée, les facteurs de risque identifiés sont : un SCA ST+ antérieur (100% vs 47% ; p<0.001), intéressant l'Interventriculaire Antérieure (100% vs 46% ; p<0.001), FEVG plus basse à l'admission (35% vs 46% ; p<0.001) et après revascularisation (45% vs 52% ; p<0.001), akinésie antérieure (75% vs 20% ; p<0.001), apicale (92% vs 31% ; p<0.001), anévrisme VG (42% vs 2% ; p<0.001), volumes télédiastolique et télésystolique VG plus élevés (65 vs 55 ml/m² ; p=0.04 et 38 vs 27 mL/m² ; p<0.01), ITV sous-aortique plus basse (17 vs 19 cm/s ; p<0.01), Strain Global Longitudinal plus bas (-10 vs -14% ; p=0.02), présence de fièvre (33% vs 12% ; p=0.04), débit de filtration glomérulaire plus élevé (110 vs 95 ml/min/m² ; p=0.01), taux de créatinine plus bas (65 vs 76 µmol/L ; p=0.04), pic de Créatine Phospho Kinase plus élevé (5773 vs 2776 UI/L ; p<0.001).

Conclusion– Le thrombus VG reste fréquent en post SCA ST+, surtout si infarctus antérieur, avec FEVG altérée et/ou VG dilaté. L'IRM est plus sensible que l'ETT mais du fait de sa disponibilité limitée, les examens à proposer et leur temporalité restent à mieux définir.

Mots clés :

Syndrome coronarien aigu – thrombus intraventriculaire gauche – anticoagulation – Echocardiographie transthoracique – Imagerie par résonance magnétique cardiaque

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