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Par

PONTOIS ANN-ELISABETH, née le 23 Août 1996 à Paris

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ANTICORPS MONOCLONAUX ET PROTEINES DE FUSION DANS LA PREVENTION DES LESIONS D'ISCHEMIE-REPERFUSION MYOCARDIQUES: DONNEES PRECLINIQUES ET CLINIQUES - REVUE SYSTEMATIQUE

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SERMENT DE GALIEN

En présence des Maitres de la Faculté, je fais le serment :

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L'étudiant
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La seule réelle prison est la peur et la seule vraie liberté est de se libérer de la peur

Aung San Suu Kyi

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Abréviations

APEX-AMI: Assessment of PEXelizumab in Acute Myocardial Infarction

ASSAIL-MI: ASSessing the effect of Anti-IL6 treatment in MI

ATP: Adenosine Triphosphate

CABG: Coronary Artery Bypass Graft

CKMB_AUC: Creatine Kinase Myocardial Band_Area Under the Curve

CNS: Central Nervous System

COMMA: The COMplement inhibition in Myocardial infarction treated with Angioplasty

COMPLY: The COMPlement inhibition in myocardial infarction treated with thromboLYtics

FP: Fusion Protein

FUP: Follow-up

hs-CRP: high sensitivity C-reactive Protein

IDM: Infarctus Du Myocarde

I/R: Ischémie/Reperfusion

LIMIT-AMI: Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction

LV: Left Ventricle

mAb: Monoclonal Antibody

MD: Mean Difference

MI: Myocardial Infarction

MRI: Magnetic Resonance Imaging

NR: Not Reported

NSTEMI: Non-ST Elevation Myocardial Infarction

PRIMO-CABG: Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery

PTP: Pore de Transition de Perméabilité

ROS: Reactive Oxygen Species

RR: Relative Risk

SAEs: Serious Adverse Events

SELECT-ACS: Effects of the P-selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST Elevation Myocardial Infarction

SPECT: Single-Photon Emission Computed Tomography

STEMI: ST Elevation Myocardial Infarction

TIMI: Thrombolysis In Myocardial Infarction

ANTICORPS MONOCLONAUX ET PROTEINES DE FUSION DANS LA PREVENTION DES LESIONS D'ISCHEMIE-REPERFUSION MYOCARDIQUES : DONNEES PRECLINIQUES ET CLINIQUES

REVUE SYSTEMATIQUE

Les mécanismes d'ischémie-reperfusion (I/R) à l'échelle de l'organe correspondent à une période d'hypoxie associée à une privation de nutriments suivie d'une réoxygénation avec rétablissement de l'apport en nutriments au niveau de la cellule. Ainsi, après une période d'ischémie conduisant à des dégâts cellulaires, la reperfusion entraine elle-même d'autres dommages.(1) Ce sont in fine des lésions d'I/R, lésions qui sont associées à un pronostic défavorable dans différentes pathologies comme l'accident vasculaire cérébral, l'infarctus du myocarde, ou des interventions comme la transplantation d'organe ou encore le pontage aorto-coronarien. Les mécanismes physiopathologiques d'I/R sont complexes et responsables de lésions plus ou moins irréversibles et font l'objet d'une littérature abondante depuis le début des années 1980.

Au cours de l'ischémie myocardique, définie comme la diminution ou l'arrêt du flux sanguin myocardique, les apports en oxygène et en substrats énergétiques sont inférieurs aux besoins ce qui entraîne des lésions cellulaires. A la reperfusion, la restauration du flux sanguin permet entre autres de réoxygéner le cœur. Cependant, ce mécanisme de reperfusion est aussi, paradoxalement, à l'origine de lésions de reperfusion ce qui a donné lieu au concept « d'infarctus de reperfusion » (2). En effet, au cours de l'ischémie, la production d'énergie est assurée par la glycolyse anaérobie. Néanmoins, cette voie énergétique produit peu d'adénosine triphosphate (ATP) et est donc peu rentable en énergie, en comparaison à la glycolyse aérobie et à la beta oxydation des acides gras. (3) Le pyruvate, produit par la glycolyse anaérobie, est transformé en lactate à l'origine d'une acidose lactique intracellulaire. Cette acidose active les échangeurs ATP dépendants : activation de l'échangeur Na^+/H^+ et donc une accumulation intracellulaire de Na^+, qui active à son tour l'échangeur Na^+/Ca^{2+}, à l'origine d'une accumulation intracellulaire de Ca^{2+}. Cette surcharge calcique active des protéases, lipases, NO synthétases et déshydrogénases. (3) Il en résulte une perte de polarité membranaire, un gonflement cellulaire, une désorganisation du cytosquelette aboutissant à la production d'espèces réactives à l'oxygène (ROS) et des lésions cellulaires irréversibles pouvant aboutir à la mort cellulaire. (3,4)

Lors de la reperfusion, l'apport brutal d'oxygène et de substrats énergétiques dans les cardiomyocytes endommagés ne peut être utilisé correctement par la chaine respiratoire mitochondriale. Par conséquent, la mitochondrie produit majoritairement des ROS et de faibles quantités d'ATP ce qui aboutit à la réactivation des échangeurs ATP dépendants et donc de nouveau à une surcharge calcique.(3) Cette dernière entraîne l'ouverture du pore de transition de perméabilité

mitochondrial (PTP). Du fait de cette ouverture, la membrane interne de la mitochondrie se retrouve en communication avec le cytosol, engendrant la libération du cytochrome C et l'activation des voies de mort cellulaire. (3) De plus, les ROS entraînent une peroxydation lipidique, des lésions membranaires (cardiomyocytes et mitochondries), l'activation des leucocytes (polynucléaires neutrophiles), la production de cytokines pro-inflammatoires ainsi que l'activation des voies de mort cellulaires (apoptose, nécrose). (4)

Cet infarctus de reperfusion serait responsable de lésions pouvant constituer jusqu'à 50% de la taille finale de l'infarctus. (3,5) De plus, des études expérimentales ont montré qu'une intervention pharmacologique (bloqueurs des canaux calciques ou de l'échangeur Na^+/H^+) avant la reperfusion permettrait de réduire la taille d'infarctus par rapport au groupe recevant une reperfusion seule. (6)

Le phénomène d'ischémie-reperfusion peut être responsable de quatre lésions principales (4): le « myocardial stunning » ou dysfonction post-ischémique, le phénomène de « no-reflow », les arythmies ventriculaires et les lésions de reperfusion létales.

Le « myocardial stunning » correspond à une dysfonction mécanique qui persiste après la reperfusion malgré l'absence de dommages irréversibles et malgré la restauration du flux sanguin coronaire. (7) Cette dysfonction myocardique se caractérise par une non-récupération de la contraction du myocarde vivant en période post-ischémique, qui sera suivie d'une récupération retardée des performances contractiles. Ces anomalies sont dues aux mécanismes de l'ischémie-reperfusion et notamment à la présence de ROS ainsi qu'à la surcharge calcique. Cette-dernière entraine le découplage excitation-contraction des cardiomyocytes et donc une dysfonction contractile et des arythmies. (8)

Le phénomène de « no-reflow » correspond à la restauration incomplète du flux sanguin artériel dans le tissu ischémique après reperfusion en lien avec une dysfonction microvasculaire en aval de l'artère coronaire initialement occluse et qui a été désobstruée. (9) D'après une étude animale d'occlusion de l'artère coronaire suivie d'une reperfusion, la désorganisation structurelle des capillaires d'aval causée par des œdèmes interstitiels, un gonflement des cellules endothéliales et des mitochondries et l'infiltration de polynucléaires neutrophiles, ou l'obstruction de la microvasculature, seraient à l'origine du phénomène de « no-reflow ». (10) Les patients soumis à ce phénomène de « no-reflow » après un infarctus du myocarde (IDM) présentent un moins bon pronostic clinique car ils sont plus à risque de développer une insuffisance cardiaque post-IDM voire un décès. (11) Une étude clinique a montré que les patients soumis au phénomène de « no-reflow » présentaient une mauvaise récupération de la fonction ventriculaire gauche et donc une majoration des arythmies ventriculaires par rapport aux patients dont la reperfusion n'avait pas entraîné de « no-reflow ». (12)

Les arythmies ventriculaires font parties des lésions de reperfusion. Les arythmies de reperfusion sont définies comme des troubles du rythme qui surviennent à la suite d'une restauration partielle ou totale du flux sanguin dans un tissu qui a été précédemment ischémié. (13) Les arythmies de reperfusion ont deux origines : le trouble de l'activité électrique du cœur causé par l'ischémie et la production d'espèces nocives (ROS, Calcium) lors de la reperfusion. En effet, la durée de la période d'ischémie détermine la vulnérabilité du tissu myocardique aux lésions de reperfusion. L'ischémie induit une diminution temps-dépendant de la durée et de l'amplitude du potentiel d'action et du potentiel de membrane. (14) Cela se traduit par une diminution et une hétérogénéité de l'activité électrique du cœur potentiellement génératrice d'arythmies. Mais, la restauration du flux sanguin via la reperfusion rétablit cette activité électrique ce qui majore, paradoxalement, les arythmies (fibrillation et tachycardie ventriculaires). (14,15) De plus, les arythmies de reperfusion peuvent apparaître lors de la production de ROS ou de calcium (surcharge calcique) à la suite de la reperfusion. (13)

Par conséquent, de nombreuses études cliniques et précliniques ont testé différents médicaments afin de prévenir ces lésions de reperfusion. Ces médicaments (insuline, adénosine (16) , inhibiteurs de canaux calciques (6), cyclosporine (17), anticorps monoclonaux et protéines de fusion, etc…) agissent sur différentes cibles impliquées dans les mécanismes physiopathologiques de l'I/R comme les acteurs de la cascade de l'inflammation (polynucléaires neutrophiles, cytokines pro-inflammatoires), cascade du complément (C5a), PTP. Des études prometteuses ont évalué la place des anticorps monoclonaux et des protéines de fusion dans la prévention des lésions d'ischémie-reperfusion myocardiques. (4)

Afin de recenser ces études, nous avons réalisé une revue systématique de la littérature avec méta-analyse des études précliniques et cliniques évaluant les anticorps monoclonaux et les protéines de fusion dans la prévention des lésions d'I/R myocardiques. Cette revue systématique permet d'obtenir une synthèse exhaustive, rigoureuse et reproductible de la littérature afin d'orienter les futures recherches dans ce domaine et de limiter les études redondantes. La méta-analyse permet une synthèse statistique des études incluses dans une revue systématique afin d'évaluer un effet global tout en prenant en compte les différents biais identifiés. La revue systématique couplée à la méta-analyse est le plus haut niveau de preuve scientifique.

ARTICLE

Evaluation of monoclonal antibodies and fusion proteins in cardiac ischemia-reperfusion injury: systematic review of clinical and experimental studies

INTRODUCTION

Ischemia-reperfusion injury is a major cause of morbidity and mortality in cardiac ischemic situations such as myocardial infarction, or cardiac surgery such as cardiopulmonary bypass or heart transplantation. In acute myocardial infarction due to acute coronary artery thrombosis, a situation of complete myocardial ischemia, the most efficient treatment is to restore blood flow in the ischemic area as fast as possible to salvage myocardium. However, several animal studies have shown that reperfusion also can induce so called myocardial reperfusion injuries. Reperfusion injury can account for up to 50% of the final myocardial infarct size according to experimental studies. (6) Several treatment strategies have been tested to prevent or reduce reperfusion injury such as ischemic preconditioning (brief episodes of myocardial ischemia and reperfusion before the sustained ischemic episode) (18) , ischemic postconditioning (interruption of myocardial reperfusion with repeated brief cycles of myocardial ischemia and reperfusion early after reperfusion), (19) preservation solution during heart transplantation surgery, and drugs targeting mitochondria or the inflammatory response (neutrophils, complement system or cytokines). While some drugs studied showed interesting results such as adenosine (16) and cyclosporin A (17), others like monoclonal antibodies or fusion proteins had mixed results.

Our objective was to systematically review all monoclonal antibodies or fusion proteins investigated in clinical or experimental studies to reduce cardiac ischemia-reperfusion injury, as well as the effects they yielded.

METHODS

This review was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria (20). Two study protocols were published in the PROSPERO international prospective register of systematic reviews: CRD42023407476 for clinical studies and CRD42023407486 for experimental studies. Ethical approval for these studies was not required.

Information Sources and Search Strategy

PubMed, Embase and Cochrane databases were screened until July 8th, 2022 by two authors (A-E P., T B-A.), without language restriction. We used the following key words regarding the three domains of interest (ischemia/reperfusion, myocardial/cardiac, monoclonal antibodies/fusion proteins): *ischemia/reperfusion, reperfusion lesion, reperfusion injury, myocardial, myocard*, heart, cardiac, cardio*, cardiovascular, monoclonal antibody, monoclonal antibodies, mab, mabs, therapeutic antibody, therapeutic antibodies, fusion protein, fusion proteins, cept, recombinant fusion protein, recombinant fusion proteins* (supplemental Table 1).

Eligibility Criteria and Study Selection

The selection of eligible studies was conducted by two independently authors (A-E P., O. L-T). First the screening was done by title and abstract, followed by full-text review for final study inclusion and data extraction. In case of conflicts, there were resolved on case-by-case basis with help from a third reviewer (T. B-A) as necessary.

Inclusion criteria consisted in the pathology studied, the population, the drugs and intervention, the placebo/comparator, and the study types.

Concerning the human systemic review, inclusion criteria were clinical trials (randomized or non-randomized) that included adult patients (18 years and over) and evaluated a monoclonal antibody, or a fusion protein administered before or after the ischemic situation to treat ischemia-reperfusion injury in three ischemic situations, reperfused myocardial infarction or cardiopulmonary bypass or heart transplantation surgery. The comparator was placebo or no treatment. Studies on resuscitated cardiac arrest, or non reperfused myocardial infarction or non-original studies such as observational studies, reviews or case reports were excluded.

Concerning the animal systematic review, inclusion criteria were administration of a monoclonal antibody or a fusion protein before or after experimental in vivo or ex vivo myocardial ischemia-reperfusion studies, reperfused myocardial infarction or cardiopulmonary bypass or heart transplantation surgery, with a control group. We focused on studies with mammalian species or mammalian organs. The comparator was a vehicle/placebo or no treatment. In sillico, in vitro (except for qualitative synthesis), non-animal or non-comparative experimental studies, studies without reperfusion after myocardial infarction, studies with no monoclonal antibody or fusion protein were excluded.

Risk Of Bias Assessment

Risk of bias was assessed in clinical trials (human systematic review) following the Cochrane risk of bias tool. (21) Risk of bias in animal experimental studies (animal systematic review) was assessed with the SYRCLE's risk of bias tool. (22) Risk of bias assessment was conducted independently by two reviewers (T. B-A, A-E. P or O.L-T) and conflicts were resolved by discussion. For human studies, we considered the following domains: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcomes assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), others bias. For experimental animal studies we considered the following domains: sequence generation, allocation concealment and baseline characteristics (selection bias), random housing and blinding (performance bias), random outcome assessment and blinding (detection bias), incomplete data outcome (attrition bias), selective outcome reporting (reporting bias), other sources of bias. Based on the above criteria, studies were divided in three categories: low (all criteria were a low risk of bias), high (at least one criterium was at high risk of bias), and some concerns regarding the risk of bias otherwise.

Outcomes

The main clinical outcome was mortality (cardiovascular and overall). The secondary outcomes related to myocardial injuries following ischemia-reperfusion were infarct size, heart failure, ventricular arrythmia, and stroke. Infarct size was observed as measured by animal tissues analysis (histology, cells viability), imaging procedures (echocardiography, MRI, and other procedures), and biomarkers release (troponin, CK, CKMB).

Data collection

The data from eligible studies were extracted by one author (A-E P.) and collected in a reporting document, double checked by a second author (O.L-T, T. B-A). Extracted data included type of study, population characteristics (sex, age, number of patients or animals treated, type of animal species, type of ischemic pathology), drug (type, target, dose, time and site of administration), comparator, and outcomes (primary and secondary).

Statistical Analysis

Findings were summarized qualitatively and quantitatively by means of tables and summary of included studies. Whenever possible, studies results were pooled in meta-analyses by using published aggregate data. A random effect Mantel-Haenszel model was used since we anticipated heterogeneity to be present at least regarding patient's settings and treatment targets. Summary statistics used were risk ratios for binary outcomes and standardized mean differences for continuous outcomes, with their 95% Confidence Interval. Whenever possible extracted data were means +/- SD; however, when data were reported as medians (IQR) we imputed means as medians, and estimated SD as IQR distance/1.35.

Heterogeneity was assessed with the Cochrane heterogeneity test and I^2. Planned subgroup analyses included type and/or dose of the drug, target antigen, type of disease, study quality (high vs low/intermediate). All analyses were done using RevMan 5.4.1. (23)

RESULTS

Study selection

The systematic review of the literature retrieved 2,795 articles in the 3 databases and other sources (Figure 1). After duplicates and retracted articles removal (n=354) 2,441 articles were screened on title and abstract, allowing to exclude 1,775 articles with reasons (Figure 1). Therefore, 666 full text articles were reviewed allowing to include eventually 147 articles: 23 articles (24–46) account for 13 clinical studies and 124 experimental studies articles (supplementary Table 2) have been included (111 animal studies, 11 ex-vivo studies, and 2 in vitro studies – Figure 1).

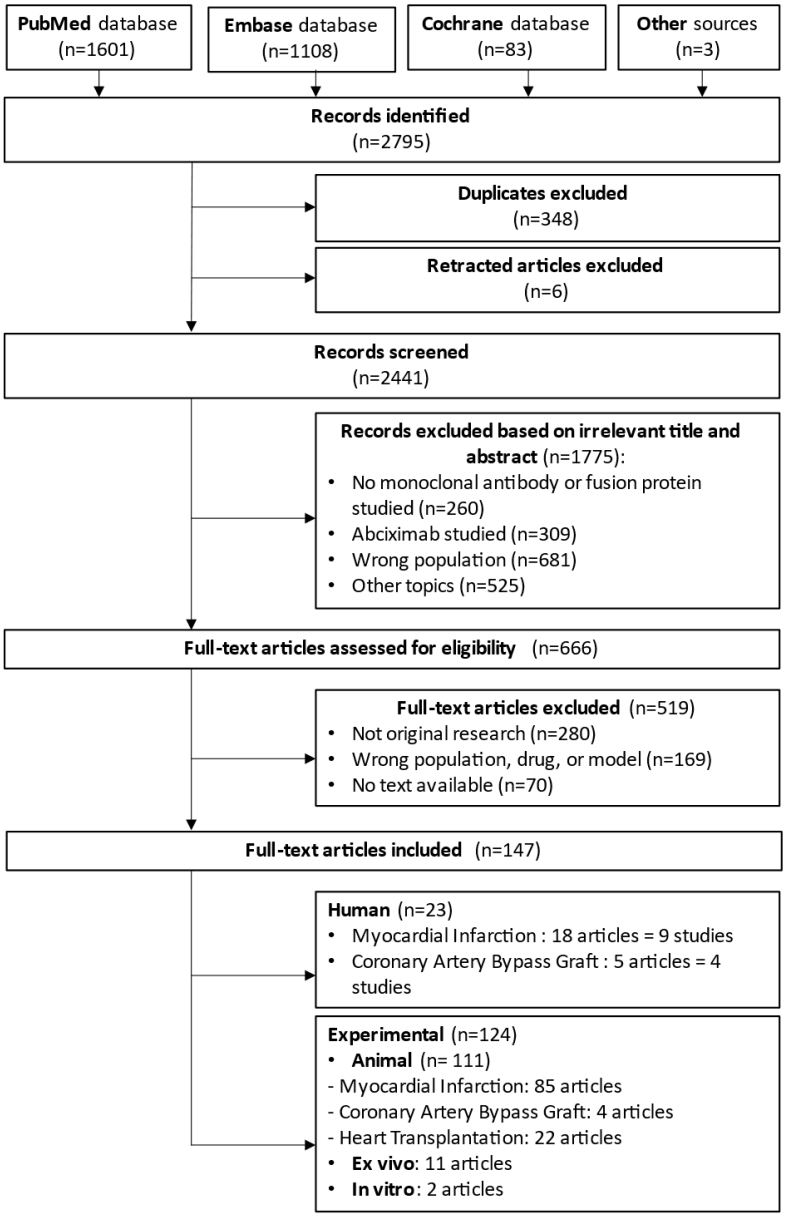


Figure 1: Flow Diagram Study Selection

Human studies

Study characteristics and analysis

Main characteristics of included clinical studies were described in Table 1.

We included 13 clinical trials: 4 studies included CABG patients (7,949 patients), 7 studies included STEMI patients (8,721 patients) and 2 studies included NSTEMI patients (439 patients). No studies evaluating fusion proteins were retrieved in Humans. All studies were multicenter studies, except for Fitch-1999, Kleveland-2016 and ASSAIL-MI-2021 which included patients from 2, 2 and 3 centers respectively. All studies were randomized double-blinded studies except for Fitch-1999 which was designed as an open label dose escalation study but with the use of placebo (simple blinded). All experimental drugs were administered by IV route from 10 minutes to 24 hours before either CABG or PCI and compare to placebo administration.

The target antigen was C5 component of complement by Pexelizumab in 4 CABG and 3 STEMI studies (15,597 patients), CD11/CD18 integrin receptor on leukocytes by leukarrest (Hu23F2G) in 2 STEMI studies (480 patients) and by rhuMAb CD18 in 1 STEMI study (394 patients), P-selectin by Inclacumab in 1 NSTEMI study (322 patients) and IL-6R by Tocilizumab in 1 STEMI and 1 NSTEMI studies (316 patients). Three Pexelizumab studies were phase III 2-arm studies and one Pexelizumab was an early 4-arm I-II study; the other seven studies were all 3-arm phase II studies and two 2-arm phase II study.

Main outcomes and results of included clinical studies were described in Table 2.

Mean or median patients' age in included studies was close to 61 years, and less than 40% were women. Eleven studies reported a main outcome, and 2 early phases were exploratory studies with objectives of safety, pharmacokinetics and/or pharmacodynamics outcomes. Main outcomes of the 3 phase III studies were clinical either death (APEX-AMI) or a composite of death and MI (PRIMO-CABG and PRIMO-CABGII). The other main outcomes were surrogate outcomes mainly infarct size by either imaging (SPECT or MRI) or biological markers (CK-MB or troponin I) or TIMI grade, or hs-CRP as inflammatory marker. Only two studies evaluating Tocilizumab found a significant reduction in hs-CRP in 117 NSTEMI patients and in myocardial salvage index via MRI in 199 STEMI patients compared to placebo, the other studies were negative, including the 3 phase III studies and 5 phase II studies.

Table 1: Main characteristics of clinical studies

Study Reference	Phase Registry Nb	Condition Nb of patients	Experimental drug	Target antigen	Study arms	First Dose / Maintenance dose
Fitch-1999 Circulation (39)	Phase I-II NR	CABG 35	Pexelizumab (h5G1.1-scFv)	C5	4 arms bolus in phase 1, 3 arms bolus in phase 2	Bolus 0,2-2 mg/kg / -
Shernan-2004 Ann Thorac Surg (36)	Phase II NR	CABG 914	Pexelizumab	C5	3 arms: bolus, bolus+infusion, placebo	Bolus 2 mg/kg / 0,05 mg/kg/h x 24h
PRIMO-CABG-2004 JAMA (45)	Phase III NCT00048308	CABG 2746	Pexelizumab	C5	2 arms: bolus+infusion, placebo	Bolus 2 mg/kg / 0,05 mg/kg/h x 24h
PRIMO-CABGII-2011 JTCVS (32)	Phase III NCT00088179	CABG 4254	Pexelizumab	C5	2 arms: bolus+infusion, placebo	Bolus 2 mg/kg / 0,05 mg/kg/h x 24h
LIMIT-AMI-2001 Circulation (28)	Phase II NR	STEMI 394	rhuMAb CD18	CD18	3 arms: low-dose, high-dose, placebo	Bolus 0.5 mg/kg; 2.0 mg/kg / -
FESTIVAL-2001 Am J Cardiol (25)	Phase II NR	STEMI 60	Leukarrest (Hu23F2G)	CD11/CD18 Leukocytes	3 arms: low-dose, high-dose, placebo	Bolus 0,3 mg/kg; 1 mg/kg / -
HALT-MI-2002 JACC (46)	Phase II NR	STEMI 420	Leukarrest (Hu23F2G)	CD11/ CD18 Leukocytes	3 arms: low-dose, high-dose, placebo	Bolus 0,3 mg/kg; 1 mg/kg / -
COMMA-2003 Circulation (38)	Phase II NR	STEMI 960	Pexelizumab	C5	3 arms: bolus, bolus+infusion, placebo	Bolus 2 mg/kg / 0,05 mg/kg/h x 20h
COMPLY-2003 Circulation (31)	Phase II NR	STEMI 943	Pexelizumab	C5	3 arms: bolus, bolus+infusion, placebo	Bolus 2 mg/kg / 0,05 mg/kg/h x 20h
APEX-AMI-2007 JAMA (37)	Phase III NCT00091637	STEMI 5745	Pexelizumab	C5	2 arms: bolus+infusion, placebo	Bolus 2 mg/kg / 0,05 mg/kg/h x 24h
SELECT-ACS-2013 JACC (34)	Phase II NCT01327183	NSTEMI 322	Inclacumab	P-selectin Leukocytes	3 arms: low-dose, high-dose, placebo	One infusion 5 mg/kg; 20 mg/kg / -
Kleveland-2016 Eur Heart J (29)	Phase II NCT01491074	NSTEMI 117	Tocilizumab	IL-6R	2 arms: one infusion, placebo	One infusion 280 mg / -
ASSAIL-MI-2021 JACC (42)	Phase II NCT03004703	STEMI 199	Tocilizumab	IL-6R	2 arms: one infusion, placebo	One infusion 280 mg / -

APEX-AMI: Assessment of PEXelizumab in Acute Myocardial Infarction; ASSAIL-MI: ASSessing the effect of anti-IL6 treatment in MI; CABG: Coronary Artery Bypass Graft; COMMA: The COMplement inhibition in Myocardial infarction treated with Angioplasty; COMPLY: The COMPlement inhibition in myocardial infarction treated with thromboLYtics; LIMIT-AMI: Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction; NR: not reported; NSTEMI: Non-ST elevation myocardial infarction; PRIMO-CABG: Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery; SELECT-ACS: Effects of the P-selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST Elevation Myocardial Infarction; STEMI: ST elevation myocardial infarction

Table 2: Main outcomes and results of clinical studies

Study Reference	Experimental drug	Condition Phase	Women Age*	Main outcome	Main result	Study conclusion
Fitch-1999 Circulation (39)	Pexelizumab	CABG I-II	NR NR	NR (possibly, safety) FUP to 4-6 weeks	NR (no increase in SAEs)	Exploratory
Shernan-2004 Ann Thorac Surg (36)	Pexelizumab	CABG II	NR NR	Composite: death / MI / LV dysfunction / CNS deficit At 4 days	NR	Negative
PRIMO-CABG-2004 JAMA (45)	Pexelizumab	CABG III	25% 65 years	Composite: death / MI in patients with CABG surgery At 30 days	RR 0.82 [0.66-1.02], p=0.07	Negative
PRIMO-CABGII-2011 JTCVS (32)	Pexelizumab	CABG III	40% 66 years	Composite: death / MI in patients with CABG surgery At 30 days	MI: RR 0.93, p=0.31 Death: RR 0.82, p=0.18	Negative
LIMIT-AMI-2001 Circulation Circulation (28)	rhuMAb CD18	STEMI II	27% 59 years	Corrected TIMI frame count at 90 minutes	No differences between placebo and active rhuMAb CD18 groups in any efficacy end point	Negative
FESTIVAL-2001 Am J Cardiol (25)	Leukarrest	STEMI II	27% 61 years	NR (possibly, PK) FUP until 25 weeks	NR (no significant difference between Leukarrest arms and placebo)	Exploratory
HALT-MI-2002 JACC (46)	Leukarrest	STEMI II	29% 60 years	Infarct size by myocardial imaging (SPECT) At 5-9 days	NR (no significant difference between Leukarrest arms and placebo)	Negative
COMMA-2003 Circulation (38)	Pexelizumab	STEMI II	24% 61 years	Infarct size by CKMB_AUC Through 72h	NR (no significant difference between Pexelizumab arms and placebo)	Negative
COMPLY-2003 Circulation (31)	Pexelizumab	STEMI II	31% 61 years	Infarct size by CKMB_AUC Through 72h	NR (no significant difference between Pexelizumab arms and placebo)	Negative
APEX-AMI-2007 JAMA (37)	Pexelizumab	STEMI III	23% 61 years	Death At 30 days	RR 1.04 [0.80-1.35], p=0.78	Negative
SELECT-ACS-2013 JACC (34)	Inclacumab	NSTEMI II	21% 61 years	Troponin I (change from baseline) At 16h and 24h	NR (no significant difference between Inclacumab arms and placebo)	Negative
Kleveland-2016 Eur Heart J (29)	Tocilizumab	NSTEMI II	12% 60 years	AUC for hs-CRP days 1 to 3	2.0 vs 4.2 mg/L/h, p<0.001	**Positive**
ASSAIL-MI-2021 JACC (42)	Tocilizumab	STEMI II	16% 61 years	Myocardial salvage index via MRI At 3-7 days	MD 5.6% [0.2-11.3], p=0.042	**Positive**

* For age, mean or median (depending on the results) were retrieved

APEX-AMI: Assessment of PEXelizumab in Acute Myocardial Infarction; ASSAIL-MI: ASSessing the effect of anti-IL6 treatment in MI; CABG: Coronary Artery Bypass Graft; CKMB_AUC: creatine kinase myocardial band_area under the curve; CNS: central nervous system; COMMA: The COMplement inhibition in Myocardial infarction treated with Angioplasty; COMPLY: The COMPlement inhibition in myocardial infarction treated with thromboLYtics; FUP: follow-up; hs-CRP: high sensitivity C-reactive protein; LIMIT-AMI: Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction; LV: left ventricle; MD: mean difference; MI: myocardial infarction; MRI: magnetic resonance imaging; NR: not reported; NSTEMI: Non- ST elevation myocardial infarction; PK: pharmacokinetic; PRIMO-CABG: Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery; RR: relative risk ; SAEs: serious adverse events; SELECT-ACS: Effects of the P-selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST Elevation Myocardial Infarction; ; SPECT: single-photon emission computed tomography; STEMI: ST elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

Risk of bias

The global quality of included studies was moderate with only one study at low risk of bias (37), 7/13 (54%) of studies at intermediate risk of bias and 4/13 (31%) at high risk of bias mainly due to incomplete outcome data (Figure 2). Ten studies (77%) were industry sponsored with some authors being employed by the sponsor and/or having conflicts of interest with the sponsor (Figure 3).

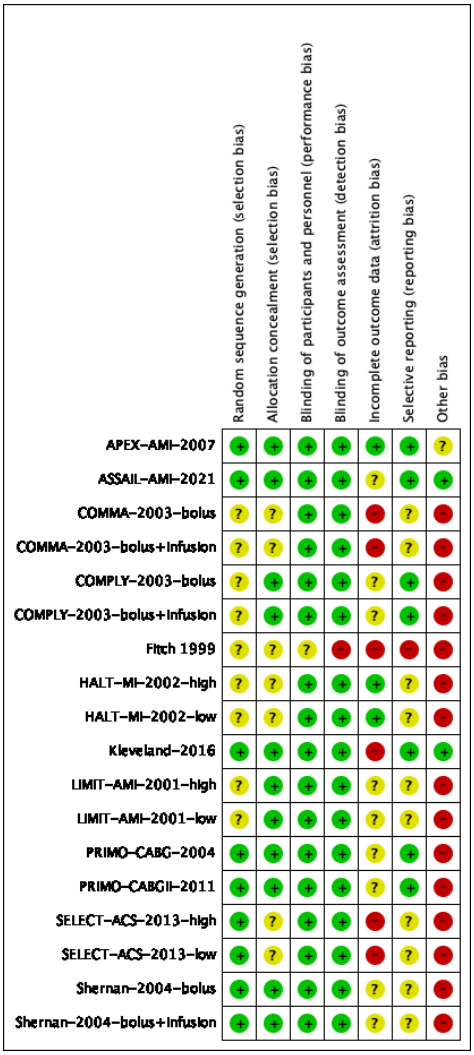


Figure 2 – Authors' judgements about each risk of bias item for each included study

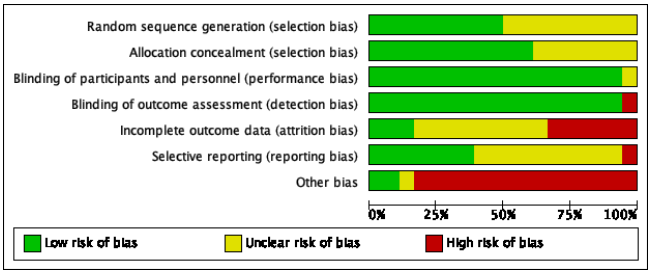


Figure 3 - Authors' judgements about each risk of bias item presented as percentages across all included studies

Meta-analysis of clinical events

Meta-analyses of clinical studies were conducted on mortality (30-days and 90-days), heart failure, serious infections, rehospitalizations and serious adverse events and biomarkers.

Data for 30-days mortality was available for 9 clinical studies and 90-days mortality data were available in 6 clinical studies (Figure 4). Meta-analysis showed that there was no significant difference on mortality between mAb and placebo for 30-days mortality (RR = 0.89; [0.77; 1.03]) and for 90-days mortality (RR = 0.97; [0.79; 1.18]). There was no heterogeneity for 30-days mortality (I^2 = 0%, p-het = 0.52) nor for 90-days mortality (I^2 = 25%, p-het = 0.22). (Figure 4)

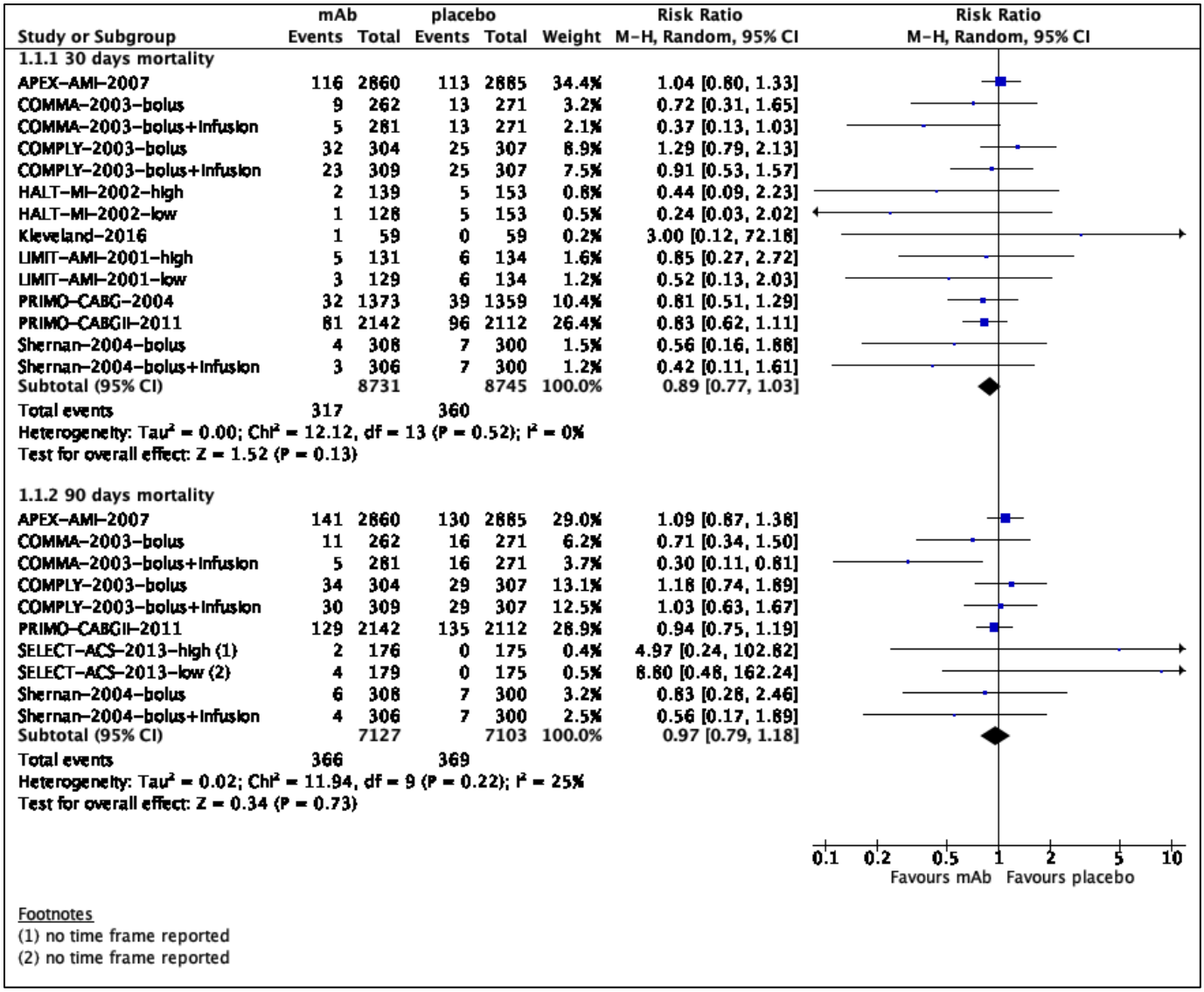


Figure 4 – Forest plot of mortality at 30 and 90-days.

Heart failure data was available in 10 clinical studies. Meta-analysis showed that there was no significant difference in heart failure events between mAb and placebo (RR = 0.97; [0.85; 1.11]). There was no heterogeneity (I^2 = 0%, p-het = 0.67). (Figure 5)

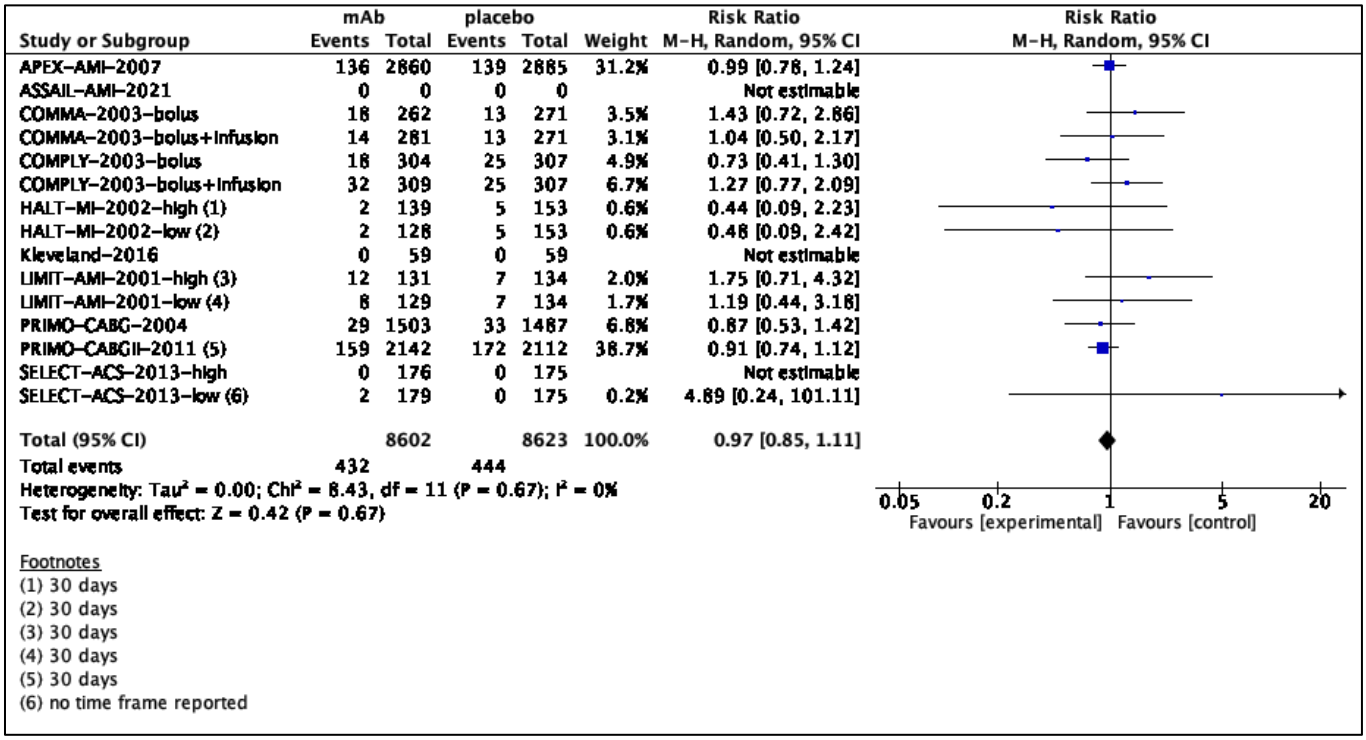


Figure 5 – Forest plot of heart failure

Serious infections data was available in 11 clinical studies. Meta-analysis showed no significant difference in serious infections between mAb and placebo (RR = 1.09; [0.94; 1.27]), with no meaningful heterogeneity (I^2 = 15%, p-het = 0.28). (Figure 6)

Rehospitalizations data was available in only one study (HALT-MI) that showed no significant difference between mAb and placebo (RR = 0.72; [0.45; 1.15]) with no heterogeneity (I^2 = 0%, p-het = 0.74). (Figure 6)

Serious adverse events data was available in 5 studies. Meta-analysis showed a borderline significantly increased risk of serious adverse events with mAb administration compared to placebo (RR = 1.13; [0.99; 1.29]) with no heterogeneity (I^2 = 0%, p-het = 0.58). (Figure 6)

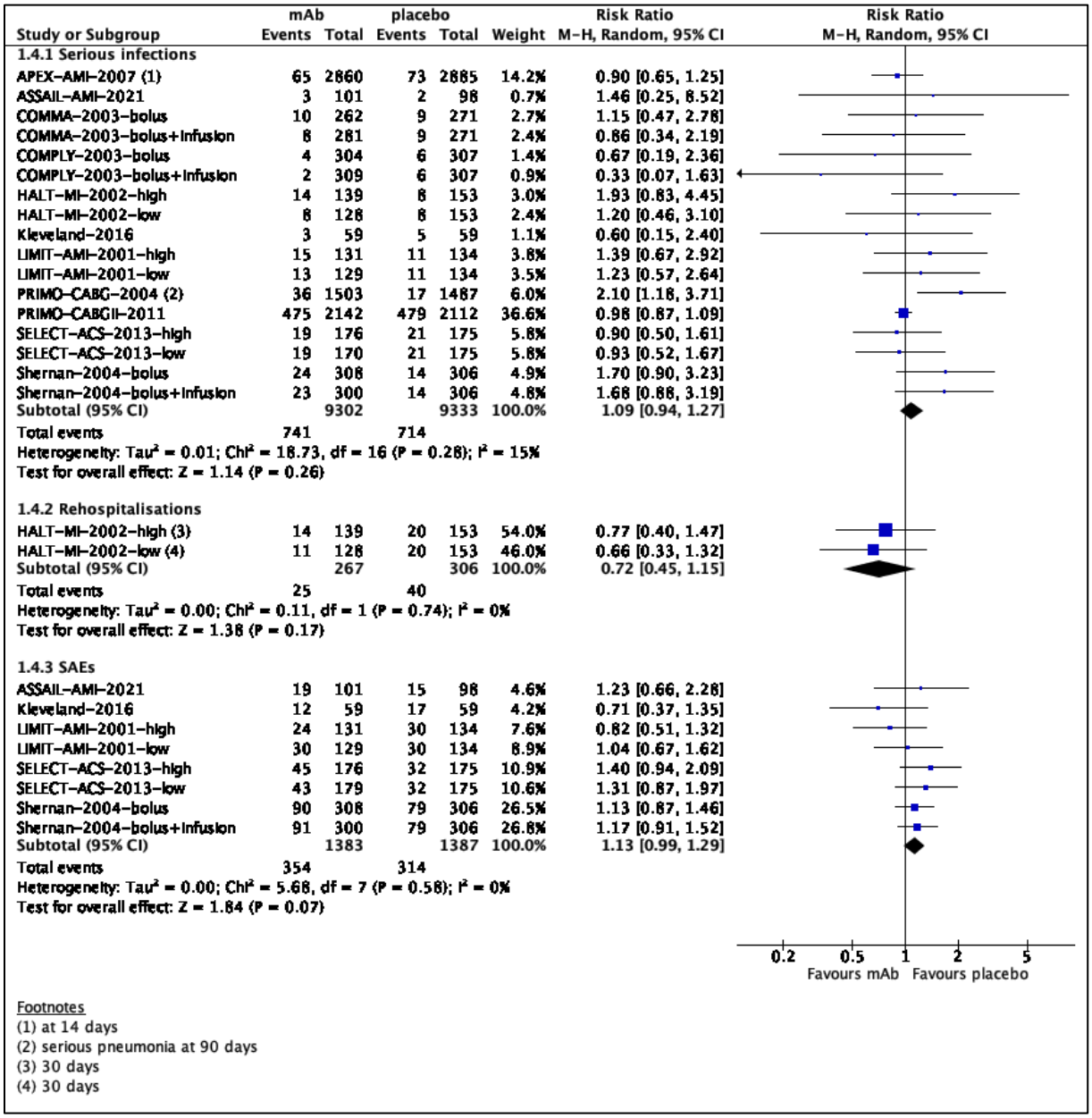


Figure 6 – Forest plot of adverse events

Efficacy of mAbs on biomarkers was heterogeneously and rarely reported (Figure 7) and showed no clear reduction in biomarkers' release, either on CK-MB (area under the curve or peak) in two STEMI and two CABG studies, nor on troponins (T or I) in two acute myocardial infarction studies.

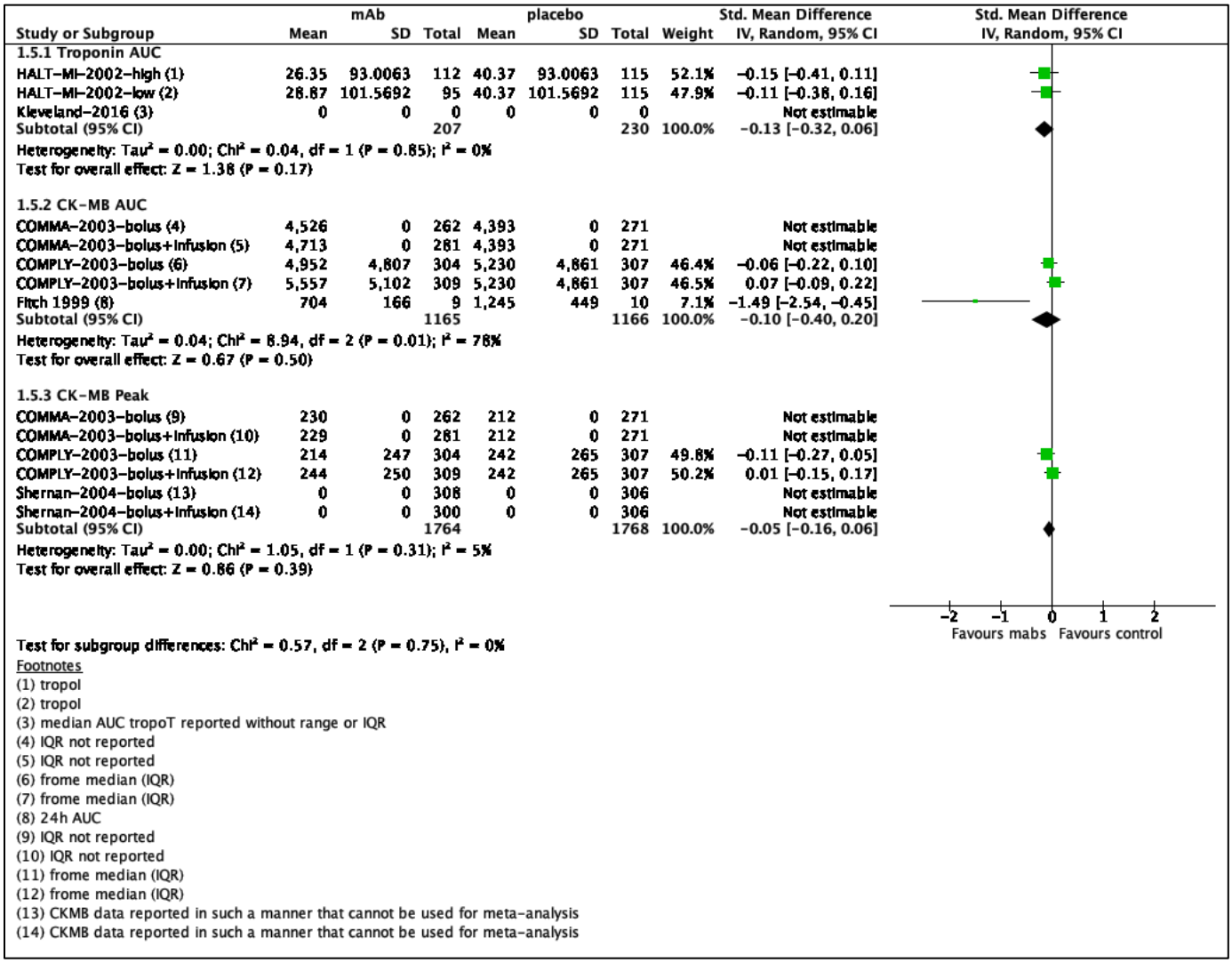


Figure 7 – Forest plot of biomarkers release

Some asymmetry was visible in the funnel plots of 30-days and 90-days mortality (Figure 8) and therefore publication bias cannot be ruled-out, while no clear asymmetry was clearly visible for heart failure or serious infections (Figure 9).

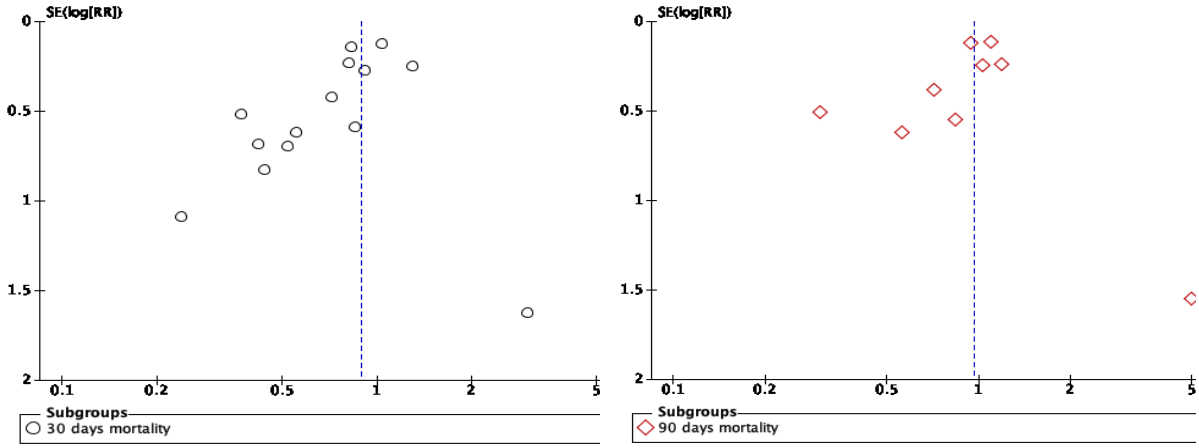
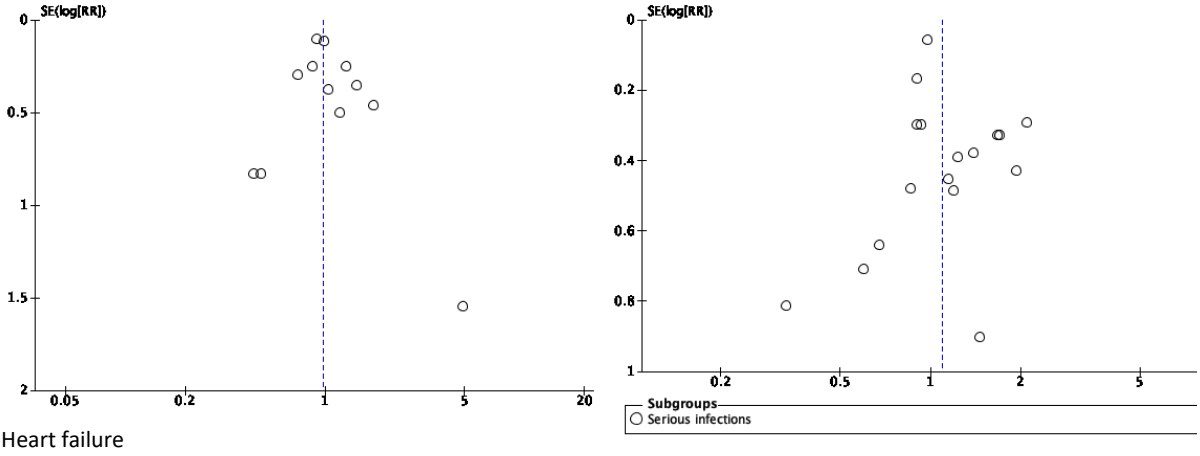


Figure 8 – Funnel plots of 30-days (left) and 90-days (right) mortality



Heart failure

Figure 9 – Funnel plots of heart failure (left) and serious infections (right)

Animal studies' characteristics and synthesis

We retrieved and included 124 experimental articles (Supplementary Table 2) published since 1988 (Figure 10).

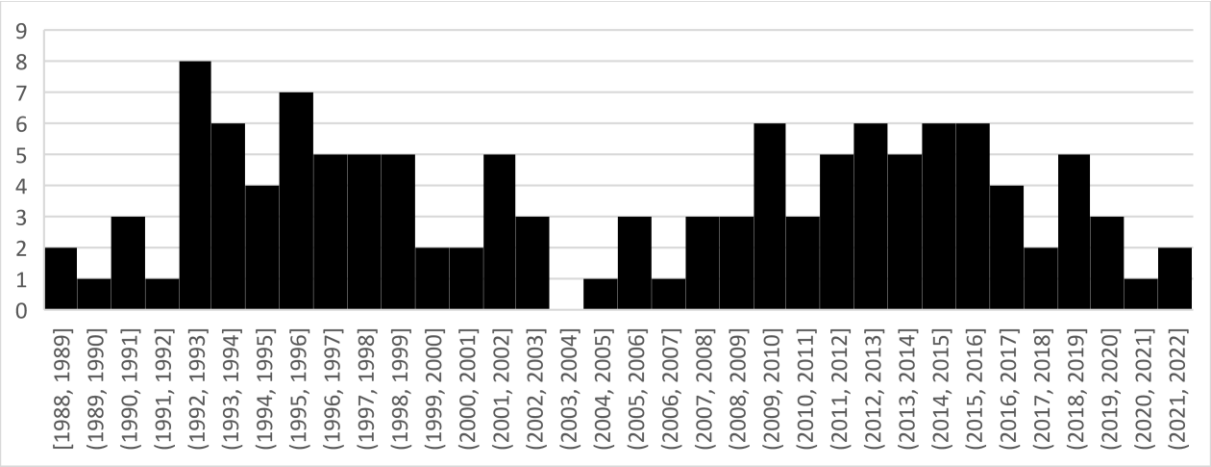


Figure 10 – Experimental studies published since 1988.

Most experimental studies used myocardial infarction animal models (n = 85 studies, 69%), followed by heart transplantation surgery models (n = 22 studies, 18%) and cardiopulmonary bypass (n = 4 studies, 3%) models (Figure 11). We retrieved only 11 articles having studied ex-vivo models (myocardial infarction by Langendorff model) and 2 articles having studied in vitro models (hypoxia-reoxygenation model on cultured cardiomyocytes).

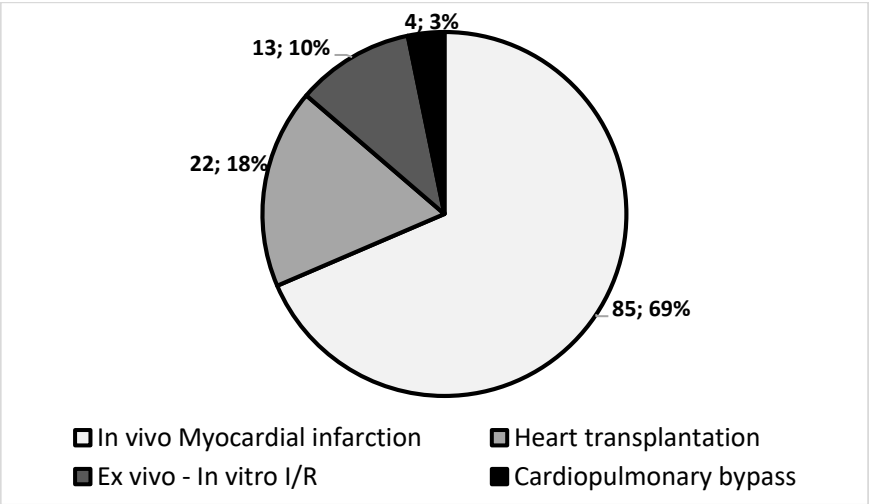


Figure 11 – Repartition of experimental models of ischemia / reperfusion

Rat (n = 47 studies, 38%), mouse (n = 34 studies, 27%), dog (n = 15 studies, 12%) and rabbit (n = 11 studies, 9%) were the main animal models used (Figure 12).

Cardiopulmonary bypass models were in pigs (n = 3 studies) and dogs (n = 1 study). Homograft heart transplantation was performed in rats (n = 9 studies), mice (n = 9 studies), and other animals (rabbits, monkeys, ovines) and one heterograft transplantation was performed in guinea pig / rat. Myocardial infarction models mainly used rats (n = 27, 32%), mice (n = 25, 29%), dogs (n = 14, 16%) and rabbits (n = 10, 12%) (Figure 12).

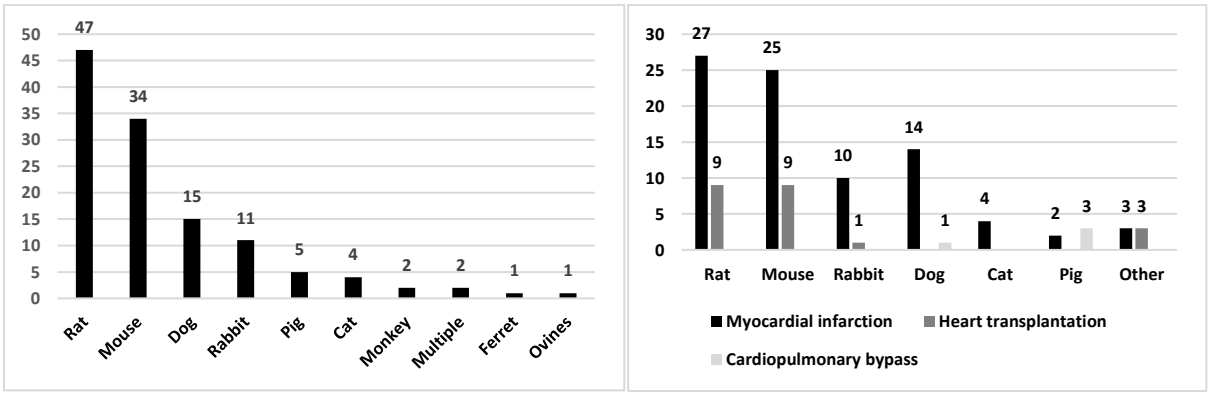


Figure 12 – Animal models repartition, overall (left) and by type of ischemia / reperfusion model (right).

Ninety articles (72%) have tested mAb and 33 (27%) have tested fusion protein (Figure 13). The main targets were leukocytes adhesion molecules (n = 41, 33%), followed by cytokines (n = 15, 12%), complement (n = 10, 8%), apoptosis (n = 8, 6%), coagulation proteins or factors (n = 6, 5%), oxidative stress (n = 6, 5%). Other targets (n = 38, 31%) included endothelin, immune cells, TLR2, GLP1, mitochondria respiratory chain and other intracellular pathways such as PLC, PI3K-AKT, … (Figure 13, Supplemental Table 2)

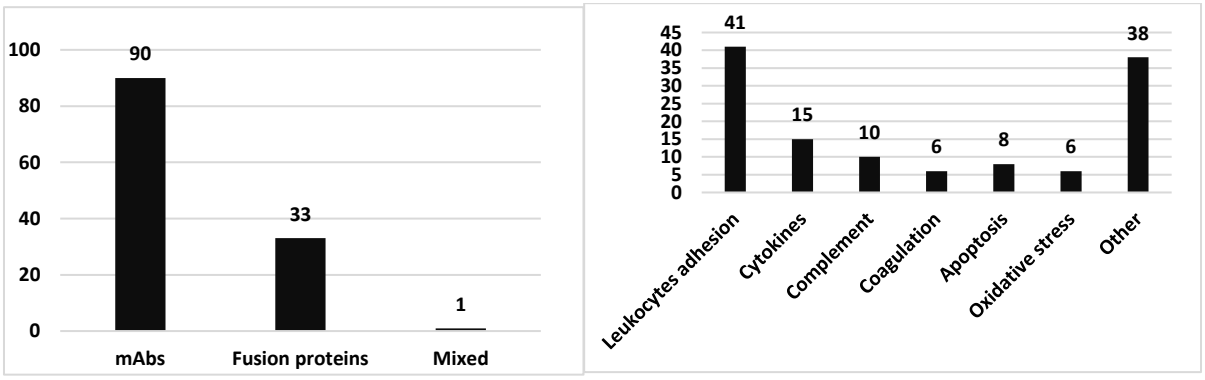


Figure 13 – Main therapeutics used in experimental studies (left) and their main target domains (right)

The main endpoint for cardiopulmonary bypass (CPB) models (4 articles) was endothelial function (relaxation and permeability). Models evaluated only mAbs, administered as IV bolus before CPB, targeting CD18 leukocytes component (2 studies) and C5 complement component (2 studies), compared to placebo (saline) infusion (4 articles). Results have shown "positive" effects of the mAbs, yet 1 study showed no improvement in heart function.

Twenty-two studies evaluated heart transplantation models. All transplantation models were homograft transplantation except for one article (Hori S et al. – 1997). Eighteen articles (82%) evaluated mAbs (17 mAbs + 1 minibody), 3 articles evaluated fusion proteins and 1 article evaluated both. Targets were leukocytes adhesion molecules (CD18, CD11a, E/L-selectin, ICAM-1, Lipocalin-2) in 7 studies, complement (C5a, CR2, C2-CR1) in 5 studies, inflammatory cytokines (IL-6, IL-1R, TNF) in 3 studies, chemokines (FKN-CX3CR1, CXCR3/IP10) in 2 studies, memory T-cells (VLA-1), natural killer cells (NKG2D), angiotensin 2, and anti-cells IgM (neutrophils, macrophages). All therapeutics were mostly IV or peritoneum infused, although intracoronary route was found in 2 articles and subcutaneous route in 1 article, before heart transplantation or before ischemia or before or after reperfusion or at reperfusion. Comparators were isotype mAb or placebo (saline, vehicle). Half of the studies (n = 11) had graft survival as the main outcome, and the other half had surrogate outcomes such as biomarkers, histology (cell infiltrates), LV function. All studies reported "positive" effects of therapeutics.

Eighty-five articles have studied myocardial infarction animal models: 62 articles (73%) have evaluated mAb and 23 (27%) have evaluated fusion proteins. Main targets for mAbs (44 studies, 71%) were leukocytes adhesion molecules (CD11/CD18, CD18, ICAM, selectins, Sialyl Lewis) in 28 studies, cytokines (IL6, IL8, IL17, IL18, TNF) in 6 studies, C5 complement component in 3 studies, coagulation process (tissue factor, platelets glycoproteins) in 4 studies, and TLR2 in 3 studies. For the other 18 studies targets were: CCL5 chemokine, CTGF, endothelin-1, death factor Fas-L, phosphorylcholine on apoptotic cells, TRAIL protein, lectin (MASP2 and LOX-1), monocytes, HMGB1, Dectin-1, Myosin, PSCK9 and VLDL-R. Comparators were placebo (PBS, vehicle or saline) or control mAb. Treatments were administered mostly as IV bolus, although intramyocardial, intraperitoneal, or subcutaneous routes were also used, before or after ischemia, or after reperfusion. Infarct size was analysed by histology (except for 4 studies) and sometimes completed by biomarkers released (CK, Troponin) or imaging analyses (echocardiography, MRI). Most studies (n = 48, 77%) reported "positive" results, yet "negative" results were reported in 5 studies and 9 other studies reported mixed findings. Main targets for fusion proteins were cytokines in 5 studies, oxidative stress in 4 studies, and the other 14 studies evaluated coagulation, apoptosis, incretins, mitochondria, inflammation, angiotensin 1, CD39, phospholipase C, α1-antitrypsin. Comparators were placebo (PBS, vehicle or saline) or control FP. Treatments were administered mostly by IV bolus, although intramyocardial, intraperitoneal, or

subcutaneous routes were used, before or after ischemia or after reperfusion. Infarct size was analysed by histology and sometimes completed by biomarkers released (CK, Troponin) or imagery analysis (echocardiography, MRI). All studies (100%) reported “positive” results.

Eleven ex-vivo studies, all conducted in rats, evaluated a mAb in 6 studies, targeting leukocytes adhesion molecules (CD18, selectins, ICAM) in 4 studies, TNF and Sodium-Bicarbonate cotransporter, and a fusion protein in 5 studies, targeting oxidative stress, mitochondria, endonuclease, apoptosis, and myosin. Comparators were no treatment, or placebo (vehicle, saline, Krebs solution), or control mAb or fusion protein. Two in vitro studies evaluated a fusion protein targeting SOD and PI3K-AKT. As expected, all studies reported “positive” findings.

All 5 clinical targets (Table 1) have also been tested in experimental studies (Supplementary Table 3) while some other 57 targets have been investigated in preclinical studies, but not in Humans. Leukocytes adhesion molecules, cell homeostasis, cytokines and apoptosis pathways seem to be the domains with the highest number of targets studied (Figure 14).

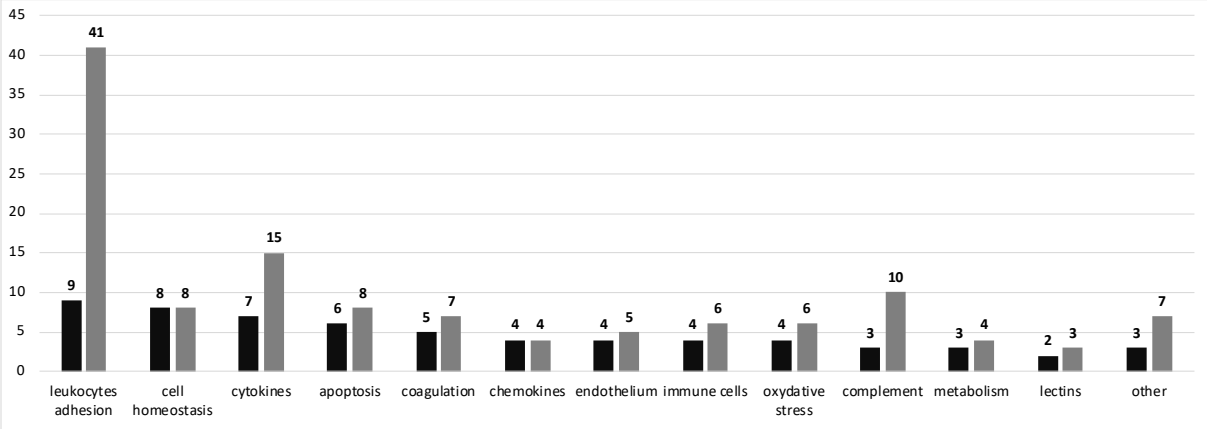


Figure 14 – Main domains of mAbs and FP targets identified in preclinical studies: number of different targets identified within each domain (black histograms) and number of preclinical studies identified for each domain (grey histograms).

DISCUSSION

This systematic review and meta-analysis investigated if a monoclonal antibody or a fusion protein administered before or after the ischemic assault or after reperfusion can reduce cardiac ischemia-reperfusion injury in three clinical or experimental situations: myocardial infarction, cardiopulmonary bypass, and heart transplantation surgery. We showed that 5 targets have been studied in clinical studies, especially in acute myocardial infarction: C5 fraction of the complement blocked by pexelizumab, CD11/CD18, CD18 and P-selectin as molecules involved in leukocytes adhesion process, and IL-6 receptor blocked by tocilizumab. No benefit was observed in neither biomarkers nor clinical events, except for one small study that showed a reduction in MRI estimated myocardial salvage index with tocilizumab. These findings contrast with animal studies that showed globally mostly positive results. The limits of such preclinical models have already been discussed in the literature and propositions have been made to improve the design of animal studies (47). Other pharmacological reasons could also be advocated to explain actual failure to translate benefit to Humans, such as the choice of the dose of a given the drugs to Humans (lower doses could be related to inefficacy, and higher doses to increased toxicities). In line with this thinking, we observed that adverse events might be increased in mAbs groups in Human studies which could also be a factor that limit the demonstration of benefit. For example, in the ATTACH trial (48) ,infliximab 10 mg/kg in patients with moderate to severe heart failure, while slightly improving clinical status at 14 weeks also increased mortality and heart failure hospitalizations.

Some systematic reviews and meta-analyses have investigated other therapeutics such as cyclosporine (49–51), luteolin (52), nitric oxide agents (53), stem-cell derived extracellular vesicles (54) or pre- and post-conditioning (55–57), with heterogeneous results. However, to our knowledge, no systematic review has investigated monoclonal antibodies of fusion proteins. Our systematic review and meta-analysis suggest that IL-6 receptor might offer some cardio protection, but other targets failed to demonstrate cardioprotective effects. Such conclusion should be cautious since the authors of a recent systematic review and meta-analysis of IL6 inhibition in animal models concluded to a “limited contribution of IL6 inhibition to cardiac remodelling” (58).

The interest in myocardial I/R is still present given the steady increase of PubMed articles (over 43,000 as to date). Regarding mAbs and FP, clinical studies were regularly published from 1999 to 2021 and experimental studies from 1988 to 2022. Myocardial infarction was the main model studied because of the morbidity and mortality it causes, despite timely coronary angioplasty and pharmacological treatments targeting platelets, cholesterol, and renin-angiotensin system.

We found 62 various targets in preclinical studies, all of them roughly in line with ischemia-reperfusion pathophysiology. The main targets were similar in clinical and experimental studies. The main domains studied so far were leukocytes adhesion, cell homeostasis, cytokines, and apoptosis pathways.

As expected, this systematic review retrieved more included articles for experimental studies compares to clinical studies. Most experimental studies showed a “positive” effect of the mAb or the fusion protein but most of their targets have not been tested in Humans. Moreover, the type of animal model influences the results and the potential to transpose results to clinical studies. Indeed, rats were the main animal population but the similarities with humans are low compares to large animals such as dogs or pigs models. (59)

Finally, inhibition of inflammation in the hours/days after of acute myocardial infarction with the objective to improve reperfusion injuries, was evaluated through other therapeutics with no clear clinical benefit. (60,61)

Limits

Our work has several limitations. First, the search equation from the three databases has been analysed in July 2022 and has retrieved 2792 articles. We can assume that if we re-analyze the three databases, more articles will be found. Also, the search equation did not include studies that have not specifically mentioned “ischemia/reperfusion” in the text, even if the drug could target reperfusion injuries. This was the case for a safety study that evaluated rituximab (62) in acute STEMI patients. Post-hoc, we reviewed the protocols registered in Clinicaltrials.gov regarding “ischemia reperfusion injury” and found 385 studies 184 of which (48%) regarding cardiac / myocardial I/R in various conditions. Only 3 studies on pexelizumab (43%) were registered in Clinicaltrials.gov. None of the registered protocols included terms such as “ischemia-reperfusion injury” or “reperfusion injury” and were not retrieved in the “ischemia reperfusion injury” list. This point out a limit of our search and potential pitfalls that must be addressed in future systematic reviews.

Second, the systematic review showed of clinical studies revealed the potential for publication bias regarding 30-days and 90-days mortality according to the funnel plots. The limits of search strategy could explain some of this potential bias. Other factors such as the existence of clinical trial registries only since 2000 and not before could also play a role (URL: https://clinicaltrials.gov/about-site/about-ctg, accessed on Sept 23, 2023). Further, the risk of publication bias was not assessed in animal studies because no attempt to summarize outcomes was not attempted. Yet such bias is most probably very high in animal studies given the high observed rate of “positive” effects.

Third, the global quality of included clinical studies was moderate and bias arising from industry sponsorship may be present, while difficult to assess. The quality of animal studies was not formally addressed. A systematic review in 2013, found over 30 published tools regarding the quality of animal studies (63) and showed that only 2/30 of these tools were validated and not developed for a specific disease, so the use could be generalized. Yet no tool was validated by the Cochrane collaboration so far. One recent tool, SYRCLE, was developed in collaboration with the Dutch Cochrane centre but was not validated (64). It is unclear if quality of animal studies should be assessed specifically developed tools or use a more general tool that could marginally be adapted. Therefore, some more work still needs to be done in this field.

Conclusion and prospects

Our systematic review and meta-analysis is the first one to study the effect of mAbs and FP to reduced ischemia/reperfusion injury in clinical and preclinical studies. We showed that even if several targets were evaluated with positive results in preclinical studies, no clear benefit was visible in Human studies when these targets were evaluated in clinical studies. More research is necessary to 1) improve preclinical models and evaluate the risk of bias in ischemia/reperfusion animal studies, 2) correctly summarize preclinical research results in order to correctly transpose the best pharmacological interventions at the best dose in clinical studies.

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Supplementary data

Supplementary Table 1 - search equation in the 3 databases

Database	Search equation	Articles
PubMed	(((((((((ischemia reperfusion) OR (ischemia / reperfusion)) OR (reperfusion lesion)) OR (ischemia - reperfusion)) OR (ischemia AND reperfusion) OR "Reperfusion Injury"[Mesh]) OR (reperfusion injury)) OR (ischemia/reperfusion)) OR (I/R)) AND ((((((((myocardial) OR (myocarde)) OR (heart)) OR (cardiac)) OR (cardio*)) OR (cardiovascular)) OR (myocard*)) OR (myocard))) AND ((((((((((monoclonal antibody) OR (monoclonal antibodies)) OR (mabs)) OR (mab)) OR (fusion protein)) OR (fusion proteins)) OR (cept)) OR ("Recombinant Fusion Proteins"[Mesh])) OR ("Antibodies, Monoclonal"[Mesh])) OR (therapeutic antibody)) OR (therapeutic antibodies))	1 601
Embase	('reperfusion injury'/exp OR (reperfusion AND lesion) OR (reperfusion AND injury) OR (ischemia NEAR/0 reperfusion)) AND (myocardial OR myocarde OR heart OR cardiac OR cardio* OR cardiovascular OR myocard* OR myocard) AND ('fusion protein'/exp OR 'monoclonal antibody'/exp OR 'therapeutic antibody'/exp OR (monoclonal NEAR/0 antibodies) OR (monoclonal NEAR/0 antibody) OR mabs OR mab OR (fusion NEAR/0 protein) OR (fusion NEAR/0 proteins) OR cept OR (recombinant AND fusion AND proteins) OR (recombinant AND fusion AND protein) OR (therapeutic NEAR/0 antibody) OR (therapeutic NEAR/0 antibodies))	1 108
Cochrane	ischemia reperfusion OR ischemiareperfusion OR reperfusion lesion OR ischemia-reperfusion OR ischemia AND reperfusion OR "Reperfusion Injury" OR reperfusion injury OR ischemiareperfusion OR IR AND myocardial OR myocarde OR heart OR cardiac OR cardio* OR cardiovascular OR myocard* OR myocard AND monoclonal antibody OR monoclonal antibodies OR mabs OR mab OR fusion protein OR fusion proteins OR cept OR "Recombinant Fusion Proteins" OR "Recombinant Fusion Protein" OR "Antibodies, Monoclonal" OR therapeutic antibody OR therapeutic antibodies	83

Supplementary Table 2 – Main characteristics of experimental animal, ex-vivo, in vitro studies

Article	Model	Animals Number total (actif/comp*)	Drug Target	Domain	Comparator Route of administration	Time of infusion Dose	Endpoints Time of analyse	Conclusion
(Paul J Simpson, Iii, et Fantone 1988) The Journal of clinical investigation	Myocardial Infarction LCCA occlusion - 90 min I/6h R	Dogs 21 (8/8/5)	mAb (IgG1) CD11b/CD18 (Mo1=Mac1)	Leuko adhesion	Placebo (vehicle) or control mAb IV	After occlusion and after reperfusion 1 mg/kg after occlusion	Histology, Ventricular arrhytmias After reperfusion	Positive
(Schott et al. 1989) Circulation research	Myocardial Infarction LADCA occlusion - 15 min I/3h R	Dogs 11 (6/5)	mAb (IgG1k) CD11b/CD18 (Mo1=Mac1)	Leuko adhesion	IgG control IV	Before occlusion 0,5 mg/kg	Histology, Ejection fraction After reperfusion	Negative
(P J Simpson et al. 1990) Circulation	Myocardial Infarction LCCA occlusion - 90 min I/72h R	Dogs 16 (8/8)	mAb (IgG1) CD11b/CD18 (Mo1=Mac1)	Leuko adhesion	Control mAb IV	After occlusion and after reperfusion 1 mg/kg after occlusion (bolus) 0,5 mg/kg after reperfusion, 48h (continuous)	Histology, Ventricular arrhytmias After reperfusion	Positive
(Gomoll, Lekich, et Grove 1991) Jour of cardiovasc pharmaco	Myocardial Infarction LAD occlusion – 90 min I/6h or 24h R	Ferrets NR	mAb CD18 (Leukocytes)	Leuko adhesion	Placebo (saline) IV	During occlusion or after reperfusion 2 mg/kg	Histology After reperfusion	Positive
(Ma, Tsao, et Lefer 1991) The Journal of clinical investigation	Myocardial Infarction LADCA occlusion - 90 min I/4,5h R	Cats 13 (7/6)	mAb (IgG1) CD18 (Leukocytes)	Leuko adhesion	Control IgG1 IV	Before reperfusion 1 mg/kg	Histology, CK After reperfusion	Positive
(Watanabe et al. 1991) Circulation research	Myocardial Infarction LADCA occlusion - 60 min I/24h R	Rats Multiple groups	mAb (IgG1k) ET-1 (endothelin)	Endothelium	Placebo (saline) or IgG control IV	Before occlusion or after reperfusion 22,5 mg/kg x1 or 1,5 mg/kg x7 or 4,7 mg/kg x7	Ejection fraction After reperfusion	Positive
(Ma et al. 1992) Circulation	Myocardial Infarction LAD occlusion - 90 min I/4,5h R	Cats 14 (7/7)	mAb (IgG) ICAM-1	Leuko adhesion	IgG control IV	Before reperfusion 2 mg/kg	Histology, CK After reperfusion	Positive

(Byrne J et al. 1993) The Jour of Surg Res	Homograft heart transplantation	Rabbits 15 (7/8)	R15.7 mAb (IgG1) CD18 (Leukocytes)	Leuko adhesion	Placebo (saline) IV	Pre-reperfusion 2 mg/kg	LV pressure (pression-volume related)	Positive
(Tanaka et al. 1993) Circulation	Myocardial Infarction LCCA occlusion - 90 min I/3h R	Dogs 23 (10/13)	mAb (Fab) CD18 (Leukocytes)	Leuko adhesion	Placebo (saline) NR	Before occlusion and at the beginning of reperfusion NR	Histology, Ventricular arrhytmias Leukocytes via MPO After reperfusion	Positive on leukocytes infiltration No effects on infarct size and area at risk
(Ma et al. 1993) Circulation	Myocardial Infarction LAD occlusion - 90 min I/4,5h R	Cats 18 (6/6/6)	mAb (IgG1) L-selectin (Leukocytes)	Leuko adhesion	Control IgG1 or sham IV	Before reperfusion 1 mg/kg	Histology After reperfusion	Positive
(Weyrich et al. 1993) The Jour of Clin Inves	Myocardial Infarction LAD occlusion – 90 min I/4,5h R	Cats 12 (6/6)	mAb (IgG1) P-selectin (Leukocytes)	Leuko adhesion	Non blocking mAb IV	Before reperfusion 1 mg/kg	Histology, Echocardiography After I and after R	Positive
(Yamazaki et al. 1993) The Amer Jour of Pathology	Myocardial Infarction LCA occlusion – 30 min I/ 48h R	Rats 48 (8 rats/group)	mAb (x4) ICAM-1, CD11a, CD11b+c, CD18	Leuko adhesion	IgG control or sham IV	Before ligation 5 mg/kg	Histology After reperfusion	Positive
(Kusumoto et al. 1993) Journal of cardiovascular pharmacology	Myocardial Infarction LCCA occlusion - 30 min I/ 24h R	Rabbits 10 (5/5)	mAb (IgG1k) Endothelin-1 (ET-1)	Endothelium	IgG1k control IV	Before occlusion 10 mg/kg	Histology After reperfusion	Positive
(Lefer et al. 1993) Circulation	Ex vivo - Langendorff 20 min I/ 45 min R	Rats Multiple groups	mAb (R15.7) CD18 (Leukocytes)	Leuko adhesion	No treatment Ex vivo	At first reperfusion 20 µg/mL	Ejection fraction After reperfusion	Positive
(McDonagh et al. 1996) The Journal of surgical research	Ex vivo - Langendorff Right innominate artery and ascending aorta (30 min I/ NR R)	Rats 15 (7/8)	mAb (Fab2) CD18 (Leukocytes)	Leuko adhesion	Placebo (vehicle) Ex vivo	During reperfusion 11 µg/mL	Ejection fraction After reperfusion	Positive
(Yamamoto, Tamiya, et Uede 1994) Immunopharmacology	Homograft heart transplantation	Rats 20 (10/10)	mAb (IgM) Leukocytes neutrophiles, macrophages	Immune cells	IgM control IV	Before reperfusion 1 mg/kg	Graft survival	Positive

(Williams F et al. 1994) Bristish Jour of Pharmaco	Myocardial Infarction Coronary occlusion - 30 or 45 min I/3h R	Rabbits 23 (11/5/7)	mAb (IgG2) CD18 (Leukocytes)	Leuko adhesion	Placebo (saline) or control mAb IV	Before reperfusion 1 mg/kg	Histology, Ventricular arrhytmias Leukocytes via MPO After reperfusion	Positive if 30 min ischemia No effects if 45 min ischemia
(Altavilla et al. 1994) Euro Jour of Pharmaco	Myocardial Infarction LCA occlusion - 60 min I/1h R	Rats NR	mAb (IgG1) E-selectin (Leukocytes-Endothelial cells)	Leuko adhesion	Non immune serum IV	Before occlusion 2 mg/kg	Histology, CK After reperfusion	Positive
(Ioculano et al. 1994) Euro Jour of Pharmaco	Myocardial Infarction LMCA occlusion - 60 min I/1h R	Rats 24 (12/12)	mAb (IgG1) ICAM-1	Leuko adhesion	Non immune serum IV	Before occlusion 1 mg/kg	Histology, CK After reperfusion	Positive
(Chen et al. 1994) Cardiovasc Research	Myocardial Infarction LADCA occlusion - 60 min I/1h R	Dogs 16 (NR)	mAb (IgG1) P-selectin (Leukocytes)	Leuko adhesion	Placebo (phosphate buffered saline) IV	During occlusion 2 mg/kg	Histology, Ejection fraction After reperfusion	Positive
(Herzog et al. 2014) Cardiovascular research	Myocardial Infarction LAD occlusion - 30 min I/24h and 7d R	Mice 10 (5/5)	mAb TLR2	TLR2	Control antibody Peritoneum	Before occlusion 70 µg	Histology, Troponin T After reperfusion	Positive
(Aoki et al. 1995) Journal of cardiac surgery	Cardiopulmonary bypass	Piglets 17 (9/8)	mAb CD 18 (Leukocytes)	Leuko adhesion	Placebo (saline) IV	pre-CPB 6,4 mg	Endothelial functions Pulmonary heamodynamics (vasodilatation, MPO, NOS)	Positive
(Amsterdam et al. 1995) Amer Jour of Physio	Myocardial Infarction LADCA occlusion - 50 min I/3h R	Pigs 22 (9/6/2/5)	mAb (IgG1k) C5a (complement)	Complement	Vehicle PBS or Control mAb IV	Before IR 0,5 or 1 mg/kg	Histology After reperfusion	Negative
(Aversano et al. 1995) Journal of the Amer Coll of Cardio	Myocardial Infarction LADCA occlusion - 90 min I/4h R	Baboons 19 (9/10)	mAb (IgG4) CD18 (Leukocytes)	Leuko adhesion	Placebo (saline) IV	Before reperfusion 11 mg/kg (mean)	Histology, LV function, Echocardiography After reperfusion	Positive
(Tamiya, Yamamoto, et Uede 1995) Immunopharmacology	Ex vivo 30 min I/ 40 min R	Rats 30 (20/10)	mAb LFA1 and ICAM-1	Leuko adhesion	Control IgG In vitro	Before reperfusion 2 mg/kg	Ejection fraction After reperfusion	Positive

(Mayers et al. 1996) Journal of critical care	Cardiopulmonary bypass	Dogs 18 (6/6/6)	mAb CD 18 (Leukocytes)	Leuko adhesion	Placebo (saline) IV	pre-CPB 6 mg/kg	Endothelial functions Pulmonary heamodynamics (vasodilatation, MPO, NOS)	Positive
(Arai et al. 1996) Journal of the Amer Coll of Cardio	Myocardial Infarction LCCA occlusion - 90 min I/48h R	Dogs 24 (12/12)	mAb (IgG1) CD18 (Leukocytes)	Leuko adhesion	Placebo (saline) IV	Before reperfusion 1 mg/kg	Histology, LV function After reperfusion	Positive
(Perez et al. 1996) The Amer Journ of Physio	Myocardial Infarction LCA occlusion - 90 min I/3,5h R	Dogs 49 (31/18)	mAb (IgG1) - R15.7, PLM-2, MHM.23 CD18 (Leukocytes)	Leuko adhesion	Placebo (saline) IV	Before reperfusion 1 or 2 mg/kg	Histology After reperfusion	Positive for R15.7 mAb
(Lefer et al. 1996) The Amer Jour of Physio	Myocardial Infarction LCCA occlusion - 80 min I/5h R	Dogs 25 (18/7)	mAb (IgG1) P-selectin (Leukocytes) and ICAM-1	Leuko adhesion	Placebo (saline) IV	Before reperfusion 1,5 mg/kg (Pselectin mAb); 0,5 mg/kg (ICAM1 mAb); combinaison	Histology After reperfusion	Positive if not combinated
Lefer D et al. - 1996 The Amer Jour of Physio (Lefer, Flynn, et Buda 1996)	Myocardial Infarction LCCA occlusion - 120 min I/4h R	Dogs 19 (7/5/7)	mAb (IgG1) P-selectin (Leukocytes)	Leuko adhesion	Non blocking mAb or Placebo (saline) IV	Before reperfusion 1 mg/kg	Histology, Ejection fraction After reperfusion	Positifve necrosis and MPO Negative blood flow et contractility
(Tojo et al. 1996) Glycobiology	Myocardial Infarction LMCA occlusion - 30 min I/24h R	Rats 30 (12/18)	mAb (IgG1k) P-selectin	Leuko adhesion	Placebo (saline) or control mAb IV	Before occlusion 1 mg/kg	Histology After reperfusion	Positive
(Seko et al. 1996) The Journal of pathology	Myocardial Infarction LCA occlusion - 30 min I/ 48h R	Rats 24 (8/8/8)	mAb (IgM) Sialyl Lewis (Leukocytes)	Leuko adhesion	IgM control or Placebo (saline) IV	Before occlusion 2 mg/kg	Histology After reperfusion	Positive
(Robert S Poston et al. 1997) The Ann of Thor Surg	Homograft heart transplantation	Rats 102 (NR)	mAb (IgG1) ICAM-1	Leuko adhesion	Placebo (saline) IV	Before ischemia 2 mg/kg	Graft survival	Positive
(Hori et al. 1997) Transplant	Heterograft heart transplantation	Donors: guinea pigs Recipients: rats Multiple groups	mAb IgM	Immune cells	Superoxyde dismutase mimetic Peritoneum	Before HT	Graft survival	Positive

(Horwitz, Kaufman, et Kong 1997) The Amar Journ of Physio	Myocardial Infarction LAD occlusion - 60 min I/48h R	Dogs 20 (NR)	mAb (IgG1) CD18 (Leukocytes)	Leuko adhesion	No treatment IV	Before occlusion 1 mg/kg	Relaxation	Positive
(Zhao et al. 1997) Journal of leukocyte biology	Myocardial Infarction LCA occlusion - 30 min I/2h R	Rabbits 26 (10/8/8)	mAb ICAM-1	Leuko adhesion	Control mAb or Placebo (saline) IV	Before reperfusion 2 mg/kg	Histology, CK After reperfusion	Positive
(Gurevitch et al. 1997) JACC	Ex vivo - Langendorff 60 min I/ 30min R	Rats 27 (9 per group)	mAb TNFα	Cytokines	No treatment or IgG Cardioplegic solution	/ 1,5 mg	Histology, CK, LV function	Positive
(Tofukuji et al. 1998) The Journal of thoracic and cardiovascular surgery	Cardiopulmonary bypass	Pigs 18 (6/6/6)	mAb C5a (complement)	Complement	Placebo (saline) IV	pre-CPB 1,6 mg/kg	Endothelial functions Pulmonary heamodynamics (vasodilatation, MPO, NOS)	Less leukocytes;no improvment in heart preservation functions
(Vakeva et al. 1998) Circulation	Myocardial Infarction LAD occlusion - 30 min I/4h R	Rats 39	mAb (IgG2b) C5a (complement)	Complement	Placebo (PBS) IV	Before ischemia or before reperfusion 20 mg/kg	CPK, Histology 7 days	Positive on necrosis Negative on blood flow and contractility
(Boyle et al. 1998) The Journal of thoracic and cardiovascular surgery	Myocardial Infarction LAD occlusion - 45 min I/2h R	Rabbits 46 (NR)	mAb IL-8	Cytokines	Ig control anti-GP120 IV	Before occlusion 2 mg/kg	Histology, Ejection fraction After reperfusion	Positive
(Yamada et al. 1998) European journal of pharmacology	Myocardial Infarction LCCA occlusion - 30 min I/5h R	Rabbits Multiple groups	mAb (IgG1) P-selectin (Leukocytes)	Leuko adhesion	Placebo (saline) or Others drugs (sialyl lewis or sulfatide) IV	Before ischemia 2 mg/kg or 5 mg/kg	Histology After reperfusion	Positive
(P J Simpson et al. 1988) Circulation research	Myocardial Infarction LCCA occlusion - 90 min I/72h R	Dogs 34 (11/13/10)	mAb Leukocytes	Leuko adhesion	Placebo (saline) or Iloprost IV	Before and afte reperfusion 0,3 mL/kg	Histology After reperfusion	Positive
(Robert S. Poston et al. 1999) The Jour of Surg Research	Homograft heart transplantation	Rats 72 (NR)	mAb (IgG1) ICAM-1	Leuko adhesion	Placebo (vehicle) IV	Before ischemia 2 mg/kg	LV function, Necrosis /	Positive

(Feeley et al. 1999) The Ann of Thor Surgery	Homograft heart transplantation	Rats 30 (6 groups of 5 rats)	mAb LFA1 and ICAM-1	Leuko adhesion	Placebo (saline) NR	Before reperfusion 80 µmol/L (ICAM1 mAb)	Mean heart score, MPO, Contraction band necrosis	Positive
(Park et al., s. d.) Anesthesia and analgesia	Cardiopulmonary bypass	Pigs 20 (7/6/7)	mAb C5a (complement)	Complement	Placebo (saline) IV	pre-CPB 1,6 mg/kg	Endothelial functions Pulmonary heamodynamics (vasodilatation, MPO, NOS)	Positive
(Arai et al. 1999) JACC	Myocardial Infarction LAD occlusion - 90 min I/48h R	Dogs 20 (11/7/2)	mAb (IgG1) P-selectin	Leuko adhesion	Non blocking mAb or saline IV	Before reperfusion 1mg/kg	Histology, LV function After reperfusion	Moderate effects
(Ohnishi et al. 1999) Eur Jour of Pharmacology	Ex vivo - Langendorff 20 min I/ 45 min R	Rats NR	mAb (IgG1) P-selectin	Leuko adhesion	Placebo (saline) or sialyl lewis Ex vivo	At the first 5 min of reperfusion 0,6 mg/min	Histology, LV function After reperfusion	Positive
(R. S. Poston et al. 2000) Transplant	Homograft heart transplantation	Monkeys 12 (7/5)	mAb CD11a	Leuko adhesion	No treatment IV	Before HT 8-20 mg/kg, day 1 and 10mg/kg/day after	Graft survival	Positive
(Erlich et al. 2000) The Amer Jour of Pathology	Myocardial Infarction LAD occlusion - 45 min I/2h R	Rabbits 16 (11/5)	mAb (IgG1) Thrombin Factor	Coagulation	Placebo (saline) IV	Before or after occlusion 2 mg/kg	Histology After reperfusion	Positive
(Hancock et al. 2001) The Jour of Exp Med	Homograft heart transplantation	Mice NR	mAb CXCR3/IP10 interferon (IFN)-gamma-inducible protein of 10 kD (IP-10, or CXCL10)	Chemokines	IgG control Peritoneum	From engraftment to 14 days post-HT 200µg every 2 days for 14 days	Graft survival	Positive
(Jordan, Montalto, et Stahl 2001) Circulation	Myocardial Infarction LCA occlusion - 30 min I/4h R	Rats 21 (15/6)	mAb (IgG1k) - P7E4 and 14C3.74 MBL (complement) mannose-binding lectin (rMBL)	Lectin	No treatment NR	Before ischemia 0,05 or 1 mg/kg	Histology, CK After reperfusion	Positive P7E4 Negative 14C3.74
(Carter et al. 2002) The Ann of Thor Surgery	Homograft heart transplantation	Ovines 12 (6/2/4)	mAb (IgG1) E/L selectin (Leukocytes)	Leuko adhesion	Isotype control mAb/Saline Intracoronary	Before reperfusion 0,2 mg/kg	Mean PP/area	Positive
(Shiraishi et al. 2002) Laboratory investigations	Myocardial Infarction LCA occlusion - 30 min I/24h R	Rats 24 (8/8/8)	mAb (IgG) Fas-L	Apoptosis	IgG control IV	Before occlusion 0,1 mg/kg	Histology After reperfusion	Positive

(Kohtani et al. 2002) Eur Surg Research	Myocardial Infarction LCA occlusion - 60 min I/24h R	Rats 60 (40/20)	mAb (IgG1k) Leukocytes	Immune cells	Control mAb IV	Before and after reperfusion 250 µg/kg	Histology After reperfusion	Positive
(Gao 2002) Cardiovascular research	Myocardial Infarction LCA occlusion - 30 min I/ 24h R	Rats 110 (sham 28; vehicle 29; drug SB 29; mAb 12; SB+mAb 12)	mAb (R15.7) CD18 (Leukocytes)	Leuko adhesion	Placebo (vehicle) or sham or SB drug IV	Before oclusion 1 mg/kg (mAb)	Histology After reperfusion	Positive (R15.7)
(Gustafsson et al. 2002) Circulation	Ex vivo - Langendorff 30 min I/ 2h R	Rats NR	FP (TAT-ARC and TAT-beta-gal) Cells	Apoptosis	Krebs solution alone Langendorff	Before ischemia 20 nmol/L	Histology, CK After reperfusion	Positive
(Kataoka et al. 2003) Biochemical and biophysical res com	Myocardial Infarction LCA occlusion - 60 min I/2h R	Rats 21 (7/7/7)	mAb LOX-1 Lectin-like oxidized low-density lipoprotein (LDL) receptor-1 (LOX-1)	Endothelium	Normal IgG or Placebo (saline) NR	Before and after occlusion 5 mg/kg	Histology After reperfusion	Positive
(Belosjorow et al. 2003) American journal of physiology	Myocardial Infarction Coronary occlusion - 30 min I/3h R	Rabbits 31 (12/7/6/6)	mAb (IgG) TNFα	Cytokines	No treatment or ischemic preconditionning or IgG control IV	Before occlusion NR	Histology After reperfusion	Positive
(Chong et al. 2003) The Annals of thoracic surgery	Myocardial Infarction LMCA occlusion - 45 min I/2h R	Rabbits 16 (11/5)	mAb Tissue Factor (coagulation)	Coagulation	Placebo (saline) IV	Before or after ischemia 2 mg/kg	Histology After reperfusion	Positive
(Yu et al. 2005) Journal of cardiovascular pharmacology	Myocardial Infarction LAD occlusion - 2h or 24h I/4h R	Dogs Multiple groups	FP (Entanercept) TNFα	Cytokines	Placebo (saline) IV	Before occlusion 2mg/kg	Histology, Echocardiography, Ventricular arrhytmias After reperfusion	Positive
(Fukushima et al. 2006) Circulation	Myocardial Infarction LCA occlusion - 30 min I/NR R	Rats NR	mAb P-selectin (Leukocytes) and ICAM-1	Leuko adhesion	Control mAb Intracoronary	Before reperfusion 150 µg/kg (P-selectin), 200 µg/kg (ICAM1)	Histology, Echocardiography, Ejection fraction After reperfusion	Positive
(Gu et al. 2006) Journal of cardiovascular pharmacology	Myocardial Infarction LAD occlusion - 90 min I/60 min or 3h R	Dogs 31(NR)	FP (Entanercept) TNFα	Cytokines	Placebo (saline) IV	Before occlusion 0,5 mg/kg	Histology After reperfusion	Positive

(Verma et al. 2006) Journal of drug targeting	Ex vivo - Langendorff	Rats NR	FP (ATP-liposome-mAb) Myosin ATP-loaded liposomes (ATP-L) was further improved by attachment of cardiac myosin-specific monoclonal 2G4 antibody onto the surface of ATP-L	Myosin	ATP-liposome without mAb Ex vivo	Prior to the onset of ischemia 9 +/-1 mmol/g wet weight of the heart	LV pressure and myocardium protection	Positive
(Simeoni et al. 2007) Eur Jour of cardio-thorac surgery	Homograft heart transplantation	Rats Multiple groups	FP (Il-1R2-Ig) IL-1R2	Cytokines	Virus dilution buffer/ AdNull Intracoronary	Before HT 10^10 PFU	Graft survival	Positive
(Ferraresso et al. 2008) Transplant	Homograft heart transplantation	Rats 15 (5/5/5)	scFv-IgG1 minibody (MB-12/22) C5a	Complement	Placebo (saline) IV	Pre-reperfusion 1 mg	Histology, CPK, TNF, Necrosis	Positive
(Oozawa et al. 2008) Circulation journal	Myocardial Infarction LCA occlusion - 30 min I/ 1h R	Rats 31 (18/13)	mAb (IgG2a) HMGB1 = high mobility group box1	Cell homeostasis	IgG control IV	Before reperfusion NR	Histology, Troponin T After reperfusion	Negative
(Toufektsian et al. 2008) Cardiovascular drugs and therapy	Myocardial Infarction LCA occlusion - 60 min I/NR R	Rats 36 (10/10/8/8)	FP (sTNFR-Fc) TNFα	Cytokines	(MI+saline) or sham or (sham+mAb) IV	Before reperfusion 10 µg/kg	Histology, Echocardiography, Ejection fraction After reperfusion	Positive
(Venkatachalam et al. 2009) The Journal of biological chemistry	Myocardial Infarction LAD occlusion - 30 min I/2h R	Mice 12 (4/4/4)	mAb IL-18	Cytokines	Ischemia alone or sham IV	Before occlusion 0,5 mg/kg	Histology After reperfusion	Positive
(Souktani et al. 2009) Journal of mol and cell cardiology	Myocardial Infarction Coronary occlusion 30 min I/24h R	Mice NR	FP (PTD-BIR3/RING) XIAP (apoptosis)	Apoptosis	Placebo (PBS) IV	Before or after reperfusion 0,8 µg/g	Histology After reperfusion	Positive
(Zhang et al. 2009) Molecules and Cells	Myocardial Infarction LADA occlusion - 60 min I/ 2h R	Rats 60	FP (PEP-1-SOD1) Oxidative stress	Oxidative stress	SOD-1 IV	Before occlusion 100µg, 300µg, 500 µg	Histology, CK, LV function	Positive
(Ishii et al. 2010) Amer Jour of Transplant	Homograft heart transplantation	Mice NR	mAb TNFα	Cytokines	IgG control NR	At reperfusion NR	Graft survival	Positive

(Atkinson et al. 2010) Journ of Immnulogy	Homograft heart transplantation	Mice NR	FP (CR2-Crry; Cr2-fH) Complement	Complement	Placebo (PBS vehicle control) NR	NR group 2: 0,25 mg CR2-Crry ; group 3: 0,4mg CR2-fH	Troponin I cardiac serum level	Positive
(Busche et Stahl 2010) GMS	Myocardial Infarction LAD occlusion - 30 min I/4h R	Mice NR	mAb C5a	Complement	Placebo (vehicle) or C3aRA NR	Before reperfusion 50 mg/kg	Histology, Troponin I, Echocardiography, Ejection fraction After reperfusion (4h)	Positive
(Arslan et al. 2010) Circulation	Myocardial Infarction LAD occlusion - 30 min I/NR R	Mice NR	mAb (IgG) TLR2	TLR2	Placebo (saline) or IgG control IV	Before reperfusion NR	Histology, Echocardiography, Ejection fraction, MRI After reperfusion	Positive
(Haas et al. 2010) Cardiovascular research	Myocardial Infarction LAD occlusion - 60 min I/24h R	Mice NR	mAb (IgG1) Self-antigen N2 (non-muscle myosin heavy chain II)	Myosin	Placebo (saline) IV	Prior I/R NR	Troponin I After reperfusion	Positive
(Won et al. 2010) Journal of controlled release	Myocardial Infarction LADCA occlusion - 60 min I/NR R	Rats NR	FP (TAT-Hsp27) HSP27	Apoptosis	NR Intracardiac	NR	Histology, Ejection fraction After reperfusion	Positive
(Matsubara et al. 2011) The Journal of surgical research	Myocardial Infarction LACA occlusion - 30 min I/3h R	Rabbits 43 (20/19/4)	FP (GLP1-Tf) GLP1	Incretins	Sham saline or post-occlusion transferrin group NR	Pre-occlusion et post-reperfusion 10 mg/kg	Histology, Echocardiography, Ejection fraction After reperfusion	Positive
(G.-Q. Huang et al. 2011) Journal of translational medicine	Myocardial Infarction LAD occlusion - 60 min I/2h R	Rats 100 (5 groups of 20)	FP (PEP-1-SOD1 and PEP-1-CAT) Oxidative stress	Oxidative stress	No treatment or PEP-SOD1 or PEP-1-CAT Peritoneum	Before ischemia 2 mg/kg	Histology, Troponin TnT, CKMB After reperfusion	Positive
(Perry et al. 2011) PloSone	Ex vivo - Langendorff 30 min I/ 2h R	Rats NR	FP (TAT-Ndi1) Mitochondrial respiratory chain (complex I)	Mitochondria	Placebo (vehicle) Ex vivo	Before ischemia or at the onset of reperfusion 500 nM	Histology, CK After reperfusion	Positive
(Montecucco et al. 2012) EHJ	Myocardial Infarction LACA occlusion - 30 min I/24h R	Mice NR	mAb (IgG2a) CCL5 (Chemokine)	Chemokines	IgG control IV	After ischemia 0,1 or 1 mg/mouse	Histology, Troponin I, MRI, VA, Heart failure, Ejection fraction After reperfusion	Positive
(Arslan et al. 2012) Circulation	Myocardial Infarction LCCA occlusion - 75 min I/24h R	Pigs 38 (NR)	mAb (IgG4) TLR2	TLR2	Placebo (saline) IV	Before reperfusion 12,5 mg/kg or 6,25 mg/kg or 1,56 mg/kg	Histology, Troponin I, Echocardiography, After reperfusion	Positive

(Schönberger et al. 2012) Amer Jour of Physio	Myocardial Infarction LAD occlusion - 30 min I/ 24h R	Mice 10 (5/5)	FP (GPVI-Fc) Platelets	Coagulation	IgG1-Fc IV	Before reperfusion 10 µg/g	Histology, Echocardiography After reperfusion	Positive
(Liao et al. 2012) JACC	Myocardial Infarction LADCA occlusion - 30 min I/ various time of R	Mice 80	mAb (IgG1) IL-17a	Cytokines	Isotype control mAb or recombinant IL17 or vehicle IV	Before reperfusion 100 µg	Histology, Troponin T After reperfusion	Positive
(Saito et al. 2012) Amer journ of physiology	Myocardial Infarction LADCA occlusion - 1h I/24h R	Mice NR	FP (sTNFR:Fc) TNFα	Cytokines	Placebo (vehicle) Peritoneum	Before ischemia 10 mg/kg	Histology, Echocardiography (LV function) After reperfusion	Positive
(Shen, Li, et Yang 2013) Transplant proceedings	Homograft heart transplantation	Rats NR	mAb NKG2D	Immune cells	Placebo (saline) IV	Before reperfusion 10 mg/kg	Tn T, MPO, INF, ICAM	Positive
(K. S. Lim et al. 2013) Journal of controlled release	Myocardial Infarction LADCA occlusion - 60 min I/NR R	Rats NR	FP (TAT-MT) MT Metallothionein	Oxidative stress	Multiple groups IV	During occlusion 175 µg	Histology, LV pressure After reperfusion	Positive
(Yeh et al. 2013) JTH	Myocardial Infarction LCA occlusion - 45 min I/4h R	Rats 40 (20/10/10)	FP (ANV-6L15) PLP of apoptotics cells	Coagulation	Placebo (vehicle) or hirudin IV	Before or after ligation 2,5-250 µg/kg	Histology, Troponin After reperfusion	Positive
(He et al. 2013) Journal of cardiovascular pharmacology	Myocardial Infarction LADCA occlusion - 30 min I/2h R	Rats 48 (12 sham, 18 I/R+saline, 18 I/R+PF)	FP (PEP-1-HO-1) Heme oxydase	Oxidative stress	Placebo (saline) IV	Before occlusion 0,5 mg	Histology After reperfusion	Positive
(Bao et al. 2013) Cardiovascular diabetology	Myocardial Infarction 30 min I/24h R	Rats 70 (NR)	FP (GAlbudAb) GLP1	Incretins	Placebo (vehicle) or exendin4 SC	Before ischemia 0,6 or 2 or 6 mg/kg	Histology After reperfusion (24h)	Positive
(Liu et al. 2013) Free radical research	In vitro 12h I/2h R	Cardiomyocytes	FP (pET-PTD-Cu/Zn SOD) Oxidative stress	Oxidative stress	SOD or Cu/Zn Sod Cells	After hypoxia - reoxygenation 10 µmol/L	Cell death	Positive
(Syrjälä et al. 2014) Amer Jour of Transplant	Homograft heart transplantation	Rats NR	mAb Angiotensin 2	Endothelium	IgG control Peritoneum	Before HT (and 1 group after HT) 1 mg/kg	Graft survival	Positive

(Al-Amran et al. 2014) Pharmacology	Myocardial Infarction LADCA occlusion - 30 min I/ 3d R	Mice 16 (8/8)	mAb MCP-1 (= monocytes chemoattractant protein =CCL2)	Chemokines	No treatment Peritoneum	Before ligation 500 µg	Histology, Echocardiography After reperfusion	Positive
(Mentzer et al. 2014) Journal of Cardiovascular Pharmacology and Therapeutics	Myocardial Infarction LCA occlusion - 45 min I/2h R	Rats 15 (8/7)	FP (Tat-Ndi1) Mitochondrial respiratory chain (complex I)	Mitochondria	Placebo protein Peritoneum	Before occlusion 2 mg/kg	Histology	Positive
(S. Lim et al. 2014) Molecular therapy	Myocardial Infarction LCA occlusion - 60 min I/ NR R	Rats 18 (6/6/6)	FP (Hph1-PLCδ1) PLC	Cell homeostasis	Control FP or Saline IV	At the time of reperfusion 750 ng/kg	Histology After reperfusion	Positive
(Zhu et al. 2014) PloSone	In vitro 90 min I/3h R	Cardiomyocytes	FP (TAT-p110 p85 or TAT PTEN p85) Akt	Cell homeostasis	Buffer control NR	/ 300 nM	Cell death	Positive: TAT PTEN p85 Negative: TAT-p110 p85
(Atkinson et al. 2015) Circulation	Homograft heart transplantation	Rats NR	mAb or FP (B4scFv or C2 mAb or B4scFv-Crry) Self-reactive IgM	Complement	Placebo (vehicle) NR	After reperfusion 0,1 mg (mAb)/ 0,2 mg (FP)	IgM deposition	Positive
(Cheng et al. 2015) Sacandinavian journal of immunology	Homograft heart transplantation	Mice NR	mAb Lipocalin 2 (Leukocytes)	Leuko adhesion	IgG control/ Recombinant Lcn2 IV	Before HT 75 µg	Troponin T, macrophages	Positive
(Pavlov et al. 2015) The American journal of pathology	Myocardial Infarction LADCA occlusion - 45 min I/5min, 1h or 2h R	Mice 24 (17/7)	mAb (3F8) MBL-2 (complement) mannose binding lectin 2	Lectin	Placebo (PBS) IV	Before ischemia, at time of reperfusion, after reperfusion 100 µg	Histology, Echocardiography (ejection fraction) After reperfusion	Positive
(Pei et al. 2015) Free Radical Biology and Medicine	Myocardial Infarction LCA occlusion - 30 min I/3h or 24h R	Mice NR	FP (Entanercept) TNFα	Cytokines	Placebo (vehicle) or control FP or sham Peritoneum	After occlusion 2mg/kg	Histology, Echocardiography, Ejection fraction After reperfusion	Positive
(Yang et al. 2015) Basic research in cardiology	Ex vivo - Langendorff LADCA occlusion - 30 min I/2h R	Rats Multiple groups	FP (EndoIII) Endonuclease III	Cell homeostasis	Placebo (vehicle) or EndIII mutant IV	Before reperfusion 8 mg/kg	Histology After reperfusion	Positive

(Ke et al. 2015) Experimental and therapeutic medicine	Ex vivo - Langendorff 30 min I/ 1h R	Rats 60 (10/group, 6 groups)	FP (PEP-1-SOD1) Oxidative stress	Oxidative stress	Sham or control ischemia or SOD1 IV	Before I/R 25, 50, 100 µmol/L	Histology, CKMB After reperfusion (1h)	Positive
(Qin et al. 2016) Amer Jour of Transplant	Homograft heart transplantation	Mice NR	mAb C5a	Complement	Control isotype mAb SC	Before HT 0,8 mg	T cells infiltration and rejection	Positive
(Hartman et al. 2016) PloS one	Myocardial Infarction LCA occlusion - 45 min I/NR R	Mice 2x11 = I/R ; 2x7 = sham	mAb IL-6R	Cytokines	IgG control or sham IV (bolus), peritoneum (continuous)	Before the end of ischemic time + weekly during 4 weeks Starting dose: 2 mg/mouse (before the end of I) Continuous dose: 0,5 mg/mouse (weekly)	Histology, Ejection fraction,MRI After reperfusion	Negative on cardiac remodeling
(Yi et al. 2016) Experimental and therapeutic medicine	Myocardial Infarction LADCA occlusion - 30 min I/4h R	Rats 48 (multiple groups)	mAb IL-17A	Cytokines	No treatment IV	Before occlusion 200 µg	Histology, CK Afte reperfusion	Positive
(Pachel et al. 2016) Arteriosclerosis, thrombosis, and vascular biology	Myocardial Infarction LCA occlusion – 30 min I/ 24h R	Mice NR	mAb GPVI (Platelets)	Coagulation	GPIba, GPIIbIIIa, CLEC-2 (Platelets) Retro-orbitaly (GPIba, GPIIbIIIa), Peritoneum (GPVI, CLEC-2)	Before I/R (GPVI, CLEC-2) or After reperfusion (GPIba, GPIIbIIIa) 200 µg (GPVI)	Histology, MRI After reperfusion	Positive for GPVI mab Negative for the other mAbs
(Yakovlev et al. 2016) Thrombosis and haemostasis	Myocardial Infarction LCA occlusion - 30 min I/2h R	Mice NR	mAb (IgG1k) VLDL receptor	Metabolism	Control IgG1 IV	Before and after reperfusion 100 µg	Histology After reperfusion	Positive
(Toldo et al. 2013) Journal of cardiovascular pharmacology	Myocardial Infarction LACA occlusion - 30 min I/NR R	Mice 5-8 mice per group; 4 groups	FP (rhAAT-Fc Alpha 1 anti-trypsin	Cell homeostasis	Human plasma Ig or placebo (NaCl 0,9%) Peritoneum	Upon reperfusion 2 mg/kg (rhAAT-Fc)	Histology, Echocardiography (LV function) After reperfusion	Positive
(Solhjou et al. 2017) Amer Jour of Transplant	Homograft heart transplantation	Mice NR	Nanoparticles of mAb IL-6	Cytokines	Peritoneum	Days 0 and 3 then every days until 13 days post-transplantation 100 µg	Graft survival	Positive

(Ziegler, Wang, et al. 2017) Theranostics	Myocardial Infarction LCA occlusion - 60 min I/NR R	Mice NR	mAb (Tand-scFvSca-1+GPIIb/IIIa) Platelets	Coagulation	Tand-scFvSca-1+Mutant NR	After reperfusion NR	Histology, Echocardiography After reperfusion	Positive
(Nakahara et al. 2017) Journal of Nuclear Medicine	Myocardial Infarction LCA occlusion - 40 min I/3h R	Rabbits 24 (12/6/6)	FP (Fv-HSP72) HSP72	Apoptosis	Fv or HSP72 or Placebo (phosphate buffer) IV	Before occlusion + 1 actif group after occlusion NR	Histology, Troponin I, Echocardiography, Ejection fraction After reperfusion	Positive
(DuSablon et al. 2017) PloSone	Myocardial Infarction Coronary occlusion – 30 min I/24h R	Mice 88 (NR)	FP (EphrinA1-Fc) EphrinA1	Cell homeostasis	IgG-Fc Intramyocardial	After occlusion 6 µg	Histology, Echocardiography, Ejection fraction After reperfusion	Positive
(Clark et al. 2018) Open heart	Myocardial Infarction LAD occlusion - 30 min I/2h R	Mice 41 (NR)	mAb (IgG2a) MASP-2	Lectin	Match control mAb or Placebo (saline) Peritoneum	12-18h prior to experimental infarction 1 mg/kg	Histology, Ejection fraction After reperfusion	Positive
(Ziegler, Hohmann, et al. 2017) EHJ	Myocardial Infarction LCA occlusion - NR/NR	Mice NR	FP (Targ-CD39) CD39	Platelets	Non-TargCD19 or Placebo (PBS control) NR	NR NR	Histology, Troponin, Echocardiography, Ejection fraction After reperfusion (1,2,3,4 weeks)	Positive
(Iida et al. 2019) Amer Jour of transplantation	Homograft heart transplantation	Mice NR	mAb (IgG2b) VLA-1 (memory T-cells)	Immune cells	IgG control Peritoneum	200 µg	Graft survival	Positive
(Vainio et al. 2019) JACC	Myocardial Infarction LADCA occlusion - 30 min I/NR R	Mice NR	mAb CTGF	Endothelium	IgG control Peritoneum	24h and 1h before ischemia or only at reperfusion 10 mg/kg	Histology, Echocardiography, Ejection fraction After reperfusion	Negative
(Fan et al. 2019) Circulation	Myocardial Infarction LADCA occlusion – 45 min I/12h to 7d R	Mice 4 groups	mAb Dectin-1	Immune cells	Placebo (PBS) or isotype mAb IV	Before ischemia 100 µg	Histology, Echocardiography (LV function) After reperfusion	Positive
(Li et al. 2019) Ciruclation	Myocardial Infarction 30 min I/ 1d or 28d R	Mice NR	FP (S100a9) Inflammation mitochondria	Cell homeostasis	Control antibody NR	Before and after I/R 100 µg	Histology, Echocardiography (LV function), MRI After reperfusion	Positive
(Ciocci Pardo et al. 2019) Biochemical pharmacology	Ex vivo - Langendorff 30 min I/ 60 min R	Rats 33	mAb (a-L3) Sodium-Bicarbonate cotransporter	Cell homeostasis	Non immune serum Ex vivo	During reperfusion NR	Histology, LV function After reperfusion	Positive

(Pluijmert et al. 2020) JACC	Myocardial Infarction LADCA occlusion - 45 min I/ permanent R	Mice NR	mAb (IgG1) Phosphorylcholine on apoptotics cells	Apoptosis	Placebo (NaCl 0,9%) Peritoneum	NR 10 mg/kg, every third days	Histology, Ejection fraction, MRI 2 days and 3 weeks after reperfusion	Positive at 3 weeks No difference at 2 days
(Kim et al. 2020) Molecular pharmaceutics	Myocardial Infarction LCA occlusion - 60 min I/NR R	Rats NR	FP (αAT1-ZZ-TAT-Hsp27) AT1	Apoptosis	ZZ-TAT-Hsp27 or αHER2-ZZ-TAT-Hsp27 IV	4h post-reperfusion 0,16 mg/kg	Histology After reperfusion	Positive
(Wang et al. 2020) Science Translational Medicine	Myocardial Infarction LAD occlusion (differents models)	Rats, Pigs, Monkeys	mAb (sDR5-Fc) TRAIL (death checkpoint protein)	Apoptosis	Placebo (PBS), IgG, Entanercept IV	After occlusion 15 mg/kg	CK, Troponin I, Echocardiography	Positive
(Zheng et al. 2021) The Jour of heart and lung transplantation	Homograft heart transplantation	Mice NR	FP (C2scFV) C2-CR1	Complement	Placebo (PBS) IV	Following reperfusion	Histology, Troponin I, CK After reperfusion	Positive
(Kanzawa et al. 2022) Transplant international	Homograft heart transplantation	Mice 16 (8/8)	Anti-FKN mAb FKN-CX3CR1 axis	Chemokines	IgG control NR	NR 500 µg, days 1,3,7,10,14	Graft survival	Positive
(G. Huang et al. 2022) Microvascular research	Myocardial Infarction LAD occlusion - 30 min I/2h, 4h, 6h, 8h, 1d, 2d R	Rats 720 (9 groups of 80 rats)	mAb (Evolocumab) PCSK9	Metabolism	Placebo (water) SC	Before the surgery (1 week and half an hour) 10 mg/kg	Histology, Troponin T, CKMB, Echocardiography After reperfusion	Positive

CK: Creatine Kinase; Comp*: Comparators; CPK: Creatine Phosphokinase; HT: Heart Transplantation; I/R: Ischemia-Reperfusion; IV: Intravenous; LACA: Left Anterior Coronary Artery; LAD: Left Anterior Descending; LADCA: Left Anterior Descending Coronary Artery; LCA: Left Coronary Artery; LCCA: Left Circumflex Coronary Artery; LMCA: Left Main Coronary Artery; LV: Left Ventricular; MPO: Meyloperoxidase; MRI: Magnetic Resonance Imaging; NOS: Nitricoxide species; NR: Not Reported; TNF: Tumor Necrosis Factor

Supplementary Table 3 – Targets' comparison between clinical and experimental studies

Target	Domain	Model	Animal studies	Positive effect on animal	Human studies after animal studies	Positive effect on human	Human studies before animal studies
AT1	Apoptosis	MI/EV	Yes	Yes	No	No	No
Fas-L	Apoptosis	MI/EV	Yes	Yes	No	No	No
HSP27	Apoptosis	MI/EV	Yes	Yes	No	No	No
Phosporylcholine	Apoptosis	MI/EV	Yes	Yes	No	No	No
TRAIL	Apoptosis	MI/EV	Yes	Yes	No	No	No
XIAP	Apoptosis	MI/EV	Yes	Yes	No	No	No
Alpha1AT	Cell homeostasis	MI/EV/IV	Yes	Yes	No	No	No
Endonuclease	Cell homeostasis	MI/EV/IV	Yes	Yes	No	No	No
Ephrin A1	Cell homeostasis	MI/EV/IV	Yes	Yes	No	No	No
HMGB1	Cell homeostasis	MI/EV/IV	Yes	No	No	No	No
PI3K-AKT	Cell homeostasis	MI/EV/IV	Yes	Yes	No	No	No
PLC	Cell homeostasis	MI/EV/IV	Yes	Yes	No	No	No
S100a8/a9	Cell homeostasis	MI/EV/IV	Yes	Yes	No	No	No
Sodium-Bicarbonate cotransporter	Cell homeostasis	MI/EV/IV	Yes	Yes	No	No	No
CCL2	Chemokines	HT/MI	Yes	Yes	No	No	No
CCL5	Chemokines	HT/MI	Yes	Yes	No	No	No
CXCL10	Chemokines	HT/MI	Yes	Yes	No	No	No
CX3CR1	Chemokines	HT/MI	Yes	Yes	No	No	No
Annexin V-Kunitz inhibitor	Coagulation	MI	Yes	Yes	No	No	No
CD39 platelets	Coagulation	MI	Yes	Yes	No	No	No
GP-VI platelets	Coagulation	MI	Yes	Yes	No	No	No
GP-platelets	Coagulation	MI	Yes	Yes	Yes (GPIIbIIIa - abciximab)	Yes	No
Tissue factor	Coagulation	MI	Yes	Yes	No	No	No
C5a	Complement	CPB/HT/MI	Yes	Mixed	Yes (pexelizumab)	No	No
CR2	Complement	CPB/HT/MI	Yes	Yes	No	No	No
C2-CR1	Complement	CPB/HT/MI	Yes	Yes	No	No	No
IL1R	Cytokines	HT/MI/EV	Yes	Yes	No	No	No
IL6	Cytokines	HT/MI/EV	Yes	Yes	No	No	No
IL-6R	Cytokines	HT/MI/EV	Yes	No	Yes (IL6R - tocilizumab)	Yes	No
IL8	Cytokines	HT/MI/EV	Yes	Yes	No	No	No
IL17a	Cytokines	HT/MI/EV	Yes	Yes	No	No	No
IL18	Cytokines	HT/MI/EV	Yes	Yes	No	No	No
TNF	Cytokines	HT/MI/EV	Yes	Yes	No	No	No
AGT2	Endothelium	HT/MI	Yes	Yes	No	No	No
CTGF	Endothelium	HT/MI	Yes	No	No	No	No
ET1	Endothelium	HT/MI	Yes	Yes	No	No	No
LOX1	Endothelium	HT/MI	Yes	Yes	No	No	No
Neutrophils/Macrophages	Immune cells	HT/MI	Yes	Yes	Yes	No	No
Dectin1	Immune cells	HT/MI	Yes	Yes	No	No	No
NKG2D	Immune cells	HT/MI	Yes	Yes	No	No	No
VLA1	Immune cells	HT/MI	Yes	Yes	No	No	No
GLP1	Incretins	MI	Yes	Yes	No	No	No
MBL	Lectins	MI	Yes	Yes	No	No	No
MASP2	Lectins	MI	Yes	Yes	No	No	No
CD11	Leuko adhesion	CPB/HT/MI/EV	Yes	Yes	No	No	No
CD18	Leuko adhesion	CPB/HT/MI/EV	Yes	Yes	Yes (rhuMAb)	No	No
CD11/CD18	Leuko adhesion	CPB/HT/MI/EV	Yes	Mixed	Yes (Leukarrest)	No	No
E-selectin	Leuko adhesion	CPB/HT/MI/EV	Yes	Yes	No	No	No
ICAM-1	Leuko adhesion	CPB/HT/MI/EV	Yes	Yes	No	No	No
Lipocaline 2	Leuko adhesion	CPB/HT/MI/EV	Yes	Yes	No	No	No
L-selectin	Leuko adhesion	CPB/HT/MI/EV	Yes	Yes	No	No	No
P-selectin	Leuko adhesion	CPB/HT/MI/EV	Yes	Yes	Yes (inclacumab)	No	No
Sialyl Lewis	Leuko adhesion	CPB/HT/MI/EV	Yes	Yes	No	No	No
PCSK9	Metabolism	MI	Yes	Yes	Y (evolocumab - study protocol)	/	No
VLDL	Metabolism	MI	Yes	Yes	No	No	No
Mitochondria respiratory chain	Mitochondria	MI/EV	Yes	Yes	No	No	No
Myosin	Myosin	MI/EV/IV	Yes	Yes	No	No	No
HO-1	Oxidative stress	MI/EV/IV	Yes	Yes	No	No	No
Metallothionein	Oxidative stress	MI/EV/IV	Yes	Yes	No	No	No
SOD	Oxidative stress	MI/EV/IV	Yes	Yes	No	No	No
SOD1	Oxidative stress	MI/EV/IV	Yes	Yes	No	No	No
TLR2	TLR2	MI	Yes	Yes	No	No	No

AGT2: Angiotensin 2; Alpha1AT: Alpha1 antitrypsin; AT1: Angiotensin 1; CCL2: Chemokine C ligand 2; CCL5: Chemokine C ligand 5; CD: Cluster of Differenciation; CPB: Cardiopulmonary Bypass; CR2: Complement Receptor 2; CTGF: Connective Tissue Growth Factor; CXCL10: CX Chemokine Ligand 10; CX3CR1: CX motif chemokine receptor 1; C2-CR1: C2- complement receptor 1; ET1: Endothelin 1; EV: Ex vivo; Fas-L: Fas ligand; GLP1: Glucagon-like peptide 1; HMGB1: High Mobility Group Box 1; HO-1: Heme-oxydase 1; HSP27: Heat Shock Protein 27; HT: Heart Transplantation; ICAM 1: Intercellular Adhesion Molecule 1; IL1R: IL1 receptor; IL6R: IL6 receptor; IV: In vitro; LOX1: Lectin Like Oxidized Low-density Lipoprotein receptor-1; MASP2: Mannose Binding Lectin -associated serine protease 2; MBL: Mannose Binding Lectin; MI: Myocardial Infarction; NKG2D: Natural Killer Cells Receptor; PCSK9: Proprotein Convertase Subtilisin/Kexine Type 9; PI3K-AKT: Phosphoinositide-3-kinase-Akt; PLC: Phospholipase C; SOD: Superoxide Dismutase; TLR2: Toll Like Receptor 2; TNF: Tumor Necrosis Factor; VLDL: Very Low Density Lipoprotein; VLA1: Very Late Antigen 1; TRAIL: TNF-related apopstosi-inducing ligand; XIAP: X-linked Inhibitor of Apoptosis Protein

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TITRE DE LA THESE

ANTICORPS MONOCLONAUX ET PROTEINES DE FUSION DANS LA PREVENTION DES LESIONS D'ISCHEMIE-REPERFUSION MYOCARDIQUES : DONNEES PRECLINIQUES ET CLINIQUES

REVUE SYSTEMATIQUE

RESUME DE LA THESE

Les lésions d'ischémie-reperfusion sont une cause majeure de morbi-mortalité dans des situations d'ischémie cardiaque comme l'infarctus du myocarde, le pontage aorto-coronarien ou la transplantation cardiaque. De nombreuses stratégies thérapeutiques ont été testées afin de prévenir ces lésions. L'objectif était de réaliser une revue systématique de la littérature portant sur l'intérêt des anticorps monoclonaux et protéines de fusion dans la prévention des lésions d'ischémie-reperfusion myocardiques. Cette revue a recensé les études cliniques (réalisées chez l'Homme) et précliniques expérimentales (modèles animaux in vivo, modèles animaux ex vivo, ou in vitro). La méthode a été celle d'une revue systématique portant sur tous les articles originaux ayant évalué (critères PICO) : un anticorps thérapeutique ou une protéine de fusion comparativement à un placebo ou absence de traitement dans les trois situations d'ischémie-reperfusion myocardique sus-citées. Les articles d'intérêt ont été récupérés sur Medline, Embase et Cochrane. Les articles ont été inclus ou non sur le titre et le résumé puis sur le texte entier. Cette classification a été réalisée par deux personnes. Les critères de jugement étaient les suivants : taille de l'infarctus mesurée par l'imagerie ou la libération de biomarqueurs ainsi que les évènements cliniques en lien avec les lésions d'ischémie-reperfusion (arythmies, insuffisance cardiaque, perte de greffon, mortalité). Les données recueillies étaient : la pathologie et/ou le modèle préclinique, les caractéristiques des patients et/ou des animaux inclus, le type de médicament, sa posologie et sa cible, le design et la qualité méthodologique de l'étude. Les résultats descriptifs ont été résumés dans des tableaux et des graphiques. Une méta-analyse sur les données cliniques a été réalisée en prenant comme indice d'efficacité la différence moyenne standardisée ou le risque relatif, et un modèle à effet fixe ou, en cas d'hétérogénéité, aléatoire. Les résultats ont montré que toutes les cibles des études humaines ont été testées préalablement dans les études animales. Les principales cibles étaient l'adhésion leucocytaire, l'homéostasie cellulaire, les cytokines et les voies d'apoptose. Cette revue systématique et méta-analyse a suggéré que seule l'inhibition de l'IL-6R par le tocilizumab semble offrir une cardio protection.

MOTS-CLÉS SIGNIFICATIFS DE SON CONTENU, ATTIBUÉS PAR LE CANDIDAT EN LIAISON AVEC LA BIBLIOTHÈQUE UNIVERSITAIRE ET LES MEMBRES DU JURY

Ischémie-reperfusion myocardique, anticorps monoclonaux, protéines de fusion, revue systématique

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