Do we really need aspirin loading for STEMI?

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Abstract:

Aspirin loading (chewable or intravenous) as soon as possible after presentation is a class I recommendation by current ST elevation myocardial infarction (STEMI) guidelines. Earlier achievement of therapeutic antiplatelet effects by aspirin loading has long been considered the standard of care. However, the effects of the loading dose of aspirin (alone or in addition to a chronic maintenance oral dose) has not been studied in the contemporary era. A large proportion of myocardial cell death occurs upon and after reperfusion (so called, reperfusion injury). Numerous agents and interventions have been shown to limit infarct size in animal models when administered before or immediately after reperfusion. However, these interventions have predominantly failed to show significant protection in clinical studies. In the current review, we raise the hypothesis that aspirin loading may be the culprit. Data obtained from animal models consistently show that statins, ticagrelor, opiates and ischemic postconditioning limit myocardial infarct size. In most of these studies aspirin was not administered. However, when aspirin was administered before reperfusion (as is the case in the majority of studies enrolling STEMI), the protective effects of statins, ticagrelor, morphine and ischemic postconditioning were attenuated, which can be plausibly attributable to aspirin loading. We therefore suggest studying the effects of aspirin loading before reperfusion on the infarct size limiting effects of statins, ticagrelor, morphine and/ or postconditioning in large animal models using long reperfusion periods (at least 24h). If indeed aspirin attenuates the protective effects, clinical trials should be conducted comparing aspirin loading to alternative anti-platelet regimens without aspirin loading in patients with STEMI undergoing pPCI.

Keywords: animal models; aspirin; humans; infarct size; postconditioning; reperfusion injury; statins; STEMI.

Declarations:

Funding:

The study was funded by the John S. Dunn Chair in Cardiology Research and Education.

Conflicts of interest/Competing interests (include appropriate disclosures)

Regina Ye: None

Hani Jneid:

Mahbood Alam:

Barry F. Uretsky:

Dan Atar:

Masafumi Kitakaze:

Sean M Davidson: None

Derek Yellon:

Yochai Birnbaum: Research grant from AstraZeneca

Availability of data and material (data transparency)

Original research data will be available upon request

Code availability (software application or custom code)

Not applicable.

Authors' contributions (optional: please review the submission guidelines from the journal whether statements are mandatory)

The first draft of the manuscript was written by Yochai Birnbaum and Regina Ye and all authors read and edited the manuscript. All authors read and approved the final manuscript

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals

Not applicable for a review article

Ethics approval (include appropriate approvals or waivers)

Not applicable for a review article

Consent to participate (include appropriate statements)

Not applicable.

Consent for publication (include appropriate statements)

All authors read and approved the final manuscript, submitted for consideration of publication in Basic Research in Cardiology.

Over the years several therapies t thought to be essential for patients with acute myocardial infarction have been abandoned due to lack of evidence supporting their use. These include oxygen supplementation, prophylactic use of antiarrhythmic agents and routine intravenous (iv) administration of beta blockers [1, 2]. In the following review we suggest that the role of chewable or intravenous aspirin at presentation of patients with suspected ST-elevation myocardial infarction (STEMI) should also be revisited.

Rapid administration of chewable aspirin has been considered an integral part of the initial management of patients with acute coronary syndromes. The 2004 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines for the management of patients with STEMI gave a class I recommendation: "Aspirin should be chewed by patients who have not taken aspirin before presentation with STEMI. The initial dose should be: 162 mg (Level of Evidence: A) to 325 mg (Level of Evidence C). Although some of the trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated aspirin formulations" [3]. However, the aforementioned guideline acknowledges that: "Unlike fibrinolytic agents, there is little evidence for the time-dependent effect of aspirin on early mortality. However, data do support the contention that a chewable aspirin is absorbed more quickly than one swallowed in the early hours after infarction, particularly after opiate therapy." [3]. The 2012 European Society of Cardiology (ESC) STEMI guidelines recommended initial aspirin dose of 150-300 mg chewable or intravenously if oral intake is not possible: "Aspirin should preferably be given orally (preferably 150–300 mg) including chewing, to ensure complete inhibition of TXA2-dependent platelet aggregation, but may be given intravenously in patients who are unable to swallow…. The first dose of 150–300 mg should be chewed or given intravenously (though at a lower dose range) and a lower dose (75–100 mg) given orally daily thereafter" [4]. The 2013 ACC/AHA STEMI guidelines continued to recommend aspirin load (without mentioning chewable) [2]. The only time that chewable aspirin is mentioned is: "Emergency medical dispatchers are trained to instruct patients with possible STEMI symptoms to chew non-enteric-coated aspirin unless contraindicated, while personnel are en route" [2]. The 2017 ESC STEMI guidelines maintain the recommendation for chewable or intravenous aspirin for patients triaged for fibrinolytic therapy; on the other hand, oral or intravenous aspirin was recommended for patients referred for primary percutaneous coronary interventions (pPCI) [1]. The 2020 ESC guidelines for the management of acute coronary syndromes in patients without persistent ST elevation continue to recommend aspirin, yet "chewable" is no longer mentioned [5].

All the above-mentioned guidelines reference the Second International Study of Infarct Survival (ISIS-2) as primary evidence for their recommendation. ISIS-2 is the only large-scale randomized study that assessed the effect of aspirin in patients with acute coronary syndromes [6]. In this 2x2 factorial study, 17,187 patients within 24 hours of onset of symptoms compatible with acute myocardial infarction were randomized to intravenous streptokinase or placebo and to one month of enteric coated aspirin 162.5 mg or placebo, starting immediately with the first tablet crushed, sucked, or chewed, presumably to ensure a rapid antiplatelet effect [6]. The primary endpoint of vascular death in the first 35 days was significantly reduced with aspirin (23% odds reduction), an effect that was comparable to that of intravenous streptokinase (25% odds reduction). The effect of aspirin + streptokinase was additive (42% odds reduction compared to the patients who received double placebo) [6]. The study did not compare the effect of the first-dose chewable versus oral route of the first dose and did not separate the acute effect of the first dose from that of the maintenance dose for 30 days. Following the ISIS-2 trial, all subsequent studies on new anti-platelet

agents have added new agents or placebo on top of aspirin. Thus, although the beneficial effects on mortality over 30-35 days by oral aspirin were clearly shown in ISIS-2, the need for first-dose chewable aspirin and/or iv aspirin (not tested in ISIS-2) is less certain.

The accepted concept underlying chewable or intravenous aspirin is that rapid platelet aggregation inhibition will decrease thrombotic events in patients with acute coronary syndromes. That chewable aspirin can rapidly inhibit platelet function has been clearly shown. Indeed, chewing buffered 325 mg aspirin tablets resulted in a faster decrease in thromboxane B2 levels and a higher plasma levels of aspirin than orally administered aspirin [7]. However, there are differences between oral administration and intravenous or buccal administration that may be crucial [8]. Most of the aspirin given orally is deacetylated by the liver before reaching the systemic circulation. The anti-platelet effect is probably achieved by acetylation of the platelet cyclooxygenase during the transit of blood from the gut to the liver [8]. However, chewable or intravenous aspirin is (at least partially) absorbed systematically, and non-selective inhibition of the cyclooxygenase enzymes systemically is expected.

The Potential Deleterious Effect of Aspirin in Myocardial Infarction

There is the possibility that aspirin could, in fact, have deleterious effects in myocardial infarction. Multiple studies have described worsening necrosis after reperfusion, so-called “reperfusion injury”. After major achievements in shortening the time to reperfusion and establishing complete reperfusion by pPCI, efforts are being made to minimize “ischemia-reperfusion” and “reperfusion” injury, using interventions started before, during and immediately after reperfusion [9, 10]. Many agents and interventions have shown beneficial effects in decreasing reperfusion injury in animal models but have failed to show positive impact in patients with STEMI [11-13].

In addition to the many differences between the preclinical animal models and patients with STEMI, one important issue is that use of aspirin is usually not part of the preclinical models/ protocols, whereas aspirin loading is a standard of care in the clinical setting (see above). Data have shown that aspirin can block the infarct size-limiting effects of statins, ticagrelor, opiates and ischemic post-conditioning. We thus suggest the possibility that aspirin can potentially attenuate the protective pathways that limit reperfusion injury in patients.

Interaction of Aspirin with Cardioprotective Agents in Experimental Studies

Statins

Numerous studies have shown that statins, administered before ischemia or before reperfusion reduce myocardial infarct size in mice, rats, pigs and dogs (Table 1a). The protective effect involves adenosine receptor activation [14, 15] with downstream upregulation of cyclooxygenase-2 [16]. However, several clinical trials have failed to show a significant protective effect in patients with STEMI. Birnbaum et al showed that the infarct size limiting effect of atorvastatin (10 mg/kg/d for 3 days before 30 min coronary artery occlusion and 4h reperfusion) is attenuated by

intravenous aspirin given 3 min before reperfusion in a dose-dependent manner [17]. Interestingly, when intravenous aspirin was administered 15 min after reperfusion, the protective effect of atorvastatin was not attenuated. Of note, aspirin alone without atorvastatin had no significant effect on infarct size in this model [17]. Atorvastatin increased cyclooxygenase-2 activity and aspirin, dose-dependently, attenuated this increase [17]. [16]. These results raise the possibility of early cyclooxygenase inhibition with chewable or iv aspirin may, in fact, blocks potential protective interventions.

Ticagrelor

The $P2Y_{12}$ receptor inhibitor Ticagrelor administered either before ischemia or before reperfusion limits myocardial infarct size in rats, pigs, dogs and monkeys (Table 2a). The protective effect is blocked with adenosine receptor antagonists [18]. Clopidogrel or prasugrel do not have the same protective effects despite achieving similar degree of platelet inhibition, as these agents do not increase interstitial adenosine levels (Table 2a). Downstream of adenosine receptor activation, cyclooxygenase-2 is activated. Cyclooxygenase-2 inhibition, but not cyclooxygenase-1 inhibition, blocks the protective effects [18]. Aspirin before reperfusion attenuates the protective effect of ticagrelor in a dose-dependent manner [18].

Despite experimental data showing cardioprotective effect of ticagrelor, clinical data on the protective effects of ticagrelor loading upon presentation in patients with suspected STEMI is lacking. Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial randomized 1,862 patients presenting with STEMI to pre-hospital (in the ambulance) versus in-hospital (in the catheterization laboratory) ticagrelor loading [19]. The primary endpoints of $\geq$70% ST elevation resolution before pPCI and the proportion of patients without Thrombolysis in Myocardial Infarction flow grade 3 in the infarct-related artery during the first intracoronary injection were comparable between the groups. The hypothesis was that earlier administration of ticagrelor would allow effective blood levels of ticagrelor before and during the pPCI, resulting in more complete platelet inhibition and potentially myocardial protection. The rate of $\geq$70% ST segment elevation resolution after pPCI was comparable between the two groups. Similarly, the rate of major adverse cardiovascular events was comparable between the groups. The median time between the pre-hospital and in-hospital ticagrelor loading was only 31 minutes. This might be the explanation for the lack of effect of early administration. However, almost all patients received aspirin loading. An alternate explanation is that the myocardial protective effects of early ticagrelor loading were blocked by aspirin.

Ubaid et al studied whether cangrelor, an intravenous P2Y12 inhibitor that acts faster than oral P2Y12 inhibitors, would result in better platelet inhibition and impact myocardial infarct size and microvascular obstruction following pPCI as compared to ticagrelor [20] (Table 2b). In the patients randomized to cangrelor, ticagrelor loading was given 1.5 hours after initiating the cangrelor infusion, after the pPCI procedure was completed. Despite achieving better P2Y12 inhibition at coronary reperfusion, there were no differences in peak troponin levels or infarct size (assessed by cardiac MRI) between the groups [20]. Cangrelor does not increase myocardial adenosine levels and thus, should not have protective effects against ischemia-reperfusion injury. Thus, earlier ticagrelor loading could have been expected to result in smaller infarct size.

However, all patients received 300 mg aspirin loading at the time of first medical contact. This study raises the possibility that aspirin blocked the protective effects of ticagrelor.

Khan et al conducted a prospective open-label randomized study on the effects of clopidogrel versus ticagrelor or prasugrel loading before pPCI [21] (table 2b). All patients received 300 mg aspirin loading before pPCI. Infarct size was smaller and myocardial salvage was greater in the ticagrelor or prasugrel group compared to the clopidogrel group [21]. However, they did not report on prasugrel versus ticagrelor separately.

Sabbah et al conducted a retrospective analysis of the DANAMI-3 trial program to compare the effect of clopidogrel versus ticagrelor/ prasugrel loading before pPCI on infarct size, as assessed by cardiac MRI [22] (Table 2b). Data on aspirin loading was not provided. However, as patients were treated according to current guidelines one can assume that the majority of patients received aspirin loading. Infarct size was significantly smaller and myocardial salvage index was significantly greater in the ticagrelor/ prasugrel group compared to the clopidogrel group. However, they did not provide data comparing ticagrelor and prasugrel to see if there are additional myocardial protective effects of ticagrelor.

It should be emphasized that in the rat model, ticagrelor therapy started 24h after infarction [23], and even week after infarction [24], improved remodeling and was associated with increased markers of stem cell recruitment [24]. Thus, the Ubaid et al study [20] and the Sabbah et al study [22] that assessed infarct size by CMR 3 months after infarction cannot separate the effect of the loading dose of ticagrelor (associated with aspirin lading) and the potential chronic maintenance dose (associated with low oral dose of aspirin).

Opiates

Several pre-clinical studies have shown that opioid receptor activation protects the heart against ischemia-reperfusion and reperfusion injury (Table 3a). Jiang et al showed that cyclooxygenase-2 protein expression and myocardial levels of prostaglandin E_2 and 6-keto-$PGF_{1\alpha}$ increased 24h after morphine administration, but not 1h after administration [25]. However, with co-administration of aspirin with morphine 5 min before reperfusion, the infarct size-limiting effects of morphine were not observed [26]. This finding could not be attributed to cyclooxygenase inhibition, as ibuprofen, a nonselective cyclooxygenase inhibitor, augmented the infarct size-limiting effect of morphine [26]. The authors suggested that the protective effect is dependent on activation of 12-lipoxygenase as the protective effect of both morphine and ibuprofen was blocked with a 12-lipoxygenase inhibitor [26].

de Waha et al [27] reported that among 276 STEMI patients treated with pPCI, infarct size was bigger and myocardial salvage index was lower among those who received intravenous morphine [27](Table 3b). Of note, all patients received intravenous 500 mg aspirin prior to pPCI.

Eitel et al assessed 734 patients with STEMI who were treated with pPCI within 12 h of onset of symptoms [28] (Table 3b). All patients received intravenous 500 mg aspirin. Patients were retrospectively divided to a group that received intravenous morphine (n=454) and those who did not (n=280). CMR was done within one week after presentation. Infarct size, microvascular obstruction and myocardial salvage index (MSI) were comparable between the groups, suggesting that morphine had no protective effects in patients presenting with STEMI. It has been reported

that morphine delays gastric emptying and induces nausea and vomiting; thus, a delay in absorption of orally administered drugs including aspirin and P2Y12 inhibitors may have explained the lack of protective effect of morphine [29].

In order to clarify whether delay gastric emptying could explain the potentially harmful effects of morphine in STEMI patients, Stiermaier et al studied 138 patients with STEMI. All received 180 mg ticagrelor and intravenous 500 mg aspirin loading before pPCI [30](Table 3b). Patients were randomized to intravenous morphine 5 mg, intravenous morphine + metoclopramide 10 mg or intravenous placebo before pPCI. CMR was performed in 104 patients on day 1 to 4 after presentation. Morphine reduced infarct size and microvascular obstruction. Infarct size and microvascular obstruction was not reduced in the morphine + metoclopramide group [30]. In this study, in contrast to the previous two clinical studies, morphine was associated with smaller infarct. Interestingly, metoclopramide, a drug that enhances gastric motility, did not improve outcomes in patients receiving morphine and actually blocked the protective effect of morphine. One might speculate that morphine delayed the absorption of aspirin loading and therefore, prevented the attenuation of the morphine protective effects and metoclopramide by enhancing aspirin absorption enabled this inhibition. However, in this study aspirin was given intravenously rather than orally. Thus, this is probably not the explanation. Potential interaction(s) between morphine and metoclopramide cannot be ruled out. Although several animal studies have not reported attenuation of the effects of morphine by metoclopramide [30], one study suggested that metoclopramide opens ATP-sensitive potassium channels (KATP) [31]. Opening KATP channels should mediate cardiac protection, rather than enhancing reperfusion damage, unless again, there is an interaction with aspirin. For example, it has been reported that aspirin and metoclopramide have synergistic antithrombotic effects [32, 33]. Therefore, another theoretical possibility is that metoclopramide augmented the ability of aspirin to block the protective effect of morphine.

There is always a question whether the morphine dose used in the clinical setting was high enough to induce protection. The dose of morphine was not reported in the de Waha [27] and Eitel [28], studies that showed harm or no effect, respectively. In the prospective study of Stiermaier et al that showed favorable effects, the morphine dose was 5 mg [30].

Again, one can speculate that without the aspirin loading, the beneficial effect of morphine could have been greater in these three studies.

Ischemic Postconditioning

Ischemic postconditioning refers to repeat short episodes of ischemia/ reperfusion immediately after restoration of coronary perfusion. Since the original work by Zhao et at [34], several studies have shown that in animal models, ischemic postconditioning consistently limits myocardial infarct size [35, 36] (Table 4a).

However, most clinical studies, with the exception of several small studies, have failed to show that postconditioning protects the heart and reduces infarct size or improves clinical outcomes (Table 4b). Some have even shown potential harm.

All preclinical models except one [37] did not add aspirin to their treatment, whereas aspirin loading (chewable or intravenous) was routinely employed in the clinical studies according to the present guidelines (Table 4). Birnbaum et al has recently show that aspirin before reperfusion blocks the infarct size limiting effect of postconditioning in the rat [37].

Early Aspirin Administration: Friend or Foe?

In the above sections, we have shown that adding aspirin before reperfusion, as is guideline-recommended for patients with STEMI, attenuates the infarct size-limiting effects of statins, ticagrelor, opiates and ischemic postconditioning in animal studies. Numerous articles have tried to explain why these interventions and agents that consistently protect against ischemia-reperfusion or reperfusion injury in animal models have failed to show favorable effects in the clinical studies [38]. The potential adverse effect of aspirin in attenuating protection has not yet been considered seriously in this regard. There is no evidence to support the early loading dose of aspirin, as it has never been tested separately (i.e.: no study compared outcome of loading followed by continuous oral aspirin versus oral aspirin only). Birnbaum et al showed that if aspirin is administered intravenously to rats 15 min after reperfusion, the protective effect of pretreatment with atorvastatin is maintained. However, they assessed infarct size after 4h of reperfusion [17]. Thus, it is unclear if the lack of effect on infarct size will be maintained over longer reperfusion times. If future studies in larger animals (pigs and/ or dogs) confirm this observation, clinical trials where aspirin is given only orally after reperfusion versus the current standard loading should be conducted.

As abovementioned, the ISIS-2 trial confirmed the favorable effects of aspirin in patients with acute myocardial infarction. However, in the 1980's when the study was conducted, other anti-platelet agents, intravenous anticoagulation, statins and beta blockers were not used [6]. Indeed, in most animal models, ischemia is induced by mechanical occlusion of a coronary artery, rather than a thrombus formation over a plaque rupture. Thus, the role of platelet inhibition in the clinical setting may be more critical than in the animal models. However, the evidence supporting potent platelet inhibition immediately upon reperfusion in patients with STEMI remains uncertain [39]. Moreover, nowadays it can be achieved with alternative agents. Some antiplatelet agents, such as ticagrelor, cilostazol and dipyridamole have shown additive effects when combined with statins in limiting infarct size [14]. Those agents, however, have not been tested in clinical trials without the background of aspirin therapy.

We suggest studying the effects of aspirin loading before reperfusion on the infarct size limitation effects of statins, ticagrelor, morphine and/ or postconditioning in large animal models using long reperfusion periods (at least 24h). If indeed aspirin attenuates the protective effects, clinical trials should be conducted comparing aspirin loading to anti-platelet regimens without aspirin loading in patients with STEMI undergoing pPCI.

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Table 1: Statins

a. Pre-clinical studies

First Author Name	Animal model	Drug	Route of Administration and Dose	Time of ischemia / reperfusion	Infarct size in control group	Infarct size in statin group	Statistical significance in infarct size
Jones SP [40]	Mice	Simvastatin	1 mg/kg IP 18h before ischemia	30min/ 24h	~42% of the AR	~18% of AR	P<0.05
Ye Y [41]	Mice	Atorvastatin	10 mg/kg/d via oral gavage	30min/ 4h	~42% of AR	~15% of AR	P<.00001
Tian Y [42]	Mice	Atorvastatin	10 mg/kg IV 5 min before reperfusion	45min/ 60min	62±2% of AR	~50%	P<.05
Tavackoli S [43]	Rats	Simvastatin	20 mg/kg/d for 3d via oral gavage	30min/ 3h	40.1±2.7% of AR	20.8±3.4% of AR	P=0.001
Birnbaum Y [16]	Rats	Atorvastatin	10 mg/kg for 3d via oral gavage	30 min myocardial ischemia followed by 4 hour reperfusion	44.5±3.1%	31.3±1.9% of AR	P=0.011
Birnbaum Y [17]	Rats	Atorvastatin	10 mg/kg for 3d via oral gavage	30min/ 4h	31.0±2.2%	10.1±1.4% of AR	P<0.001
Birnbaum Y [44]	Diabetic ZDF Rats	Rosuvastatin	5 mg/kg for 3d via oral gavage	30min/ 24h	52.6±1.9% of AR	31.3±1.2% of AR	P<0.001
Sanada S [45]	Dogs	Pravastatin Pitavastatin Cerivastatin	(0.2, 2, or 10 mg/kg) (0.01, 0.1 or 0.5 mg/kg)	90 min/ 6h	39.8±3.6% of AR	29.5±3.5%, 22.5±4.0%*, 18.8±3.4%* 32.9±3.9%, 23.6±3.8%*, 31.4±3.9%	P<0.05 vs. control

			(0.5, 4 or 50 µg/kg) 10 min before ischemia			26.2±3.2%*, 32.1±5.3%, 37.1±4.4%	
Bulhak AA [46]	Pigs	Rosuvastatin Pravastatin	80 mg/d 160 mg/d 160 mg/d For 5d. Oral.	45min/ 4h	82±3% of AR	69±2% of AR 61±3% of AR 61±2% of AR	P=NS P<0.05 P<0.05
Li XD [47]	Mini pigs	Simvastatin	2 mg/kg oral before reperfusion	90min/ 3h	64.1±4.5% of AR	79.0±2.7% of AR	P<0.01
Ichimura K [48]	Mini pigs	Pitavastatin nanoparticle	4 mg 8 mg 16 mg 32 mg iv 5 min before reperfusion	60min/ 24h	~75% of AR	~75% of AR ~58% of AR ~50% of AR ~55% of AR	P=NS P<0.05 P<0.01 P<0.01
Mendieta G [49]	Hypercholesterolemic pigs	Atorvastatin	0.5 mg/kg IV 15min before reperfusion followed by oral 1 mg/kg/d for 42 days	90min/ 42d	MSI 17.2±6.3%	MSI 42.1±18.3%	P<0.05

b. Clinical

First Author Name	Drug	Dose	Method	Control	Statin	P-value

Hahn J-Y [50]	Atorvastatin	80 mg before ppCI + 5 days after. Or 10 mg/d after pPCI	infarct size (technetium Tc 99m SPECT) 5-14 days after pPCI	21.6±15.4$ of the LV (n=84)	22.2±15.5% of the LV (n=89)	.79
Post S [51]	Atorvastatin	80 mg before pPCI and 80 mg/d for 1 week or placebo.	cMRI	Transmural infarct area 1 week 8.4±9.2% LVESVI at 3 months 25.0 ml/m^2 (n=22)	Transmural infarct area 1 week 7.2±11% LVESVI at 3 months 25.1 ml/m^2 (n=20)	NS .74
Fuernau G [52]	Statin pretreatment before pPCI		CMR on day 3	MSI 51.9 (32.5; 69.3) (n=652)	MSI 47.0 (33.4; 65.3) (n=118)	.40
Kim EK [53]	Atorvastatin	80 mg before ppCI + 5 days after. Or 10 mg/d after pPCI	CMR within 14 days	MSI 46.9 (31.1=60.4) (n=37)	MSI 37.1 (26.9-58.7) (n=30)	.46
Marenzi G [54]	Long term statins or not before pPCI		CMR median 4 days after pPCI	MSI 52±30 (n=180)	MSI 68±25 (n=50)	<0.006
Ko Y-G [55]	Rosuvastatin	40 mg before ppCI + 7 days after. Or 10 mg/d 7 days after pPCI	cMRI 3 months after pPCI	Infarct mass 19.3±12.7 g (n=54)	Infarct mass 19.5±13.9 g (n=67)	.943

AR: ischemic area at risk; MSI: myocardial salvage index

Table 2: $P2Y_{12}$ platelet inhibitors

c. Pre-clinical studies

First Author Name	Animal model	Drug	Route of Administration and Dose	Time of ischemia / reperfusion	Infarct size in control group	Infarct size in treated group	Statistical significance in infarct size
Bell [56]	Mice	Cangrelor	60 µg/kg intravenous bolus 10 min before reperfusion followed by a continuous infusion of 6 µg/kg/min	35min/ 2h	52 ± 5 % of AR	28 ± 6 % of AR	P<0.05
Nanhwan M [18]	Rats	Ticagrelor Clopidogrel	75 mg/kg/d 150 mg/kg/d 300 mg/kg/d 30 mg/kg/d 90 mg/kg/d Oral for 7d before ischemia	30min/ 24h	53.2±2.4% of the AR	42.2±1.6% of AR 34.7±1.3% of AR 22.3±1.3% of AR 50.8±1.4% of AR 46.9±2.4% of AR	P<0.002 P<0.002 P<0.002 P=NS P=NS
Ye Y [23]	Rats	Ticagrelor Clopidogrel	10 mg/kg 30 mg/kg 12.5 mg/kg IP 5min before reperfusion	30min/ 24h	45.3±1.7% of AR	31.5±1.8% of AR 21.4±2.6% of AR 42.4±2.6% of AR	P<0.001 P<0.001 P=NS
Birnbaum Y [44]	Diabetic ZDF rats	Ticagrelor Prasugrel	150 mg/kg/d 7.5 mg/kg/d Via oral gavage for 3d	30min/ 24h	52.6±1.9% of AR	29.5±2.6% of AR 51.8±2.2% of AR	P<0.001 P=NS
Liu X [57]	Rats	Ticagrelor	150 mg/kg by oral gavage	45min/ 3d	56.2±9.4% of AR	17.4±9.9% of the AR	P<0.01

			after coronary occlusion				
Audia JP [58]	Rats	Ticagrelor	60 µg/kg 10 min before reperfusion followed by a continuous infusion (6 µg/kg/min)	60min/2h	60.3 ± 3.8% of AR	42.8 ± 3.3 of AR	P<0.02
Hjortbak MV [59]	Rats	Clopidogrel Ticagrelor Prasugrel	15 mg/kg 4h before infarct 20 mg/kg 2h before infarct 10 mg/kg 2h before infarct	30min/ 2h	52±8% of AR	50±11% of AR 37±11% of AR 49±9% of AR	P>0.99 P<0.01 P>0.99
Vilahur G [60]	Pigs	Ticagrelor Clopidogrel	180 mg 2h before ischemia. 90 mg bid thereafter. 600 mg 4h before ischemia. 75 mg/d thereafter	60min/ 24h	Infarct mass 22.8g (17.3-25.8)	Infarct mass 12.0g (10.6-12.9) Infarct mass 15.7g (14.2-16.2)	P<0.005 P<0.05
Vilahur G [61]	Pigs	Ticagrelor Clopidogrel	180 mg loading 2h before infarct followed by 90 mg bid 600 mg loading 4h before infarct followed by 75 mg/d	60min/ 42d	13.0% of LV (11.2-15.7)	9.1% of LV (8.3-10.3) 11.6% of LV (11.2-15.7)	P<0.05 P=NS

Wang K [62]	Dogs	Ticagrelor Clopidogrel	75µg/kg bolus followed by 10µg/kg/min for 2h 10 mg/kg bolus All animals received tPA 1 mg/kg over 120 min and IV heparin.	Electrolytic injury induced coronary occlusion	28.0±9.2% of the AR	11.7±5.6% of AR 32.7±10.1% of AR	P<0.05 P=NS
Yang [63]	Rabbits	Cangrelor	60 µg/kg iv bolus 10 min before reperfusion followed by continuous infusion of 6 µg/kg/min	30min/3h	37.9±1.8% of AR	19.4±2.1% of AR	P<0.05
Yang PMID: [64]	Monkeys	Cangrelor	60 µg/kg iv bolus 10 min before reperfusion followed by continuous infusion of 6 µg/kg/min	90min/4h	49.3 ± 3.9% of AR	38.0 ± 4.9% of AR	p < 0.001 (by regression)

a. Clinical

First Author Name	Drug	Method	Control	Ticagrelor	P-value
Khan JN [21]	Clopidogrel Ticagrelor or Prasugrel	Multicenter, prospective, open-label, randomized of patients with STEMI and multivessel disease. Cardiac MRI before discharge.	Clopidogrel (n=70) Infarct size 16.0 (10.4-27.6) % of LV MSI 46.2 (24.7-70.2)%	Ticagrelor/ Prasugrel (n=133) Infarct size 10.6 (4.4-19.0) % of LV MSI 63.3 (42.9-82.6)	P=0.013 P=0.06
Ubaid S [20]	IV Cangrelor Oral ticagrelor	Open-label, prospective, randomized control trial. Cardiac MRI at 3 months.	Cangrelor (n=29) 13.7 (7.7-17.5) % of LV	Ticagrelor (n=25) 10.9 (6.6-17.5) % of LV	P=0.61
Sabbah M [22]	Clopidogrel Ticagrelor/ prasugrel	Substudy of the DANAMI-3 randomized trial. All patients were loaded prehospital with clopidogrel. prasugrel or ticagrelor. Cardiac MRI at 3 months	Clopidogrel (n=351) 12.9 (5.2-20.6) % of LV. MSI 66 (50-82)%	Ticagrelor/ Prasugrel (n=342) 10.0 (3.1-16.0) % of LV. MSI 71 (58-88)%	P<0.001 P<0.001

AR: ischemic area at risk; LV: left ventricle; MSI: myocardial salvage index

Table 3: Opiates

a. Pre-clinical studies

First Author Name	Animal model	Drug	Route of Administration and Dose	Time of ischemia / reperfusion	Infarct size in control group	Infarct size in treated group	Statistical significance in infarct size
Jiang X [25]	Mice	Morphine	0.3 mg/kg IP 1h before ischemia 24h before ischemia	45min/ 2h	43.5±5.7% of the AR	23.7±9.9% of the AR 22.4±4.4% of the AR	P=0.001 P<0.001
Schultz JE [65]	Rats	Morphine	100µg/kg X3 before ischemia	30min/ 2h	56±5% of AR	12±5% of AR	P<0.05
Ludwig LM [66]	Rats	Morphine	30 min prior to ischemia	30min/ 2h	59±2%	38±2% of AR	P<0.05
Gross ER [26]	Rats	Morphine	0.3 mg/kg 5 min before reperfusion	30min/ 2h	59.1±1.7% of AR	42.3±1.5% of AR Morphine administration 10 min after reperfusion did not affect infarct size.	P<0.01
Small BA [67]	Rats	Morphine	0.3 mg/kg 10 min before ischemia	30min/ 2h	60±1% of AR	42±2% of AR	P<0.01
Wu L [68]	Rats	Morphine	0.3 mg/kg 10 or 5 min before myocardial ischemia	30min/ 2h	52.6±4%	40.4±3% of AR	P<0.01
Xu J [69]	Isolated Rat hearts	Morphine	Isolated heart model 0.1 µM at reperfusion	30min/ 2.5h	~50% of the LV	~35% of the LV	P<0.05
Miki T [70]	Rabbits	Morphine	0.3 mg/kg 0.5 mg/kg 3 mg/kg	30min/ 3h	38.5±1.6% of the AR	41.0±3.6% of AR 38.4±3.4% of AR 20.3±3.3% of AR	P=NS P=NS P<0.005

			IV 15 min before ischemia				
Okubo S [71]	Rabbits	Morphine	0.3 mg/kg IV 15 min before ischemia	30min/ 3h	46±3.8% of AR	19.5±3.8% of AR	P<0.001
Sigg DC [72]	Pigs	DADLE DPDPE deltorphin-D	40 min before ischemia	45min/ 3h	64.7±5% of AR	66.8±3% 36.5±6% of AR 27.4±11% of AR	P=NS P<0.01 P<0.01
Coles JA [73]	Pigs	Morphine	0.5 mg/kg X2 before ischemia	45min/ 3h	65±5% of AR	~68%	P=NS
Karlsson LO [74]	Pigs	Eribis peptide 94	1 µg/kg IV 5-26 min after occlusion 26-40 min after occlusion	40min/ 4h	61.6±2% of AR	50.2±3% of AR 49.2±2% of AR	P<0.05 P<0.05
Peart JN [75]	Dogs	TAN-67 BW373U86	Intracoronary 30 min before ischemia	60min/ 3h	28±2.1% of AR	12.3±2.2% of AR 11.7±2.6% of AR	

b. Clinical

First Author Name	Drug	Method	Control	Morphine	P-value
de Waha S [27]	Morphine	276 patients with STEMI that underwent pPCI within 12h of onset of symptoms. CMR 2-4 days after presentation.	Infarct size: 14.1 (6.6-24.9)% of LV MSI: 60.5 (45.6-81.9)% (n=153)	Infarct size: 19.1 (8.9-29.2)% of LV MSI: 52.1 (33.0-73.1) (n=123)	P=0.02 P=0.003
Eitel I [28]	Morphine	734 patients with STEMI that underwent pPCI. CMR within 1 week after infarction.	(n=454) 17% of LV (8-25%) MSI 51 (32-69)%	(n=280) 16% of LV (8-26%) MSI 52 (35-69)%	P=0.67 P=0.65
Stiermaier T [30]	Morphine	104 patients with STEMI that underwent pPCI. All received ticagrelor loading. Patients were randomized to IV placebo, morphine or morphine + metoclopramide before pPCI. Infarct size was assessed by CMR on day 1-4.	17.9 (12.3 to 32.9) of the LV (n=39)	Morphine: 15.5 (5.0 to 21.4)% of LV (n=36) Morphine + metoclopramide: 23.7 (11.3 to 37.2) of the LV (n=29)	P=0.047 P=0.491

AR: ischemic area at risk; DADLE: [D-Ala^2 ,D-Leu^5] encephalin; DPDPE: [D-Pen^{2,5}]encephalin; LV: left ventricle; MSI: myocardial salvage index

Table 4: Ischemic postconditioning

d. Pre-clinical studies

First Author Name	Animal model	Postconditioning	Time of ischemia / reperfusion	Infarct size in control group	Infarct size in treated group	Statistical significance in infarct size
Zhao Z-Q[34]	Dogs	30 sec reperfusion/30sec reocclusion X3	60min/ 3h	25±3% of AR	14±2% of AR	P<0.05
Halkos ME [76]	Dogs	30sec reperfusion/30sec reocclusion X3	60min/ 3h	24±2% of AR	10±1% of AR	P<0.05
Schwartz LM [77]	Pigs	30 sec reperfusion/30sec reocclusion X3	30 min/ 3h	26.5±5.2% of AR	37.8±5.1% of AR	P=NS
Iliodromitis EK [78]	Pigs	30sec reperfusion/30sec reocclusion X4 30sec reperfusion/30sec reocclusion X8	60min/ 3h	33.5±7.6% of AR	36.7±3.7% of AR 10.5±0.5% of AR	P=NS P<0.01
Lie RH [79]	Pigs	15sec reperfusion/15sec reocclusion 10	45 min/ 3h	57.8±10.2% of AR	39.6±12.0% of AR	P=0.0056
Heusch G [80]	Mice	10sec reperfusion/10sec reocclusion X3	30min/ 2h	54±4% of AR	37±3% of AR	P<0.05
Kaljusto M-L [81]	Mice	10sec reperfusion/10sec reocclusion X3	30min/ 1h	42±7%	21±5% of AR	P<0.001
Kin H [82]	Rats	10sec reperfusion/10sec reocclusion X3 or X6	30 min/ 3h	52±3% of AR	X3 cycles: 40±2% of AR X6 cycles: 40±2.9% of AR	P<0.05 P=NS

Kin H [83]	Rats	10sec reperfusion/10sec reocclusion X3	30 min/ 3h	53±2% of AR	40±3% of AR	P<0.01
Kaljusto M-L [81]	Rats	10sec reperfusion/10sec reocclusion X3	40 min/ 3h	62±3% of AR	51±11% of AR	P=0.01
Birnbaum Y [37]	Rats	10sec reperfusion/10sec reocclusion X3	30 min/ 4h	31.0±2.2% of AR	IPC 13.9±0.4% of AR IPC+ aspirin 33.3±1.1%	P<0.001 P=NS
Yang XM [84]	Rabbits	30 sec reperfusion/30sec reocclusion X4	30 min/ 3h	35.4±2.7% of AR	19.8±1.8% of AR	P<0.05
Argaud L [85]	Rabbits	30 sec reperfusion/30sec reocclusion X4	30min/ 4h	61±6% of AR	29±4% of AR	P<0.001

a. Clinical

First Author Name	Method	Control	Postconditioning	P-value
Lonborg J [86]	118 patients with STEMI undergoing pPCI were randomized to postconditioning (30 sec ischemia/ 30 sec reperfusion X4) or standard pPCI. CMR 3 months after presentation.	Infarct size 63±17% of AR (n=43)	Infarct size 51±16% of AR (n=43)	P<0.01
Sorensson P [87]	76 patients with STEMI undergoing pPCI were randomized to postconditioning (1min occlusion/ 1 min reperfusion X4) or standard pPCI. CMR on day 6-9 after presentation	Infarct size 44% (30,56) of AR (n=38) In patients with a large AR: Infarct size 54% (50, 68)	Infarct size 47% (23, 63) (n=38) In patients with a large AR: Infarct size 33% (21, 57)	P=NS P=0.03
Freixa X [88]	79 patients with STEMI undergoing pPCI with TIMI grade 0-1 flow in the infarct related artery were randomized to postconditioning (1min occlusion/ 1 min reperfusion X4) or standard pPCI. CMR 1 week and 6 months after presentation	MSI at day 7: 30.9±20.5% Infarct size day 7: 22.1±17.2% of LV Infarct size at 6m: 18.7±13.2% of LV (n=40)	MSI at day 7: 18.9±27.4% Infarct size day 7: 27.5±10.2% of LV Infarct size at 6m: 21.8±10.6% of LV (n=39)	P=0.038 P=0.11 P=0.37
Tarantini G [89]	78 patients with first STEMI undergoing pPCI were randomized to (1min occlusion/ 1 min reperfusion X4) or standard pPCI. CMR at 28±16 days after presentation.	Infarct size 14.3±9.9% of LV mass (n=38)	Infarct size 20.2±11.9% of LV mass (n=37)	P=0.056
Hahn JY [90]	Multicenter, prospective, randomized, open-label, blinded end point trial. 700 patients undergoing pPCI for STEMI were randomized to postconditioning (1min occlusion/ 1 min reperfusion X4) or standard pPCI	Complete ST resolution at 30 min: 41.5%	Complete ST resolution at 30 min: 40.5%	P=0.79
Limalanathan S [91]	272 patients with first STEMI undergoing pPCI were randomized to postconditioning (1min occlusion/ 1 min reperfusion X4) or standard pPCI. CMR 4 months after presentation.	Infarct size 14.4 (7.7, 24.6)% of LV mass MSI 49.0 (37-61)% (n=129)	Infarct size 13.5 (8.1, 19.3)% of LV mass MSI 52.4 (41-68)% (n=120)	P=0.18 P=0.30
Eitel I [92]	Controlled, single center study. 696 patients with STEMI undergoing pPCI were randomized to standard pPCI, postconditioning, postconditioning + remote ischemic preconditioning. CMR on day 3 after presentation.	MSI 40 (16-68)% (n=160)	Postconditioning MSI (n=173)	P=0.39 P=0.02

		Infarct size 18 (8-29) % of LV	Remote ischemic preconditioning + postconditioning MSI 49 (30-72)% (n=158) postconditioning Infarct size 17 (8-26) % of LV Remote ischemic preconditioning + postconditioning Infarct size 16 (8-26) % of LV	P=NS P=NS
Pichot S [93]	Pooled data from 4 previously published multicenter, randomized, open label trials. 173 patients with STEMI undergoing pPCI were randomized to postconditioning (1min occlusion/ 1 min reperfusion X4) or standard pPCI. Infarct size was measured by total creatine kinase release over 72h.	88.2±54.5 $X10^3$ arbitrary units (n=91)	71.7±41.6 $X10^3$ arbitrary units (n=82)	P=0.027
Engstrom T [94]	Multicenter, randomized clinical trial. 1,234 patients with STEMI and TIMI grade 0-1 flow in the infarct related artery were randomized to postconditioning (30 sec ischemia/ 30 sec reperfusion X4) or standard pPCI. The primary endpoint: mortality and hospitalization for heart failure	11.2%	10.5%	P=0.66

AR: ischemic area at risk; LV: left ventricle; MSI: myocardial salvage index