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Review article

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Coronary microvascular obstruction and dysfunction in patients with acute myocardial infarction

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Supplementary Table 1 | Main studies assessing the efficacy of antithrombotic agents to reduce CMVO in patients with STEMI undergoing PPCI

Strategy	Study name and year of publication	Study design	Population (*n*)	Comparison	Dose, route and timing of administration	Primary and secondary end points assessing CMVO	Results
Anticoagulant therapy							
Pre-PCI heparin	Liem et al. HAEP (2000)[1]	Randomized	584	Different doses of heparin before PCI	High (300 UI/kg) versus low (5,000 UI) or no dose of heparin IV	- TIMI flow grade at initial angiography	Ø
	Karlsson et al. (2019)[2]	Sub-study of RCT (TASTE)	7,144	Heparin before PCI versus controls	Heparin IV (5,000 UI)	- Intracoronary thrombus - Patency of IRA at initial angiography	↓
	Emilsson et al. (2022)[3]	Observational	41,631	Heparin before PCI versus controls	Heparin IV (5,000 UI)	- Patency of IRA at initial angiography	↓
Anticoagulant and antiplatelet therapy							
Pre-PCI aspirin and heparin	HAEP pilot study (1998)[4]	Observational	108	Aspirin and heparin before PCI versus controls	Heparin IV (300 UI/kg) plus chewed aspirin (160 mg)	- TIMI flow grade at initial angiography	↓
	Zijlstra et al. (2002)[5]	Observational	1,702	Aspirin and heparin before PCI versus controls	Heparin IV (>5,000 UI) plus IV aspirin (500 mg)	- TIMI flow grade at initial angiography - LVEF - IS	↓
Pre-PCI heparin and ticagrelor	Fabris et al. (2022)[6]	Observational	537	Aspirin, heparin and ticagrelor before PCI versus aspirin alone	Heparin IV (5,000 UI) and ticagrelor 180 mg	- TIMI flow grade at initial angiography - IS - LVEF	↓
Oral $P2Y_{12}$ inhibitors							
Pre-PCI ticagrelor	Montalescot et al. (2014)[7]	Randomized (ATLANTIC)	1,862	Ticagrelor in ambulance versus ticagrelor at the moment of CA	Ticagrelor 180 mg orally on average 31 min before CA or at the moment of CA	- STR - Patency of IRA at initial angiography	Ø
High-dose clopidogrel pre-PCI	Song et al. (2012)[8]	Observational	198	High versus reduced clopidogrel pre-PCI	Clopidogrel 600 mg versus clopidogrel 300 mg	- IS - CMVO	↓

Prasugrel versus clopidogrel	Brener at al. (2014)[9]	Sub-study of RCT (INFUSE-AMI)	452	Prasugrel versus clopidogrel	Prasugrel 60 mg versus clopidogrel 600 mg	- TIMI flow grade at initial angiography - cTFC - IS	↓
Clopidogrel pre-PCI	Waha et al. (2014)[10]	Observational	423	High versus reduced clopidogrel pre-PCI	Clopidogrel 600 mg versus clopidogrel 300 mg	- IS - CMVO	
Prasugrel or ticagrelor versus clopidogrel	Khan et al. (2016)[11]	Sub-study of RCT (CvLPRIT-CMR)	203	Prasugrel or ticagrelor versus clopidogrel	Prasugrel 60 mg or ticagrelor 180 mg or versus clopidogrel 600 mg	- IS - CMVO	↓
Parenteral antiplatelet therapy							
Eptifibatide pre-PCI	Gibson et al. (2006)[12]	Randomized (TITAN-TIMI 34)	343	Eptifibatide before versus at the time of PCI	Eptifibatide 180 µg/kg as bolus followed by a second bolus at 10 min and an 18-h infusion of 2 µg/kg/min	- cTFC	↓
Abciximab pre-PCI	Maioli et al. (2007)[13]	Randomized (RELAx-AMI)	210	Abciximab before versus at the time of PCI	Abciximab 0.25 mg/kg as bolus followed by a 12-h infusion of 0.125 µg/kg/min either in the emergency room or in the catheterization laboratory	- TIMI flow grade at initial angiography - cTFC - MBG	↓
Tirofiban pre-PCI	Van't Hof et al. (2008)[14]	Randomized (On-TIME 2)	936	Pre-hospital intravenous tirofiban bolus administration versus placebo	Tirofiban 25 µg/kg bolus followed by an 18-h infusion of 0.15 µg/kg/min versus placebo	- STR	↓
Intracoronary abciximab	Stone et al. (2012)[15]	Randomized (INFUSE-MI)	452	Intracoronary abciximab at the time of PCI	Intracoronary abciximab 0.25 mg/kg as bolus versus controls	- IS	↓
Intracoronary versus intravenous abciximab	Eitel et al. (2013)[16]	Sub-study of RCT (AIDA-STEMI)	795	Intracoronary versus intravenous abciximab during PCI	Intracoronary or intravenous abciximab 0.25 mg/kg as bolus followed by a 12-h infusion of 0.125 µg/kg/min	- IS - CMVO - LVEF	Ø

Cangrelor versus ticagrelor	Ubaid et al. (2019)[17]	Randomized	100	Intravenous cangrelor versus oral ticagrelor before PCI	Intravenous 30/μg/kg bolus followed by 4 μg/kg/min versus oral 180 mg ticagrelor	- IMR - IS - TIMI flow grade at initial angiography - cTFC - STR	Ø
Intracoronary tirofiban	Huang et al. (2021)[18]	Randomized	234	Intracoronary tirofiban versus saline	Intracoronary tirofiban 10 μg/kg bolus versus saline	- cTFC - STR	↓
Subcutaneous GPI pre-PCI	Rikken et al. (2023)[19]	Sub-study of RCT (cel-02)	24	Subcutaneous RUC-4 before PPCI versus controls	Zalunfiban 0.075, 0.09 and 0.110 mg/kg in the cardiac catheterization, before vascular access	- TIMI flow grade at initial angiography	↓
Intracoronary thrombolytic agents							
Intracoronary streptokinase	Sezer et al. (2007)[20]	Randomized	41	Intracoronary streptokinase versus no therapy	Intracoronary 250 kU streptokinase versus no additional therapy	- cTFC - CFR - IMR - MBG	↓
	Sezer et al. (2009)[21]	Randomized	95	Intracoronary streptokinase versus no therapy	Intracoronary 250 kU streptokinase versus no additional therapy	- IS - CFR - IMR - MBG - LVEF	↓
Intracoronary urokinase	Greco et al. (2013)[22]	Randomized (DISSOLUTION)	102	Intracoronary urokinase versus saline infusion	Intracoronary 200,000 U urokinase versus saline infusion by infusion microcatheter before manual thromboaspiration	- TIMI flow grade at initial angiography - cTFC - MBG - STR	↓
	Zhao et al. (2015)[23]	Randomized	183	Intracoronary urokinase versus no therapy	Intracoronary 500,000-1,000,000 U urokinase versus no additional therapy	- TIMI flow grade at initial angiography - cTFC - STR	↓
Intracoronary alteplase	McCartney et al. (2019)[24]	Randomized (T-Time)	440	Intracoronary low-dose alteplase during PCI versus placebo	Intracoronary 20 or 10 mg alteplase infusion over 5–10 min versus placebo	- CMVO - IS	Ø

Intracoronary tenecteplase	Gibson et al. (2020)[25]	Randomized (ICE T-TIMI 49)	40	Intracoronary tenecteplase versus placebo	Intracoronary 4 mg tenecteplase versus placebo	- TIMI flow grade at initial angiography - cTFC	↓
Intracoronary pro-urokinase	Huang et al. (2021)[18]	Randomized	228	Intracoronary pro-urokinase versus saline	Intracoronary pro-urokinase 20 mg bolus versus saline	- cTFC - STR	↓

Randomized trials or large observational studies comprising >100 patients were included. ↓, significant reduction; Ø, no significant difference between groups, CA, coronary angiography; CMR, cardiac magnetic resonance; CMVO, coronary microvascular obstruction and dysfunction; cTFC, corrected TIMI frame count; IRA, infarct-related artery; IS, infarct size; IV, intravenous; LVEF, left ventricular ejection fraction; MBG, myocardial blush grade; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; STR, ST-segment resolution; TIMI, Thrombolysis in Myocardial Infarction; TVR, target-vessel revascularization.

Supplementary Table 2 | Main randomized clinical trials assessing the efficacy of vasodilators to reduce CMVO

Drug	Study	Population (*n*)	Comparison	Dose, route and timing of administration	Primary and secondary end points assessing CMVO	Results
Adenosine						
Adenosine versus saline	Mahaffey et al. AMISTAD (1999)[26]	236	Adenosine versus saline	Adenosine 70 μg/kg/min for 3 h, IV, before thrombolytic therapy	- IS - Myocardial salvage index	↓
	Marzilli et al. (2000)[27]	54	Adenosine versus saline	Adenosine 4 mg in 1 minute, IC, after balloon inflation	- TIMI flow - Left ventricular regional function	↓
	Ross et al. Kloner et al. AMISTAD-II (2005–2006)[28,29]	2,118	Adenosine versus placebo	Adenosine 50 or 70 μg/kg/min for 3 h, IV, either at the start of fibrinolysis or before PCI	- IS	↓
	Vijayalakshmi et al. (2006)[30]	150	Adenosine versus verapamil versus saline	Adenosine 30 μg bolus, IC, after PCI	- TFC - LWMI	↓
	Fokkema et al. (2009)[31]	448	Adenosine versus saline	Adenosine 120 μg two boluses, IC, one after thrombus aspiration and one after stenting	- STR - MBG - TIMI flow - IS	Ø
	Niccoli et al. REOPEN-AMI (2013)[32]	240	Adenosine versus nitroprusside versus saline	Adenosine 120 μg fast bolus + 2 mg slow bolus, IC, during PCI following thrombus aspiration	- STR - TIMI flow - MBG - IS	↓
	Nazir et al. REFLO-STEMI (2016)[33]	247	Adenosine versus nitroprusside versus saline	Adenosine 1 mg + 2 mg (or + 1 mg if IRA was the RCA), IC, during PCI	- IS - MVO - STR	Ø
Nicorandil						
Nicorandil versus saline	Ito et al. (1999)[34]	81	Nicorandil versus saline	Nicorandil 4 mg bolus + 6 mg/h for 24 h IV pre-PCI, followed by 15 mg/day oral until discharge	Myocardial contrast echocardiography no-reflow	↓

	Ishii et al. (2005)[35]	368	Nicorandil versus saline	Nicorandil 12 mg bolus, IV, before PCI	- TIMI flow - cTFC - STR - IS	↓
	Kitakaze et al. J-WIND (2007)[36]	538	Nicorandil versus saline	Nicorandil 0.067 mg/kg bolus, followed by 1.67 µg/kg/min for 24 h; some patients were given oral nicorandil during follow-up	- IS	↓
	Lee et al. (2008)[37]	73	Nicorandil versus saline	Nicorandil 2 mg bolus, IC, pre-PCI and post-PCI	- TIMI flow	↓
	Qian et al. CHANGE (2022)[38]	238	Nicorandil versus saline	Nicorandil 12 mg bolus, IV, pre-PCI + 144 mg 6 mg/h for 24 h	- IS - cTFC - TIMI flow - STR - MVO	↓
Nitroprusside						
Nitroprusside versus saline	Amit et al. (2006)[39]	98	Intracoronary nitroprusside versus saline	Nitroprusside 60 µg bolus, IC, during PCI	- cTFC - STR - MBG - TIMI flow	Ø
	Niccoli et al. REOPEN-AMI (2013)[32]	240	Adenosine versus nitroprusside versus saline	Nitroprusside: 60 µg bolus + 100 µg slow bolus, IC, during PCI following thrombus aspiration	- STR - TIMI flow - MBG - IS	Ø
	Nazir et al. REFLO-STEMI (2016)[33]	247	Adenosine versus nitroprusside versus saline	Nitroprusside 250 µg x 2, IC, during PCI	- IS - MVO - STR	Ø
Verapamil versus nitroprusside	Abdelaziz et al. (2017)[40]	60	Verapamil versus nitroprusside	Nitroprusside 60 µg, fast bolus IC + 120 µg in 2 min, during PCI	- TIMI flow - STR	↓
Calcium channel blockers						
Verapamil versus saline	Taniyama et al. (1997)[41]	40	Verapamil versus saline	Verapamil 500 µg IC, post-PCI, followed by 120 mg oral verapamil	- Myocardial contrast echocardiography with intracoronary microbubbles	↓

	Vijayalakshmi et al. (2006)[30]	150	Adenosine versus verapamil versus saline	Verapamil 500 µg in 1 min IC after PCI	- TFC - LWMI	↓
Diltiazem versus verapamil versus nitroglycerin	Huang et al. RECOVER (2012)[42]	102	Diltiazem versus verapamil versus nitroglycerin	Verapamil 200 µg bolus IC; nitroglycerin 200 µg bolus, IC; diltiazem 400 µg bolus IC; after PCI	- cTFC - STR - IS	↓
Verapamil versus nitroprusside	Abdelaziz et al. (2017)[40]	60	Verapamil versus nitroprusside	Verapamil 250 µg + 500 µg over 2 min, IC, during PCI	- TIMI flow - STR - LWMI	↓
Adrenaline						
Adenosine versus adrenaline	Khan et al. COAR (2022)[43]	201	Adenosine versus adrenaline	Adenosine 60–100 µg bolus, IC; adrenaline 100–600 µg bolus, IC; post-PCI	- TIMI flow - cTFC - MBG	↓

↓, significant reduction; Ø, no significant difference between groups, CABG, coronary artery bypass graft surgery; CMVO, coronary microvascular obstruction and dysfunction; cTFC, corrected TIMI frame count; IC, intracoronary; IRA, infarct-related artery; IS, infarct size; IV, intravenous; LVEF, left ventricular ejection fraction; LWMI, left ventricular wall motion index; MBG, myocardial blush grade; MI, myocardial infarction; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; RCA, right coronary artery; STR, ST-segment resolution; TFC, TIMI frame count; TVR, target-vessel revascularization.

Supplementary Table 3 | Main clinical trials on ischaemic postconditioning in patients with STEMI undergoing PPCI

Authors	Acronym	Year of publication	Placebo/ intervention	Intervention	Primary end point	Results
Bøtker et al.[44]	CONDI	2010	167/166	RIC	Myocardial salvage	↓
Sörensson et al.[45]	–	2010	33/35	PoCo	IS (MRI)	Ø
Lonborg et al.[46]	–	2010	59/59	PoCo	Myocardial salvage (MRI)	↓
Munk et al.[47]	–	2010	108/110	RIP	LVEF	Ø
Rentoukas et al.[48]	–	2010	33/30	RIP	STR	↓
Ugata et al.[49]	–	2012	42/37	PoCo	IS (CK-MB release)	↓
Frexia et al.[50]	–	2012	40/39	PoCo	IS and myocardial salvage (MRI)	Ø
Tarantini et al.[51]	POST-AMI	2012	39/39	PoCo	IS (MRI)	Ø
Thuny et al.[52]	–	2012	25/25	PoCo	IS (MRI)	↓
Dweyer et al.[53]	–	2013	52/50	PoCo	IS and myocardial salvage (MRI)	Ø
Mewton et al.[54]	–	2013	25/25	PoCo	IS (MRI)	↓
Hahn et al.[55]	POST	2013	350/350	PoCo	STR	Ø
Elzbieciak et al.[56]	–	2013	21/18	PoCo	IS (MRI)	Ø
Dwyer et al.[57]	–	2013	52/50	PoCo	IS and myocardial salvage (MRI)	Ø
Crimi et al.[58]	–	2013	50/50	RIC	IS (CK-MB release and MRI)	↓
Limalanathan et al.[59]	POSTEMI	2014	136/136	PoCo	IS (MRI)	Ø
Araszkiewicz et al.[60]	–	2014	37/35	PoCo	IS (CK-MB release)	↓
Roubille et al.[61]	PRIME	2014	44/46	PoCo	IS (MRI)	Ø
Prunier et al.[62]	RIPOST-MI	2014	44/71	RIC	IS (CK-MB release and MRI)	↓
Sloth et al.[63]	–	2014	166/167	RIC	MACCE	↓
Yellon et al.[64]	ERIC-LYSIS	2015	258/261	RIC	IS (Tn release)	↓
Luz et al.[65]	–	2015	44/43	PoCo	IS (CK-MB release)	Ø
White et al.[66]	–	2015	43/42	RIC	IS (MRI)	↓
Eitel et al.[67]	LIPSIA CONDITIONING	2015	160/173	PoCo and RIC	Myocardial salvage (MRI)	Ø
Verouhis et al.[68]	–	2016	46/47	RIC	IS and myocardial salvage (MRI)	Ø
Elbadawi et al.[69]	–	2017	35/36	RIC	LVEF	Ø
Engstrøm et al.[70]	DANAMI-3-iPOST	2017	617/617	PoCo	All-cause death and hospitalization for heart failure at 38 months	Ø
Cao et al.[71]	–	2018	44/36	RIC	IS (CK-MB release)	↓
Gaspar et al.[72]	RIC-STEMI	2018	217/231	RIC	Cardiac death and hospitalization for heart failure	Ø
Traverse et al.[73]	–	2019	57/65	PoCo	IS and myocardial salvage (MRI)	Ø
Hausenloy at al.[74]	CONDI-2/ERIC-PPCI	2019	2,701/2,700	RIC	Cardiac death or hospitalization for heart failure	Ø

↓, significant reduction; Ø, no significant difference between groups; CK, creatine kinase; IS, infarct size; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; MRI, magnetic resonance imaging; PoCo, postconditioning; PPCI, primary percutaneous coronary intervention; RIC, remote ischaemic conditioning; STEMI, ST-segment elevation myocardial infarction; STR, ST-segment resolution; Tn, troponin.

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