Table 1. Key randomized controlled trial and meta-analyses of pre-treatment in patients with acute coronary syndromes.

Study name (year)	Study population	N. of patients	Pretreatment	Timing[§]	No Pretreatment	Follow-up	Key findings	Limitations
RCT								
CURE Trial (2001) (4)	NSTE-ACS	12,562	Clopidogrel 300mg before CAG	10 days (median)	Placebo before CAG	30 days, 1 year	≈ cardiac death, MI, stroke ↑ major, ≈ life-threatening (study specific definition)	Only 43% CAG, 21% PCI
CREDO (2002)(5)	NSTE-ACS (67%) Stable CAD (33%)	2,116	Clopidogrel 300mg 3 to 24 h before PCI	9.8 hours (mean)	Placebo 3 to 24 h before PCI	28 days	≈ death MI urgent revasc.° ≈ TIMI major or minor	Coronary anatomy was known prior to PCI
ARMYDA-5 PRELOAD (2010)(6)	NSTE-ACS (39%) Stable CAD (61%)	409	Clopidogrel 600mg 4 to 8 h before CAG	6.0±0.6 hours (mean)	Clopidogrel 600mg before PCI	30 days	≈ cardiac death, MI, TVR ≈ TIMI major or minor	
ACCOAST Trial (2013)(7)	NSTE-ACS	4,033	Prasugrel 30mg 2 to 48h before PCI +30mg at time of PCI	4.3 hours (median)	Placebo 2 to 48h before PCI +Prasugrel 60mg at time of PCI	7 days, 30 days	≈ MACE* ↑ non-CABG TIMI major	
DUBIUS (2020)(8)	NSTE-ACS	1,449	Ticagrelor 180mg before CAG	23.3 hours (median)	Ticagrelor 180mg or Prasugrel 60mg at time of PCI	30 days	≈ cardio- or cerebrovascular death, MI, stroke ≈ BARC 3, 4 or 5	Earlier stop of the trial because of far lower than expected event rate (futility)
CIPAMI (2012)(13)	STEMI	337	Clopidogrel 600mg pre-hospital	47 minutes (median)	Clopidogrel 600mg before PCI	7 days (or discharge)	≈ surrogate endpoints[†] ≈ death, MI, urgent revasc. ≈ TIMI major	
Load and Go (2013)(14)	STEMI	168	Clopidogrel 600-900 mg at first medical contact	65±33 minutes (mean)	Clopidogrel 300mg at time of PCI	30 days	≈ TMPG 3 ≈ cardiovascular death, MI, stroke or definite ST ≈ major bleeding (definition missing)	
ATLANTIC (2014)(15)	STEMI	1,862	Ticagrelor 180mg prehospital	48 minutes (median)	Ticagrelor 180mg in the catheterization laboratory	30 days	≈ surrogate coprimary endpoints ≈ death, MI, stroke, urgent revasc. or definite ST ↓ definite ST ≈ TIMI major, minor	Interval between the two treatment strategies: 31 minutes

Study name (year)	Study population	N. of patients	Pretreatment	Timing§	No Pretreatment	Follow-up	Key findings	Limitations
Meta-analyses								
Bellemain et al. (2012)(10)	All clinical presentations	8,608#	Clopidogrel 300 to 900mg before CAG	2 to 24 hours	Placebo or Clopidogrel at time of PCI	7 to 30 days	≈ mortality ↓ major coronary endpoint ≈ bleeding	Studies with different design and outcomes definition
Bellemain et al. (2014)(9)	NSTE-ACS	15,410#	Clopidogrel 300 or Prasugrel 30mg	2 hours to 10 days	Placebo or Prasugrel 60mg at time of PCI	7 to 30 days	≈ mortality ≈ composite ischemic endpoint ↑ bleeding	Study with different design and different outcomes definition
Nairooz et al. (2017)(11)	NSTE-ACS STEMI	25,685#	Clopidogrel 300 or 600mg	47 minutes to 10days	Placebo or Clopidogrel 300-600mg at time of PCI	30 days	≈ mortality ↓ MACE ≈ bleeding	Study with different design and different outcomes definition

CAD= coronary artery disease; CAG= coronary angiography; MACE= major adverse cardiovascular events; MI= myocardial infarction; STEMI= ST elevation myocardial infarction; NSTE-ACS= No ST Elevation acute coronary syndrome; PCI= percutaneous coronary intervention; RCT=randomized controlled trial; ST= stent thrombosis; TMPG=Thrombolysis in Myocardial Infarction Perfusion; TVR= target vessel revascularization.

°Reduction of death MI urgent revascularization in the subgroup of patients receiving Clopidogrel >6 hours before PCI

§mean or median timing from pretreatment to CAG or PCI

*death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, glycoprotein IIb/IIIa inhibitor rescue therapy

†primary surrogate endpoints: TIMI 2/3 patency of the infarct-related artery in the first diagnostic angiogram immediately prior to PCI.

‡Absence of ST-segment elevation resolution ≥70% before PCI and proportion of patients who did not meet the criteria for TIMI flow grade 3 in the infarct-related artery at angiography before PCI.

#The reported values refer to Randomized Controlled Trials