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ESC/EACTS GUIDELINES

2018 ESC/EACTS Guidelines on myocardial revascularization - Supplementary Data

The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)

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1. Supplementary tables and text

Supplementary Table 1 Revascularization vs. medical therapy: angina, exercise time, and number of medications at early and late follow-up

Study	Angina		Exercise time		Number of medications	
	Early	*Late*	*Early*	*Late*	*Early*	*Late*
ACME[1]	64 vs. 46%* free of angina at 6 months	62 vs. 47%* free of angina at 3 years	11.2 vs. 9.5 min* exercise time duration at 6 months	10.0 vs. 8.5 min* exercise time duration at 3 years	30 vs. 50% on beta-blocker*, 35 vs. 71% on CCB*, and 24 vs. 50% on nitrate* at 6 months	28 vs. 39% on beta-blocker, 47 vs. 72% on CCB*, and 24 vs. 52% on nitrate* at 3 years
RITA-2[2]	19.4 vs. 35.9%* at 3 months	15.0 vs. 21.4%* at 5 years	37 s in favour of PCI* at 3 months	25 s in favour of PCI* at 3 years	37 vs. 57% on ≥2 drugs at 3 months	31 vs. 45% on ≥2 drugs at 5 years
AVERT[3]	Improvement in angina 54 vs. 41%* at 1.5 years	–	–	–	61 vs. 60% on beta-blocker, 44 vs. 49% on CCB, and 50 vs. 60% on nitrate at 1.5 years	–
TIME[4]	Significant improvement in angina class at 6 months	No differences in angina class at 1 year	–	–	Significant reduction of number of drugs at 6 months	Significant reduction of number of drugs at 1 year
MASS II[5]	21 (PCI) vs. 12 (CABG) vs. 54% (MT) free of angina* at 1 year	41 (PCI) vs. 36 (CABG) vs. 57% (MT) free of angina* at 10 years	–	–	–	–
SWISSI II[6]	–	–	Max workload at bicycle ergometry 169 vs. 148 W* at 4 years	Max workload at bicycle ergometry 173 vs. 136 W* at 10 years	49 vs. 86% on beta-blocker*, 21 vs. 51% on CCB*, and 12 vs. 47% on nitrate* at 4 years	39 vs. 84% on beta-blocker*, 17 vs. 32% on CCB, and 4 vs. 45% on nitrate* at 10 years
COURAGE[7]	56 vs. 47%* free of angina at 6 months	59 vs. 56% free of angina at 3 years	–	–	85 vs. 89% on beta-blocker, 40 vs. 49% on CCB*, and 53 vs. 67% on nitrate* at 1 year	85 vs. 86% on beta-blocker, 42 vs. 52% on CCB*, and 40 vs. 57% on nitrate* at 5 years
FAME II[8]	91 vs. 80%* free of angina (CCS II–IV) at 6 months	94 vs. 88%* free of angina (CCS II–IV) at 2 years	–	–	81% vs. 82 on beta-blocker and 25 vs. 30% on CCB at 6 months	77 vs. 80% on beta-blocker and 30 vs. 32% on CCB* at 2 years
ORBITA[9]	51% vs. 45% improvement by at least 1 CCS class at 6 weeks	–	Difference in increment of 16.6 s in favour of PCI at 6 weeks	–	2.9 anginal medications in both arms at 6 weeks	–

*P <0.05.
CABG = coronary artery bypass grafting; CCB = calcium-channel blocker; CCS = Canadian Cardiovascular Society; MT = medical therapy; PCI = percutaneous coronary intervention; W = watts.

Supplementary Table 2 **Revascularization vs. medical therapy: study, baseline characteristics, primary endpoint, maximum clinical follow-up**

Year of publication	Study	*n*	Baseline characteristics					Primary endpoint			Maximum clinical follow-up			
			Age (y)	Women (%)	Diabetes (%)	MVD (%)	EF (%)	Definition	Years	Results	Years	Death	MI	Revascularization
CABG vs. MT														
1980	ECSS	768	<65[b]	0	–	100	>50[b]	–	–	–	8	11.4 vs. 20.1%*	–	–
1984	VA	686	–	–	–	86	–	–	–	–	18	70 vs. 67%	49 vs. 41%	41 vs. 62%[c]
1984	CASS	780	51	10	9	73	–	–	–	–	10	19.2 vs. 21.8%	–	8.9 vs. 36.9%[d]
2011/2016	STICH	1212	60	12	39	91	27	Death	4.7	36 vs. 41%	9.8	58.9 vs. 66.1%*	–	–
PTCA vs. MT														
1997	RITA-2	1018	–	18	9	40	–	Death or MI	2.7	6.3 vs. 3.3%*	7	8.5 vs. 8.4%	6.3 vs. 4.5%[c]	27.2 vs. 35.4%[c]
1999	AVERT	341	58	16	16	43	61	Cardiac death, cardiac arrest, MI, CVA, revascularization, or hospitalization due to angina	1.5	20.9 vs. 13.4%*	1.5	0.6 vs. 0.6%[a]	2.8 vs. 2.4%[c]	16 vs. 12%[c]
2003	ALKK	300	58	13	16	0	–	MI, revascularization, or rehospitalization for severe angina	1	10 vs. 18%	4.7	4.0 vs. 11.2%*	6.7 vs. 7.9%	17 vs. 24%
2007	SWISSI-II	201	55	12	11	–	57	Cardiac death, MI, or revascularization	10.2	28.1 vs. 63.8%*	10.2	6.3 vs. 21.0%*	11.5 vs. 38.1%*	27.1 vs. 43.8%*

Continued

BMS/CABG vs. MT														
2001	TIME	305	80	43	23	79	53	Death, MI, or hospitalization for ACS	0.5	19.0 vs. 49.3%*	1	11.1 vs. 8.1%	–	–
2007	MASS-II	611	60	31	29	100	67	Cardiac death, MI, or revascularization	1	6.4 (CABG) vs. 24.4 (BMS) vs. 14.3% (MT)*	10	25.1 (CABG) vs. 24.9 (PCI) vs. 31% (MT)	10.3 (CABG) vs. 13.3 (PCI) vs. 20.7% (MT)*	7.4 (CABG) vs. 41.9 (PCI) vs. 39.4% (MT)*
BMS vs. MT														
2006	OAT	2166	59	22	21	18	48	Death, MI, or NYHA class IV heart failure	4	17.2 vs. 15.6%	4	9.1 vs. 9.4%	6.9 vs. 5.0%	18.4 vs. 22.0%*
2007	COURAGE	2287	62	15	33	69	61	Death or MI	4.6	19.0 vs. 18.5%	4.6	7.6 vs. 8.3%	13.2 vs. 12.3%	21.1 vs. 32.6%*
2008	JSAP	384	64	26	40	32	65	Death, ACS, CVA, or emergency hospitalization	3.3	22.0 vs. 33.2%*	3.3	2.9 vs. 3.9%	1.6 vs. 3.8%	21.4 vs. 36.5%*
DES vs. MT														
2012/2014	FAME-2	888	64	22	27	42	–	Death, MI, or urgent revascularization	1	4.3 vs. 12.7%*	1	1.3 vs. 1.8%	5.8 vs. 6.8%	8.1 vs. 40.6%*

Age and ejection fraction are reported as means. *P <0.05.
ACS = acute coronary syndrome; BMS = bare-metal stents; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; DES = drug-eluting stents; EF = left ventricular ejection fraction; MI = myocardial infarction; MT = medical therapy; MVD = multivessel coronary artery disease; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty.
[a]Cardiac death.
[b]Inclusion criteria.
[c]No statistical analyses performed.
[d]Repeat CABG, excluding PTCA.

Supplementary Table 3 **Percutaneous vs. surgical revascularization: study, baseline characteristics, primary endpoint, maximum clinical follow-up**

Year of publication	Study	*n*	Baseline characteristics					Primary endpoint			Max clinical follow-up				
			Age (y)	Women (%)	Diabetes (%)	MVD (%)	EF (%)	Definition	Years	Results	Years	Death	MI	Revascularization	Stroke
PTCA															
1993	RITA-I	1011	–	19	6	55	–	Death or MI	2.5	9.8 vs. 8.6%	6.5	7.6 vs. 9.0%	10.8 vs. 7.4%	44.3 vs. 10.8%*	1.8 vs. 2.0% (at 2.5 years)
1994	GABI	359	–	20	12	100	–	Angina	1	29 vs. 26%	13	25.0 vs. 21.9%	4.3 vs. 5.6%	82.9 vs. 58.8%*	–
1994	EAST	392	62	26	23	100	61	Death, MI, or a large defect at thallium scan	3	28.8 vs. 27.3%	8	20.7 vs. 17.3%	3.0 vs. 10.3%* (at 3 year)	65.3 vs. 26.5%*	0.5 vs. 1.5% (at 3 years)
1995	CABRI	1054	60	22	12	99	63	Death	1	3.9 vs. 2.7%	4	10.9 vs. 7.4%	4.9 vs. 3.5% (at 1 year)	33.6 vs. 6.5%* (at 1 year)	–
1996	BARI	1829	62	27	25	100	57	Death	5	13.7 vs. 10.7%	10	29.0 vs. 26.5%	–	76.8 vs. 20.3%*	0.2 vs. 0.8% (in hospital)
BMS															
2001	AWESOME	454	67	–	31	82	45	Death	3	20 vs. 21%	3	20 vs. 21%	–	–	–
2001	ERACI II	450	62	21	17	100	–	Death, MI, stroke, or repeat revascularization	0.1	3.6 vs. 12.3%*	5	7.1 vs. 11.5%	2.8 vs. 6.2%	28.4 vs. 7.2%*	0 vs. 0.9% (at 30 days)
2001	ARTS	1205	61	23	17	99	61	Death, MI, stroke, or repeat revascularization	1	26.2 vs. 12.2%*	5	8.0 vs. 7.6%	6.7 vs. 5.6%	30.3 vs. 8.8%*	3.8 vs. 3.5%
2002	SoS	988	61	21	14	100	57	Repeat revascularization	2	21 vs. 6%*	6	10.9 vs. 6.8%*	5 vs. 8% (at 2 years)	21 vs. 6%* (at 2 years)	–
2003	OCTOSTENT	280	60	29	11	29	–	Death, MI, stroke, or repeat revascularization	1	14.5 vs. 8.5%	1	0 vs. 2.8%	4.4 vs. 4.9%	15.2 vs. 4.2%*	0 vs. 0%
2005	Thiele	220	62	25	30	0	63	Cardiac death, MI, or TVR	0.5	31 vs. 15%*	5.6	10 vs. 12%	5 vs. 7%	32 vs. 10%* (TVR)	–

Age and ejection fraction are reported as means. *P <0.05.
BMS = bare-metal stents; EF = ejection fraction; MI = myocardial infarction; MVD = multivessel coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty; TVR = target vessel revascularization.

Supplementary Table 4 Scoring systems used in conjunction with myocardial revascularization

Score	Purpose	URL
Outcomes after myocardial revascularization or ACS		
EuroSCORE II	Prediction of in-hospital mortality	www.euroscore.org
STS	Prediction of in-hospital or 30-day mortality, and in-hospital morbidity	www.sts.org
SYNTAX	Prediction of medium- and long-term MACCE after PCI	www.syntaxscore.com
SYNTAX II	Prediction of mortality after CABG or PCI	www.syntaxscore.com
GRACE	Prediction of death or death/myocardial infarction following ACS	www.gracescore.org
DAPT treatment duration		
PRECISE-DAPT	To determine short (3–6 months) vs. standard/long (12–24 months) DAPT duration at the time of coronary stenting	www.precisedaptscore.com
DAPT	To determine standard DAPT (12 months) vs. long DAPT (30 months) after 12 months of uneventful DAPT	www.daptstudy.org
Embolic and bleeding risk prediction		
CHA_2DS_2-VASc	Prediction of stroke risk in patients with atrial fibrillation (relevant in a setting of PCI to determine the indication for OAC)	www.chadsvasc.org
HAS-BLED	Prediction of bleeding risk, e.g. in a setting of DAPT and OAC (triple treatment)	www.chadsvasc.org
ABC	Prediction of bleeding risk, e.g. in a setting of DAPT and OAC (triple treatment)	www.ucr.uu.se/en/services/abc-risk-calculators
Frailty		
Clinical Frailty Score	To assess frailty as a predictor of death and length of hospital stay	http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm

ABC = Age, Biomarkers, Clinical History; ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 and Sex category (Female); DAPT = dual antiplatelet treatment; GRACE = Global Registry of Acute Coronary Events; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol; MACCE = major adverse cardiovascular events; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STS = Society of Thoracic Surgeons; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

Supplementary Table 5 **Randomized trials on revascularization in diabetic patients**

Year of publication	Study	*n*	Baseline characteristics				Primary endpoint			Max clinical follow-up					
			Age (y)	Women (%)	MVD (%)	EF (%)	Definition	Years	Results	Years	Death	CV death	MI	Revascularization	Stroke
Revascularization vs. MT															
2009	BARI-2D[10]	2368	62	30	31[a]	57	Death	5	11.7 vs. 12.2%	5	11.7 vs. 12.2%	5.9 vs. 5.7%	11.5 vs. 14.3%	–	2.6 vs. 2.8%
CABG vs. MT															
2009	BARI-2D[b] [10]	763	63	24	52[a]	57	Death	5	13.6 vs. 16.4%	5	13.6 vs. 16.4%	8.0 vs. 9.0%	10.0 vs. 17.6%*	–	1.9 vs. 2.6%
PCI vs. MT															
2009	BARI-2D[b] [10]	1605	62	33	20[a]	57	Death	5	10.8 vs. 10.2%	5	10.8 vs. 10.2%	5.0 vs. 4.2%	12.3 vs. 12.6%	–	2.9 vs. 2.9%
PCI vs. CABG															
2009	SYNTAX[c] [11]	452	65	29	100	–	Death, MI, stroke, or repeat revascularization	1	26.0 vs. 14.2%* Sx-Sc 0-22: 20.3 vs. 18.3%; 23-32: 26.0 vs. 12.9%; ≥33: 32.4 vs. 12.2%*	5	19.5 vs. 12.9%	12.7 vs. 6.5%*	9.0 vs. 5.4%	35.3% vs. 14.6%*	3.0 vs. 4.7%
2010	CARDia[12] (DES/BMS vs. CABG)	510	64	26	93	–	Death, MI, or stroke	1	13.0 vs. 10.5%	1	3.2 vs. 3.2%	–	9.8 vs. 5.7%	11.8% vs. 2.0%*	0.4 vs. 2.8%
2012	FREEDOM[13] (DES vs. CABG)	1900	63	29	100	66	Death, MI, or stroke	3.8	26.6 vs. 18.7%* Sx-Sc 0-22: 23 vs. 17%;23-32: 27 vs. 18%*; ≥33: 31 vs. 23%	3.8	16.3 vs. 10.9%*	10.9 vs. 6.8%	13.9 vs. 6.0%*	12.6% vs. 4.8%* (at 1 year)	2.4 vs. 5.2%*
2013	VA-CARDS[14] (DES vs. CABG)	207	62	1	–	–	Death or MI	2	25.3 vs. 18.4%	2	21 vs. 5.0%*	10.8 vs. 5.0%	6.2 vs. 15.0%	18.9% vs. 19.5%	1.0 vs. 1.2%

Age and ejection fraction are reported as means. *P <0.05.
BMS = bare-metal stents; CABG = coronary artery bypass grafting; DES = drug-eluting stents; EF = ejection fraction; MI = myocardial infarction; MVD = multivessel coronary artery disease; MT = medical therapy; PCI = percutaneous coronary interventions; Sx-Sc = SYNTAX score
[a]Three-vessel disease.
[b]Randomization stratified by revascularization modality.
[c]Subgroup analysis.

Supplementary Table 6 CE-approved new-generation drug-eluting stents recommended for clinical use based on randomized trials with a primary clinical endpoint (in alphabetical order)

DES	Stent platform	Polymer coating	Drug	References
Based on durable polymer coatings				
Promus element	Platinum–chrome	PBMA and PVDF-HFP	Everolimus	15,16
Resolute	Cobalt–chrome	PBMA, PHMA, PVP, and PVA	Zotarolimus	16–18
Xience	Cobalt–chrome	PBMA and PVDF-HFP	Everolimus	19–21
EluNIR (BioNIR)	Cobalt–chrome	PBMA and TSPCU	Ridaforolimus	22
Based on biodegradable polymer coatings				
Biomatrix	Stainless steel	PDLLA	Biolimus A9	23,24
Nobori	Stainless steel	PDLLA	Biolimus A9	25–27
Orsiro	Cobalt–chrome	PLLA	Sirolimus	28,29
Synergy	Platinum–chrome	PLGA	Everolimus	29
Ultimaster	Stainless steel	PDLLA/PCL	Sirolimus	30
Yukon Choice PC	Stainless steel	PDLLA	Sirolimus	31
Polymer-free				
BioFreedom	Stainless steel	–	Biolimus A9	32
Yukon Choice PF	Stainless steel	–	Sirolimus	33

DES = drug-eluting stent; PBMA = poly n-butyl methacrylate; PC = polymer-coated; PDLLA = poly(D,L)-lactic acid; PDLLA/PCL = poly (D,L)-lactide-co-caprolactone; PF = polymer-free; PHMA = polyhexyl methacrylate; PLGA = poly(d,l-lactide-*co*-glycolide); PLLA = poly-L-lactic acid; PVA = polyvinyl acetate; PVDF-HFP = poly(vinylidene fluoride-cohexafluoropropylene); PVP = polyvinyl pyrrolidone; TSPCU = thermoplastic silicone-polycarbonate-urethane.

Supplementary Table 7 **Overview of CE-marked bioresorbable scaffolds**

Commercial name	Manufacturer	Backbone material	Coating material	Device thickness	Drug release	Drug load	Duration of drug release	Bioresorption in pre-clinical swine models	Year of CE-mark	Year of FDA approval	Year of PMDA (Japan) approval
ABSORB BVS 1.1	Abbott Vascular	PLLA	PDLLA	156 μm	Everolimus	76–308 μg/ stent	3 months	36 months	2011	2016	2016
DESolve (+ DESolve 100/ DESolve Cx/ DESolve NXT)	Elixir Medical	PLLA	PLLA	100–150 μm	Novolimus	NA	3 months	24 months	2014	NA	NA
ART Pure	ART	PDLLA	NA	170 μm	No drug elution	NA	NA	24 months	2015	NA	NA
Magmaris	Biotronik	Magnesium alloy	PLLA	150 μm	Sirolimus	1.4 μg/mm^2	3 months	9 - 12 months	2016	NA	NA
Fantom	Reva	PTD-PC	PTD-PC	125 μm	Sirolimus	115 μg	NA	<3 years	2017	NA	NA

BVS = bioresorbable vascular scaffold; FDA = US Food and Drug Administration; NA = not available; PDLLA = poly(D,L)-lactic acid; PLLA = poly-L-lactic acid; PMDA = Pharmaceuticals and Medical Devices Agency; PTD-PC = poly-tyrosine-derived polycarbonate.

Supplementary Table 8 CE-approved drug-coated balloons (in alphabetical order)

Device	Carrier	Drug	References
Agent	ATBC	Paclitaxel	
Angiosculpt	NDGA	Paclitaxel	–
Danubio	BTHC	Paclitaxel	–
Dior II	Shellac	Paclitaxel	34,35
Elutax	–	Paclitaxel	36
IN.PACT Falcon	Urea	Paclitaxel	37
MagicTouch	Phospholipid-based	Sirolimus	
Moxy	Polysorbate	Paclitaxel	38
Pantera Lux	BTHC	Paclitaxel	39
Protégé NC	BTHC	Paclitaxel	–
SeQuent Please	Iopromide	Paclitaxel	40–44

ATBC = acetyl tributyl citrate; BTHC = butyryl-tri-hexyl citrate; NDGA = nordihydroguaiaretic acid.

Supplementary Table 9 Quality indicators for coronary artery bypass grafting

Pre-operative
Beta-blocker therapy
Operative technique
Percentage of internal mammary artery use
Selection and duration of antibiotic prophylaxis
Post-operative outcome rates
Death
Stroke
Renal failure requiring dialysis
Re-exploration for bleeding
Re-intervention for graft failure
Prolonged intubation time >24 h
Deep sternal wound infection requiring sternal reconstruction
Discharge
Antiplatelet medication prescription
High-dose lipid-lowering treatment prescription
Adherence to guideline-recommended discharge medications depending on clinical setting
Follow-up
Readmission rates at 90 days
30 day and 1 year mortality
Unplanned repeat revascularization at 1 year

Reference: http://www.sts.org/quality-safety/performance-measures (accessed 4 February 2018).

Supplementary Table 10 Quality Indicators for percutaneous coronary intervention

Pre-interventional
Adherence to guideline-recommended pre-treatment
Interventional technique
Procedural success
Percentage of radial arterial access
Percentage of drug-eluting stent implantation
Peri-interventional outcome rates
Death
Periprocedural myocardial infarction
Stroke
Contrast-induced nephropathy
Major bleeding (BARC 3 - 5)
Emergency coronary artery bypass surgery
Discharge
Antiplatelet medication prescription
High-dose lipid lowering treatment prescription
Adherence to guideline-recommended discharge medications depending on clinical setting
Follow-up
Readmission rates
30 day and 1 year mortality
Unplanned repeat revascularization at 1 year
Stent thrombosis according to ARC criteria
Major bleeding (BARC 3 - 5)
Composite of all-cause death, any myocardial infarction, and any unplanned repeat revascularization at 1 year

ARC = Academic Research Consortium; BARC = Bleeding Academic Research Consortium.

Supplementary Table 11 Antithrombotic drug dose adjustment in patients with chronic kidney disease

	Normal kidney function or stage 1–2 CKD (≥60 mL/min/1.73m^2)	Stage 3 CKD (≥30–59 mL/min/1.73m^2)	Stage 4 CKD (15–29 mL/min/1.73m^2)	Stage 5 CKD (<15 mL/min/1.73m^2)
ASA	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Clopidogrel	No dose adjustment	No dose adjustment	No dose adjustment	Use only for selected indications (e.g. stent thrombosis prevention)
Prasugrel	No dose adjustment	No dose adjustment	No dose adjustment	Not recommended
Ticagrelor	No dose adjustment	No dose adjustment	No dose adjustment	Not recommended
Cangrelor	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Enoxaparin	1 mg/kg s.c. twice a day		1 mg/kg s.c. once a day; monitor anti- factor-Xa activity	Not recommended
Unfractionated heparin	• Prior to coronary angiography: 60–70 IU/kg i.v. (max 5000 IU) and infusion 12–15 IU/kg/h (max 1000 IU/h), target aPTT 1.5–2.5× control • During PCI: according to ACT or 70–1000 IU/kg i.v. in patients not anticoagulated (50–70 IU/kg if concomitant with GP IIb/IIIa inhibitors)		No dose adjustment	No dose adjustment
Fondaparinux	2.5 mg s.c. once a day	1.5 mg s.c. once a day	Not recommended if eGFR <20 mL/min/1.73m^2)	Not recommended
Bivalirudin	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/h	Bolus 0.75 mg/kg i.v., infusion 1.4 mg/kg/h	Not recommended	Not recommended
Abciximab	Bolus 0.25 mg/kg i.v., infusion rate 0.125 µg/kg/min (maximum 10 µg/min)	No specific recommendations for the use of abciximab, or for dose adjustment in the case of renal failure; careful evaluation of haemorrhagic risk is needed		
Eptifibatide	Bolus 180 µg/kg i.v., infusion rate 2 µg/kg/min	No adjustment of bolus, reduce infusion rate to 1 µg/kg/min if eGFR <50 mL/min/1.73m^2	Not recommended	Not recommended
Tirofiban	Bolus 25 µg/kg or 10 µg/kg i.v., infusion rate 0.15 µg/kg/min	No dose adjustment	No adjustment of bolus, reduce infusion rate to 0.05 µg/kg/min	Not recommended

aPTT = activated partial thromboplastin time; ACT = activated clotting time; ASA = acetylsalicylic acid (aspirin); CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; s.c. = subcutaneous.

Supplement to chapter 7: revascularization in ST-segment elevation myocardial infarction

Studies on the revascularization strategy in patients presenting with ST-elevation myocardial infarction and multivessel disease

In the PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) trial (n = 465), preventive PCI in the non-IRA with stenosis ≥50% during the index PCI, when compared with PCI limited to the IRA, was associated with a reduced risk of the composite of death, MI, or refractory angina (HR in the preventive PCI group 0.35, 95% CI 0.21–0.58, P <0.001).[45] CvLPRIT (Complete Versus Lesion-Only Primary PCI Trial) randomized 296 STEMI patients with multivessel disease into either in-hospital complete revascularization (simultaneous or staged) or IRA-only revascularization.[46] The primary endpoint-a composite of all-cause death, recurrent MI, HF, and ischaemia-driven revascularization within 12 months-occurred in 10.0% of the complete revascularization group vs. 21.2% in the IRA-only revascularization group (HR 0.45, 95% CI 0.24–0.84, P = 0.009).

The DANAMI-3-PRIMULTI study allocated 627 patients after successful IRA PCI to either no further invasive treatment or complete FFR-guided revascularization of the non-IRA before discharge. The primary endpoint of all-cause mortality, non-fatal MI, and ischaemia-driven revascularization of lesions in the non-IRA at median follow-up of 27 months occurred in 68 (22%) patients who had IRA PCI only and in 40 (13%) patients who had complete revascularization (HR 0.56, 95% CI 0.38–0.83; P = 0.004).[47] The benefit was driven by a reduction in repeat revascularization.

The Compare-Acute trial randomized 885 patients with STEMI and multivessel disease undergoing primary PCI to either complete revascularization of the non-IRA (guided by FFR) or no revascularization of the non-IRA.[48] The main finding was a reduction in the primary endpoint incidence (death, MI, revascularization, or stroke) (HR 0.35, 95% CI 0.22–0.55; P <0.001), with multivessel PCI driven mainly by a reduction in the need for revascularization at a later time point by non-IRA FFR-guided revascularization. However, it might also be observed that the overall rate of revascularization was considerably higher in the complete revascularization group.

Revascularization strategy in patients with myocardial infarction and cardiogenic shock

One-year data from the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial (n = 302) showed a significant advantage of early revascularization over medical therapy among patients younger than 75.[49] A subanalysis comparing CABG to PCI revealed similar survival rates between the two subgroups despite the fact that CABG was more often performed in patients with advanced, multivessel disease including LM disease, while patients with one- or two-vessel disease prevailed in the PCI arm.[50]

The SHOCK registry demonstrated that emergency revascularization with PCI or CABG improved long-term survival when compared with initial intensive medical therapy.[51,52] All-cause mortality at 6 months was lower in the group assigned to revascularization than in the medically treated patients (50.3 vs. 63.1%, respectively; RR 0.80, 95% CI 0.65–0.98; P < 0.03). The findings of this non-randomized comparison suggest that CABG should be considered in patients with cardiogenic shock who have suitable anatomy, particularly if successful PCI is not feasible. A recent analysis of the Korean Acute Myocardial Infarction Registry (16 620 STEMI patients) suggested that multivessel revascularization at the time of primary PCI was associated with better outcomes in patients with STEMI and cardiogenic shock compared with culprit vessel revascularization only.[53] These studies suggested that multivessel PCI should be considered in STEMI patients with cardiogenic shock.

In the CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial, patients with STEMI or non-ST-segment elevation myocardial infarction (NSTEMI) with cardiogenic shock were randomized to culprit lesion-only PCI or immediate PCI of all obstructive lesions (i.e. those with >70% stenosis of the diameter). In the multivessel PCI group, recanalization of chronic total occlusions was performed when possible, and complete revascularization was achieved in 81% of patients. Staged revascularization was performed in 17.7% of the patients in the culprit lesion-only PCI group, and the crossover rate was relatively low (12.5% in the culprit lesion-only PCI group and 9.4% in the multivessel PCI group). The primary endpoint of death or severe renal failure leading to renal replacement therapy was higher with immediate multivessel PCI than with culprit lesion-only PCI. The results were similar for death from any cause (RR 0.84, 95% CI 0.72–0.98, P = 0.03) and were consistent across pre-specified subgroups, including subgroups defined according to the presence or absence of a chronic total occlusion.

The CULPRIT-SHOCK trial used modern PCI technique and periprocedural management, and provides clear evidence that a strategy of culprit lesion-only PCI is preferred over initial multivessel PCI for patients with cardiogenic shock. Multivessel PCI should not be performed on a routine basis but may be considered in some patients, e.g. if there is uncertainty in identifying the culprit lesion.

Supplement to chapter 10: revascularization in patients with chronic kidney disease

Prevention of contrast-induced nephropathy

The risk of CIN depends on patient-related factors, such as CKD, diabetes mellitus, congestive HF, haemodynamic instability, reduced plasma volume, female sex, advanced age, and anaemia, as well as on the type and volume of contrast administered.[54,55] As compared with high-osmolar contrast agents, low- or iso-osmolar contrast agents reduce the risk of CIN.[56–58] The preference for iso- over low-osmolar contrast agents, suggested by an initial small study,[56] could not be confirmed subsequently.[59] When the ratio of total contrast volume to GFR exceeds 3.7, the risk of CIN increases significantly.[60,61] Performing diagnostic and interventional procedures separately reduces the total volume exposure to contrast media. On the other hand, the risk of renal atheroembolic disease increases with multiple catheterizations. Therefore, in CKD patients with diffuse atherosclerosis, a single invasive approach (diagnostic angiography followed by *ad hoc* PCI) may be considered if the contrast volume can be maintained at <4 mL/kg.

It is generally recommended that all patients with CKD who undergo catheterization should receive preventive hydration with isotonic saline.[62] Nevertheless, this recommendation is based on

limited data on the comparison of isotonic saline with hypotonic saline[63] or with sodium bicarbonate.[64,65] However, no randomized trial until recently had compared intravenous pre-hydration with no prophylaxis. Moreover, the superiority of isotonic saline over sodium bicarbonate seen in the initial studies did not prevail in a recent meta-analysis.[66] Likewise, in the contemporary AMACING (A Maastricht Contrast-Induced Nephropathy Guideline) randomized trial, intravenous 0.9% sodium chloride was directly compared with no prophylaxis in 660 patients with an estimated GFR of 30–59 mL/min/1.73 m^2 undergoing an elective procedure requiring iodinated contrast material.[67] Within 2 - 6 days after contrast exposure, no prophylaxis was non-inferior to intravenous hydration for the prevention of CIN and cost-saving. These findings need to be interpreted with consideration of the single-centre design of the trial and the relatively small sample size of the low-risk cohort.[67]

Given the known impact of low effective circulating volumes on the risk of CIN, there is still consensus that adequate hydration is needed to prevent CIN. Based on previous experience,[64,65,68] preventive hydration with isotonic saline should be started in patients at increased risk approximately 12 h before angiography and continued for at least 24 h afterwards to reduce the risk of CIN, especially if GFR is <40 mL/min/1.73 m^2. The optimal duration of the infusion therapy is not fully known. Recently, promising results were obtained by adjusting the infusion rate to central venous pressure.[69] Two targeted hydration regimens starting shortly before catheterization have shown superiority over conventional hydration schemes.[70,71] In the POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) study, patients with CKD stage 3 were randomly assigned to infusion rates adjusted to LV end-diastolic pressure or to standard infusion rates.[70] CIN occurred less frequently in patients of the targeted hydration group (6.7%) than in the control group (16.3%; RR 0.41, 95% CI 0.22–0.79, $P = 0.005$). Similarly in a high-risk group of patients with CKD, the REMEDIAL II (Renal Insufficiency After Contrast Media Administration II) trial showed that a strategy of controlled hydration with forced diuresis and matched saline infusion using an automated system was superior to the control group [incidence of CIN 11 vs. 20.5%; odds ratio (OR) 0.47, 95% CI 0.24–0.92).[71] The findings of REMEDIAL II were confirmed in a recent meta-analysis including three additional studies.[72] Thus, in specific patient subsets, the targeted hydration regimens represent a valuable alternative to standard hydration.

Apart from adequate hydration, several preventative strategies for CIN have been tested in a number of studies with inconsistent results, as reviewed by several meta-analyses.[66,68,73] In a recent hierarchical Bayesian network meta-analysis of 124 trials and 28 240 patients undergoing cardiac catheterization,[66] only high-dose statins showed an unequivocal beneficial effect that-according to another meta-analysis-appeared to be independent of the concomitant hydration protocol.[74] Although theophylline, N-acetylcysteine (NAC), sodium bicarbonate, peripheral ischaemic pre-conditioning, and natriuretic peptide also showed some benefit over saline alone in the overall analysis, these findings were highly heterogeneous across studies and did not prevail in sensitivity analyses.[66] None of the apparent benefits were detectable in diabetics and some (theophylline and sodium bicarbonate) were mitigated in patients with CKD stage 3 or 4.[66] The results were confounded by publication bias, the inclusion of trials with lower methodological quality, and suboptimal posology.[66] More recently, the PRESERVE (Prevention of Serious Adverse Events Following Angiography) trial tested the efficacy of intravenous sodium bicarbonate or oral acetylcysteine in preventing CIN.[75] This randomized controlled trial included 5177 patients at high risk for renal complications who were scheduled for angiography. Using a two-by-two factorial design, PRESERVE did not show any benefit of intravenous sodium bicarbonate over intravenous sodium chloride, or of oral acetylcysteine over placebo, for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days.

In summary, adequate hydration remains the mainstay of CIN prevention. High-dose statins are also beneficial. Since they are indicated for secondary prevention in patients undergoing coronary revascularization irrespective of the risk of CIN, no specific recommendation for CIN is needed. All other strategies for the prevention of CIN do not have sufficient evidence to justify a recommendation in favour or against.

For patients undergoing CABG, the effectiveness of the implementation of pharmacological preventive measures—such as clonidine, fenoldopam, natriuretic peptides, NAC, or elective pre-operative haemodialysis—remains unproven.

Supplement to chapter 11: revascularization in patients requiring valve interventions

Surgical repair of secondary mitral regurgitation in patients undergoing coronary artery bypass grafting

Controversy exists regarding the definition of 'moderate' MR used in the CTSN trial. In the CTSN trial, the integrative approach for the classification of MR, inclusive of an EROA of 0.2–0.39 cm^2, as described by the American Society of Echocardiography (ASE), was used to define moderate MR. However, both the ASE and European Association for Cardiovascular Imaging Guidelines for valvular regurgitation acknowledge that in ischaemic MR (IMR), an EROA of >0.2 cm^2 and a regurgitant volume of >30 mL indicates a worse prognosis and greater risk of cardiovascular events.[76,77] The 2017 ESC/EACTS Guidelines for the management of valvular heart disease define an EROA of >0.2 cm^2 and a regurgitant volume of >30 mL as the cut-off for severe secondary MR.[78] Furthermore, due to several screening failures in the early phase of the CTSN trial, thought to be due to overly restrictive EROA, the criteria were broadened to include patients with EROA <0.2 cm^2 and other integrative criteria of more than mild MR.[79] In summary therefore, the CTSN trial on moderate IMR included patients with IMR defined by EROA <0.4 cm^2, and did not demonstrate an improvement in outcomes with surgical correction of secondary MR in combination with CABG compared with CABG alone. While this is not consistent with current Guidelines on the classification of IMR as described above, the main value of the reduced threshold for severe IMR is based on prognostic outcomes of patients with EROA >0.2 cm^2. The use of this classification in guiding treatment would present challenges with either leaving clinically significant IMR (EROA >0.4 cm^2) untreated or the over-treatment of patients with EROA <0.4 cm^2, where the addition of mitral repair has not been shown to improve outcomes.

The dynamic nature of IMR also needs consideration and stress echo may be used to guide treatment, although no robust evidence is

available to guide this recommendation. Ultimately, IMR remains a complex area with unanswered questions despite several randomized trials. The present Guidelines express the expert opinion and consensus of the Task Force, and are also in keeping with the valvular heart disease Guidelines. Treatment decisions should be made in the context of the Heart Team taking into account the severity of MR, comorbidities, symptoms, LV and LA size, the viability of revascularized myocardium, completeness of revascularization, tenting area, and coaptation height. Additionally, with the advent of rapidly advancing techniques for transcatheter mitral valve repair/replacement and mitral annuloplasty, a Heart Team discussion on the feasibility of future transcatheter treatment options in patients undergoing myocardial revascularization may be used as a guide to decision-making.

Supplement to chapter 16: procedural aspects of percutaneous coronary intervention

Studies on the Absorb bioresorbable vascular scaffold

Primary endpoint results from the ABSORB II (A Bioresorbable Everolimus-Eluting Scaffold Versus a Metallic Everolimus-Eluting Stent II) trial failed to demonstrate superiority of the Absorb BVS (bioresorbable vascular scaffold) vs. conventional DES in terms of vasomotor response to intracoronary nitrate in the stented segment at 3 years.[80] Moreover, the co-primary endpoint late lumen loss was inferior with BVS and there was no difference in terms of patient-reported angina symptoms. There was a significant increase in the device-oriented composite endpoint of cardiac death, target vessel MI, and clinically indicated target lesion revascularization (TLR) with BRS compared with DES (10.4 vs. 4.9%; $P = 0.043$), which was driven by a significant difference in target vessel MI (6 vs. 1%; $P = 0.011$) and in definite or probable device thrombosis (3 vs. 0%; $P = 0.033$). This excess in late adverse clinical events was also seen in the 2 year results of the ABSORB III and ABSORB Japan trial.[81]

ABSORB IV, the largest available trial on BRS, which applied a dedicated technique for BRS implantation, showed inferior procedural outcomes with BRS as compared with EES. The ABSORB IV demonstrated the non-inferiority of BRS as compared with EES for the primary endpoint target lesion failure (a composite of cardiac death, MI, and ischaemia-driven TLR) at 30 days (HR 1.36, 95% CI 0.93–1.97, $P_{\text{non-inferiority}} = 0.02$). Device thrombosis tended to be higher with BRS than EES at 30 days (HR 4.05, 95% CI 0.86–19.07; $P = 0.06$).

The AIDA (Amsterdam Investigator-Initiated Absorb Strategy All-Comers) investigator-initiated trial[82] enrolled relatively unselected patients undergoing intervention in routine practice including patients with ACS. The trial intended to test the non-inferiority of BRS vs. EES at 2 years. However, during follow-up and after full enrolment, the data and safety monitoring board of the trial recommended early reporting due to safety concerns. At the time of reporting, the median duration of follow-up was 707 days. The primary endpoint—a composite of cardiac death, target vessel MI, or TVR—was similar in both groups (11.7 vs. 10.7%; HR 1.12, 95% CI 0.85–1.48, $P = 0.43$). Definite/probable stent thrombosis was significantly higher in the BRS treatment group (3.5 vs. 0.9%; $P < 0.001$).

Meta-analyses including mid- to long-term follow-up of randomized trials of Absorb BRS vs. conventional DES showed that the risk of adverse events beyond 1 year is also significantly increased with BRS.[83–86]

A recently published individual patient data pooled analysis of 3389 patients from four randomized trials on BRS vs. EES (ABSORB II, ABSORB III, ABSORB China, and ABSORB Japan) showed a higher risk of target lesion failure (a composite of cardiac death, MI, and ischaemia-driven TLR) with BRS as compared with EES at 3 years. This difference was the result of inferior effectiveness (ischaemia-driven TLR; HR 1.46, 95% CI 1.06–2.02) and inferior safety (device thrombosis; HR 3.79, 95% CI 1.72–8.36) with BRS compared with EES at 3 years of follow-up.[83]

Supplement to chapter 17: antithrombotic treatments

TRITON-TIMI 38: NSTEMI and STEMI patients

Prasugrel, a third-generation thienopyridine, is a pro-drug that irreversibly inhibits the $P2Y_{12}$ receptor on blood platelets. The drug, administered at a 60 mg loading dose and a 5/10 mg maintenance dose, shows fast and predictable platelet inhibition.[87] Prasugrel was tested against clopidogrel in the TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction 38) study.[88] In the entire trial cohort[88] ($n = 13\,608$) and specifically for the 10 074 NSTE-ACS patients in TRITON-TIMI 38,[89] the primary endpoint was reduced in prasugrel- vs. clopidogrel-treated patients, while TIMI non-CABG major bleeding complications were more common with prasugrel, as were fatal bleeds. Excluding patients with a higher bleeding risk, prasugrel offers significant benefit over clopidogrel with respect to ischaemic events without significantly increasing major bleeding.[89] Especially in diabetic ACS patients, prasugrel showed a net clinical benefit with a substantial reduction in ischaemic events without a significantly increased bleeding risk.[90] Based on an unfavourable risk-benefit profile observed in the TRITON TIMI 38 study cohort,[88] a maintenance dose of prasugrel is contraindicated in patients with a history of stroke or TIA. Further on, treatment with prasugrel should be used with caution in patients ≥75 years of age or with a low body weight (<60 kg). If, after a careful assessment of thrombotic and bleeding risk, treatment is deemed necessary in these patients, a reduced maintenance dose of 5 mg should be prescribed.[91]

In a pre-specified subgroup analysis of STEMI patients ($n = 3534$) in the TRITON-TIMI 38 trial,[92] the benefit of prasugrel was consistent for the primary endpoint and stent thrombosis risk at 15 months. Of note, no significant increase in non-CABG-related major bleeding events was observed and cardiovascular mortality was in favour of prasugrel at 30 days. Thus, for the STEMI group of patients, prasugrel was found to be more effective when compared with clopidogrel, without an apparent excess in bleeding complications.

PLATO: NSTEMI and STEMI patients

Ticagrelor is a cyclopentyl triazolopyrimidine that reversibly inhibits the $P2Y_{12}$ receptor. Along with a PCI procedure, it is administered at a 180 mg loading dose followed by a 90 mg b.i.d. daily maintenance dose. Ticagrelor was tested against clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial in medically and invasively (PCI or CABG) managed patients.[93] The PLATO study randomly assigned 18 624 ACS patients to treatment with ticagrelor or clopidogrel and

showed a significant improvement in the composite ischaemic endpoint, including a mortality benefit in favour of ticagrelor.[93] Ticagrelor was associated with a higher rate of major non-CABG-related bleeding events, including more fatal intracranial bleeds and fewer fatal bleeds of other types. Within the PLATO study cohort, 11 080 patients[94] were categorized as NSTE-ACS at randomization and 46% of those were treated with PCI. In the NSTEMI cohort, the primary study endpoint of cardiovascular death as well as all-cause death was reduced with ticagrelor. Of note, ticagrelor was associated with an increase in non-CABG major bleeding and with an increased rate of adverse effects including dyspnoea, increased frequency of ventricular pauses, and asymptomatic increases in uric acid in all its major trials.[93–95] These adverse effects, especially the temporary occurrence of dyspnoea, may influence patient compliance, and close surveillance and patient education is required to avoid premature treatment discontinuation. Comparative data coming from randomized comparisons of ticagrelor vs. prasugrel in NSTEMI patients are limited. The ongoing ISAR-REACT 5 trial, enrolling NSTEMI as well as STEMI patients (>4000) with planned invasive management, will provide evidence in this respect.[96]

In the subset of STEMI patients randomized in the PLATO trial,[97] the benefit of ticagrelor over clopidogrel for the primary endpoint was borderline significant but consistent with the overall study results. As for prasugrel, no excess in bleeding events was observed. In a pooled analysis of 48 599 patients, of whom 94% presented with ACS and 84% had PCI, novel $P2Y_{12}$ inhibitors, including prasugrel and ticagrelor, have been associated with a mortality benefit and no significant excess of major bleeding among STEMI patients.[98]

Studies on cangrelor for percutaneous coronary intervention

In two initial clinical trials on clopidogrel-naïve patients, cangrelor was compared with clopidogrel, administered either before PCI in CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition)-PCI (n = 8714) or after PCI in CHAMPION-PLATFORM (n = 5362). Both studies failed to show a significant benefit with respect to the composite endpoint of death, MI, or ischaemia-driven revascularization at 48 h. Yet, in CHAMPION-PLATFORM, there was a significant reduction in the rate of stent thrombosis from 0.6 to 0.2% (OR 0.31, 95% CI 0.11–0.85; P = 0.02), which was not seen in CHAMPION-PCI with upfront administration of clopidogrel. In both trials, there was an increase in ACUITY major bleeding that approached (P = 0.06 in CHAMPION-PCI) or reached (P <0.001 in CHAMPION-PLATFORM) statistical significance.

A third trial, CHAMPION PHOENIX, was designed that administered clopidogrel after PCI, included stent thrombosis in the primary endpoint, and chose GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) severe bleeding as the primary safety endpoint. In this trial including 11 145 $P2Y_{12}$ inhibitor-naïve patients, the primary efficacy endpoint of death, MI, ischaemia-driven revascularization, and stent thrombosis at 48 h was met (4.7% in the cangrelor group and 5.9% in the clopidogrel group; adjusted OR 0.78, 95% CI, 0.66–0.93, P = 0.05). There was a significant reduction in stent thrombosis (0.8 vs. 1.4%) that was predominantly driven by intra-procedural stent thrombosis (0.6 vs. 1.0%; P = 0.04). A subsequent meta-analysis of all CHAMPION trials revealed a statistically significant 0.7% absolute reduction in death, MI, ischaemia-driven revascularization, and stent thrombosis at 30 days (P = 0.008), and a significant 0.5% absolute reduction in death, Q-wave MI, and stent thrombosis (P = 0.009), which includes a significant 0.4% absolute reduction in intra-procedural and post-procedural stent thrombosis (P = 0.018). These benefits occurred at the expense of a significant increase in ACUITY major bleeding (4.2 vs. 2.8%, P <0.001), which prevailed after the exclusion of major haematomas. There were no significant differences in GUSTO severe or TIMI major bleeding. In the meta-analysis as well as in CHAMPION PHOENIX, the benefit of cangrelor with respect to ischaemic endpoints was independent of the clinical presentation with stable angina, NSTE-ACS, or STEMI.

In summary, the available evidence on cangrelor suggests a numerically small benefit with respect to major ischaemic endpoints that is counterbalanced by an increase in relevant bleeding, but not severe bleeding. Moreover, comparison between CHAMPION-PLATFORM and CHAMPION-PCI suggests that the benefit of cangrelor might have been diminished by upstream administration of clopidogrel at the time of PCI. Of note, the drug was never evaluated in a randomized fashion for NSTEMI or STEMI patients when potent $P2Y_{12}$ inhibitors were used for oral antiplatelet treatment (either upfront or subsequently). Nevertheless, due to its proven efficacy in preventing intra-procedural and post-procedural stent thrombosis, cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients, particularly when the risk of PCI is high.

Studies on bivalirudin vs. unfractionated heparin

A number of large-scale clinical trials have compared bivalirudin vs. UFH (plus GP IIb/IIIa blockade). In the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial,[99] no significant differences were observed for UFH/LMWH plus GP IIb/IIIa inhibitor vs. bivalirudin plus GP IIb/IIIa inhibitor for the composite ischaemia endpoint at 30 days or for major bleeding complications. Bivalirudin alone (with bail-out use of a GP IIb/IIIa inhibitor) was also non-inferior to UFH/LMWH combined with a GP IIb/IIIa inhibitor with respect to the ischaemic endpoint, but it was associated with a significantly lower rate of major bleeding. ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment) compared the outcome of UFH plus abciximab vs. bivalirudin.[100] The primary ischaemic endpoint did not differ between the two groups, while the risk of major bleeding was significantly higher in the UFH plus abciximab group. It must be acknowledged that the above-mentioned evidence in support of bivalirudin is derived from clinical trials where bivalirudin was compared with UFH plus the use of a GP IIb/IIIa inhibitor, a combination that is not used on a routine basis anymore.

In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial in 3602 STEMI patients,[101] bivalirudin was superior to UFH with respect to the two primary endpoints of net adverse clinical events, which included a significant survival benefit. In contrast to that, the risk of stent thrombosis was higher during the first 24 h in the bivalirudin group. In a background of potent antiplatelet agents (approximately 50% utilization of prasugrel or ticagrelor) including pretreatment and a high rate of radial access (47%), the open-label EUROMAX (European Ambulance Acute Coronary Syndrome

Angiography) trial compared a strategy of pre-hospital bivalirudin vs. UFH or LMWH with optional use (69%) of GP IIb/IIIa inhibitors in 2218 STEMI patients.[102] The primary endpoint of death or non-CABG major bleeding at 30 days was significantly reduced by pre-hospital administration of bivalirudin compared with UFH plus optional GP IIb/IIIa inhibitors. Mortality rates were similar and a lower risk of major bleeding (mainly driven by blood transfusion) was observed for bivalirudin. Again, the risk of stent thrombosis was higher in the bivalirudin group. Further data on bivalirudin vs. UFH was generated in the single-centre HEAT-PPCI (How Effective are Antithrombotic Therapies in primary PCI) study,[103] a randomized trial comparing bivalirudin and UFH in 1829 STEMI patients undergoing primary PCI. Of note, HEAT-PPCI is characterized by contemporary practice including the restriction of GP IIb/IIIa inhibitors to bail-out situations (<10% patients) only, frequent (>90%) use of potent $P2Y_{12}$ inhibitors, and a radial approach with preferred DES implantation in STEMI. The primary endpoint was significantly higher in the bivalirudin compared with the UFH group, which includes a substantially higher risk of stent thrombosis for bivalirudin vs. UFH but no significant difference in mortality. For major bleeding events, no significant differences were observed either. The BRAVE (Bavarian Reperfusion Alternatives Evaluation) 4 trial examined the hypothesis of whether a strategy of prasugrel plus bivalirudin (n = 269) was superior compared with a strategy of clopidogrel plus UFH (n = 275) in primary PCI STEMI patients.[104]

While it has to be acknowledged that the trial was terminated prematurely, the investigators were unable to show any significant differences in net clinical outcome between prasugrel plus bivalirudin and clopidogrel plus UFH.

More data on the comparison of bivalirudin vs. UFH alone and with very limited use (<1%) of GP IIb/IIIa inhibitors in the study arms comes from the MATRIX trial,[105] where 7213 ACS patients with planned PCI were enrolled. Patients in the bivalirudin group were also randomized to post-PCI bivalirudin infusion or not. The primary outcomes, 30 day MACE and net adverse clinical events (a composite of major bleeding or MACE), were not significantly lower with bivalirudin than with heparin (10.3 vs. 10.9%, P = 0.44, and 11.2 vs. 12.4%, P = 0.12, respectively). Concerning secondary endpoints, bivalirudin compared with heparin was associated with a lower rate of death from any cause (1.7 vs. 2.3%, P = 0.04), a higher rate of definite stent thrombosis (1.0 vs. 0.6%, P = 0.048), and a lower rate of major bleeding (1.4 vs. 2.5%, P <0.001). Of note, a post-PCI bivalirudin infusion, as compared with no infusion, did not affect outcome.

Recently, the VALIDATE-SWEDEHEART study,[106] a randomized, registry-based, open-label clinical trial, enrolled 6006 patients with STEMI or NSTE-ACS who were undergoing PCI by predominantly radial access and receiving treatment with a potent $P2Y_{12}$ inhibitor (ticagrelor, prasugrel, or cangrelor) without the planned use of GP IIb/IIIa inhibitors. The primary endpoint-the 180 day composite incidence of death from any cause, MI, or major bleeding-was reached in 12.3% of the patients in the bivalirudin group and 12.8% in the heparin group (P = 0.54). There were no significant differences in any component of the primary endpoint or in stent thrombosis. Thus, the study demonstrated similar risk patterns for both ischaemia and bleeding when comparing the two drugs.

Summarizing currently available evidence on the comparison between bivalirudin and heparin for PCI in ACS, a recent study-level meta-analysis identified 12 randomized trials with 33 844 patients included.[107] The 30 day incidences of MACE and all-cause mortality were not significantly different between bivalirudin and heparin (OR 1.06, 95% CI 0.96–1.17, P = 0.24 and OR 0.95, 95% CI 0.76–1.20, P = 0.68, respectively). There were trends for an increased risk of stent thrombosis (OR 1.24, 95% CI 0.99–1.56; P = 0.06) and for a decreased risk of major bleeding (OR 0.68, 95% CI 0.41–1.11; P = 0.07) with bivalirudin as compared with heparin. Except for bleeding risk, the findings were consistent irrespective of balanced use of GP IIb/IIIa inhibitors in both arms or preferential use in the heparin arms. Concerning the bleeding risk, there was a significant heterogeneity between trials stratified by use of GP IIb/IIIa inhibitors (P <0.01), with a significant reduction of bleeding risk only in trials with preferential GP IIb/IIIa inhibitor use in the heparin arms (OR 0.53, 95% CI 0.41–0.68, P <0.0001). In the subsets with STEMI or NSTE-ACS, the findings were also largely consistent with the overall analysis. There was only a trend towards a lower risk of death with bivalirudin in the subgroup of patients presenting with STEMI (OR 0.84, 95% CI 0.70–1.01, P = 0.06) with P = 0.07 for heterogeneity. Yet, no firm conclusion could be drawn from this finding given the inconclusive P-values, the absent effect in the overall analysis, and the fact that the STEMI subset comprised a higher proportion of trials with predominant use of GP IIb/IIIa inhibitors in the UFH arm than the studies in NSTE-ACS. In summary, the available evidence from randomized trials does not favour bivalirudin use over heparin as the anticoagulant of choice for PCI in ACS.

Revascularization in patients with renal failure

Renal dysfunction is present in 30–40% of patients with CAD and the extent of CKD is strongly related to the risk of in-hospital adverse outcomes.[108–110] Creatinine clearance should be calculated with the Cockroft–Gault formula to comply with drug labelling and avoid overdosing with antithrombotics leading to increased bleeding risk.[111,112] In patients referred for acute PCI, the first dose of an antithrombotic drug does not usually add to the risk of bleeding in the case of CKD. Repeated infusion or intake might lead to drug accumulation and an increase in bleeding risk. Accordingly, patients with CKD should receive the same first-line treatment as any other patient in the absence of contraindications. Thereafter, dose adaptation is mandatory with respect to kidney function and specific antithrombotic agents may be preferred (Supplementary Table 11).

Monitoring of antiplatelet drugs (platelet function testing and genotyping)

There is a potential value of antiplatelet treatment monitoring on a prognostic level, and on the level of testing for modifying and individualizing treatment. Based on the results of a collaborative meta-analysis that represents the largest dataset available to date (n = 20 389 patients), platelet reactivity assessment during $P2Y_{12}$ inhibitor treatment identifies PCI-treated patients with a high on-treatment platelet reactivity who are at higher risk for mortality and stent thrombosis, and patients with a low on-treatment platelet reactivity who are at an elevated risk for major bleeding.[113] This dataset and study data from the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) trial,[114] representing the largest prospective registry in this field, showed that platelet function (PF) testing provides relevant prognostic information on the outcome of PCI-treated patients.

Prior randomized trials [GRAVITAS (Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety), TRIGGER-PCI (Testing platelet Reactivity In patients underGoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel), and ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting)], testing the hypothesis of the clinical benefit of PF monitoring to adjust therapy, have so far failed to demonstrate clinical benefit with PF monitoring.[115–117] These initial trials had a common approach of escalating treatment based on testing results obtained during or early after PCI. A further study, the ANTARCTIC (Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome) trial, addressed some limitations of prior studies and specifically focused on elderly ACS patients. This study also provided neutral results and utilized a standard treatment with a reduced dose of 5 mg prasugrel,[118] aiming to treat patients towards a therapeutic window of platelet inhibition.

A pure DAPT de-escalation strategy with a stage-adapted treatment approach was investigated in the randomized TROPICAL-ACS (Testing responsiveness to platelet inhibition on chronic antiplatelet treatment for acute coronary syndromes) trial.[119] In that trial, the primary endpoint was met and a strategy of PF testing-guided DAPT de-escalation (early switch from prasugrel to clopidogrel) was found to be non-inferior and safe in terms of ischaemic risk when compared with potent platelet inhibition for 12 months after ACS-PCI. Thus, a guided de-escalation of $P2Y_{12}$ inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative treatment strategy in ACS patients, and especially for patients deemed unsuitable for 12 months potent platelet inhibition.

The influence of genetic variants on the response to antiplatelet agents, especially clopidogrel, has been well established in patients with ACS and planned PCI.[120] Rapidly obtained genetic information on the 2C19 genotype can help in reaching the optimal window of $P2Y_{12}$ inhibition according to the cytochrome P2C19 profile,[121,122] but no randomized trial has ever demonstrated any clinical benefit of such an approach. A number of clinical trials in this field are ongoing.

In summary, neither PF testing nor genetic testing can be recommended on a routine basis for tailoring and escalating DAPT after stenting in all PCI-treated patients. Testing may be considered to: (i) de-escalate DAPT treatment, (ii) test the compliance to treatment, or (iii) obtain prognostic information on the individual patient for the time period after PCI.

2. References for material in supplementary appendix

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