Koronare Herzerkrankung

News 2017 aus dem Blickwinkel eines interventionellen Kardiologen

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1.) Stent und Vorhofflimmern

Goldstandard: Aspirin/Clopidogrel plus OAK

Problem: Blutungsrisiko stark erhöht unter Dreifach-Therapie

Stent und Vorhofflimmern: Blutungsrisiko

patients (11.4%) experienced a nonfatal or fatal bleeding. The crude incidence rate for bleeding was highest for dual clopidogrel and warfarin therapy (13.9% per patient-year) and triple therapy (15.7% per patient-year). Using warfarin monotherapy as a reference, the hazard ratio (95% confidence interval) for the combined end point was 0.93 (0.88-0.98) for aspirin, 1.06 (0.87-1.29) for clopidogrel, 1.66 (1.34-2.04) for aspirin-clopidogrel, 1.83 (1.72-1.96) for warfarin-aspirin, 3.08 (2.32-3.91) for warfarin-clopidogrel, and 3.70 (2.89-4.76) for warfarin-aspirin-clopidogrel.

Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 2010;170:1433-1441

Stent und Vorhofflimmern: Blutungsrisiko

Kann auf einen Blutverdünner verzichtet werden ohne dass das Risiko für Stentthrombosen, Herzinfarkte oder einen Schlaganfall steigt ?

ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

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BACKGROUND

Triple antithrombotic therapy with warfarin plus two antiplatelet agents is the standard of care after percutaneous coronary intervention (PCI) for patients with atrial fibrillation, but this therapy is associated with a high risk of bleeding.

METHODS

In this multicenter trial, we randomly assigned 2725 patients with atrial fibrillation who had undergone PCI to triple therapy with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy group) or dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups).

The primary end point was a major or clinically relevant nonmajor bleeding event during follow-up (mean follow-up, 14 months).

Vergleich:

Marcumar plus Aspirin und Clopidogrel

versus

Dabigatran 2xtgl. plus Clopidogrel bzw. Ticagrelor

Baseline Characteristics of the Patients

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin† (N=764)
Age — yr	71.5±8.9	71.7±8.9	68.6±7.7	68.8±7.7
Elderly age group — no. (%)‡	225 (22.9)	225 (22.9)	8 (1.0)	8 (1.0)
Male sex — no. (%)	728 (74.2)	750 (76.5)	592 (77.6)	594 (77.7)
Diabetes mellitus — no./total no. (%)	362/981 (36.9)	371/980 (37.9)	260/763 (34.1)	303/763 (39.7)
Previous stroke — no./total no. (%)	74/981 (7.5)	100/980 (10.2)	52/763 (6.8)	77/763 (10.1)
CHA_2DS_2-VASc score§	3.7±1.6	3.8±1.5	3.3±1.5	3.6±1.5
HAS-BLED score¶	2.7±0.7	2.8±0.8	2.6±0.7	2.7±0.8
Creatinine clearance — ml/min‖	76.3±28.9	75.4±29.1	83.7±31.0	81.3±29.6
Previous myocardial infarction — no. (%)	237 (24.2)	268 (27.3)	194 (25.4)	211 (27.6)
Previous PCI — no./total no. (%)	326/981 (33.2)	347/980 (35.4)	239/763 (31.3)	272/763 (35.6)
Previous CABG — no./total no. (%)	97/981 (9.9)	111/980 (11.3)	79/763 (10.4)	87/763 (11.4)
Type of atrial fibrillation — no./total no (%)				
Persistent	174/981 (17.7)	178/980 (18.2)	132/763 (17.3)	149/763 (19.5)
Permanent	320/981 (32.6)	318/980 (32.4)	250/763 (32.8)	238/763 (31.2)
Paroxysmal	487/981 (49.6)	484/980 (49.4)	380/763 (49.8)	376/763 (49.3)
Indication for PCI — no. (%)				
Stable angina or positive stress test	433 (44.1)	429 (43.7)	320 (41.9)	339 (44.4)
Acute coronary syndrome	509 (51.9)	475 (48.4)	391 (51.2)	369 (48.3)
Staged procedure	156 (15.9)	168 (17.1)	138 (18.1)	134 (17.5)
Other	43 (4.4)	62 (6.3)	65 (8.5)	50 (6.5)
Type of stent — no./total no. (%)				
Drug-eluting	804/979 (82.1)	826/976 (84.6)	621/762 (81.5)	638/759 (84.1)
Bare-metal	148/979 (15.1)	133/976 (13.6)	123/762 (16.1)	107/759 (14.1)
Drug-eluting and bare-metal	19/979 (1.9)	12/976 (1.2)	10/762 (1.3)	9/759 (1.2)
Other	8/979 (0.8)	5/976 (0.5)	8/762 (1.0)	5/759 (0.7)

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† The corresponding triple-therapy group included only patients who had been eligible to be assigned to the 150-mg dual-therapy group (i.e., did not include elderly patients outside the United States).
‡ Elderly was defined as 80 years of age or older (≥70 years of age in Japan). Stratification according to age group was performed with the use of an interactive voice-response system.
§ The CHA_2DS_2-VASc score reflects the risk of stroke, with values ranging from 0 to 9 and higher scores indicating greater risk.
¶ The HAS-BLED score reflects the risk of major bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy, with values ranging from 0 to 9 and with higher scores indicating greater risk.
‖ Creatinine clearance was calculated with the use of the Cockcroft–Gault equation. Data are missing for 91 patients in the 110-mg dual-therapy

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Safety End Point: Blutungskomplikationen

Table 2. Safety End Points.*

End Point	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Hazard Ratio (95% CI)	P Value†	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*			
Primary end point: ISTH major or clinically relevant nonmajor bleeding	151 (15.4)	264 (26.9)	0.52 (0.42–0.63)	<0.001 (<0.001 for noninferiority)	154 (20.2)	196 (25.7)	0.72 (0.58–0.88)	0.002 (<0.001 for noninferiority)
ISTH major bleeding	49 (5.0)	90 (9.2)	0.52 (0.37–0.74)	<0.001	43 (5.6)	64 (8.4)	0.64 (0.43–0.94)	0.02
Total bleeding	266 (27.1)	421 (42.9)	0.54 (0.46–0.63)	<0.001	254 (33.3)	316 (41.4)	0.72 (0.61–0.84)	<0.001
Intracranial hemorrhage	3 (0.3)	10 (1.0)	0.30 (0.08–1.07)	0.06	1 (0.1)	8 (1.0)	0.12 (0.02–0.98)	0.047
TIMI major bleeding	14 (1.4)	37 (3.8)	0.37 (0.20–0.68)	0.002	16 (2.1)	30 (3.9)	0.51 (0.28–0.93)	0.03
TIMI major or minor bleeding	29 (3.0)	69 (7.0)	0.41 (0.26–0.63)	<0.001	27 (3.5)	48 (6.3)	0.53 (0.33–0.85)	0.009

* Comparisons between the 110-mg dual-therapy group and the triple-therapy group were stratified according to age group (nonelderly or elderly [<80 or ≥80 years of age; <70 or ≥70 years of ag… …nary end point were … …ementary Appendix. T…
† P values fo… …riority and were calcul…

Weniger Blutungen mit 2 statt 3 Blutverdünnern, d.h. ohne Aspirin!

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Efficacy End Point: Schlaganfall, Stentthrombose

Table 3. Efficacy End Points.*

End Point	Dual Therapy with Dabigatran (Combined) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin			
	Combined Dual-Therapy Groups (N=1744)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual-Therapy Group (N=981)	Triple-Therapy Group (N=983)	Hazard Ratio (95% CI)	P Value†	150-mg Dual-Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)											
Composite efficacy end point: thromboembolic events, death, or unplanned revascularization	239 (13.7)	131 (13.4)	1.04 (0.84–1									4
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
Death					55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Myocardial infarction					44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stroke					17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Definite stent thrombosis					15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

Kein Unterschied!

* Thromboembolic events were myocardial infarction, stroke, or systemic embolism. Unplanned revascularization was percutaneous coronary intervention or coronary-artery bypass grafting. Comparisons between the 110-mg dual-therapy group and the triple-therapy group and between the combined dual-therapy groups and the triple-therapy group were stratified according to age group (nonelderly or elderly [<80 or ≥80 years of age; <70 or ≥70 years of age in Japan]). Comparisons between the 150-mg dual-therapy group and the corresponding triple-therapy group were unstratified. All end points other than the composite efficacy end point and the combined end point of thromboembolic events or death were considered to be descriptive.

† P values for noninferiority were calculated at a one-sided alpha level of 0.025 and are provided only if a noninferiority margin was prespecified. All other P values are for superiority and were calculated at a two-sided alpha level of 0.05; these P values are provided for descriptive purposes only.

Schlussfolgerung

- **Among patients with atrial fibrillation who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a $P2Y_{12}$ inhibitor than among those who received triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin.**

- **Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events.**

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Cave: Eine Studie ist keine Studie!

Aber: Es sind zwei weitere seriöse Studien publiziert mit derselben Fragestellung

WOEST

Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013;381:1107-1115

PIONEER-AF-PCI

Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423-2434

Unterschiede WOEST, PIONEER-AF-PCI und Re-DUAL-PCI

WOEST: Warfarin, kein NOAK
Clopidogrel, kein Ticagrelor oder Prasugrel

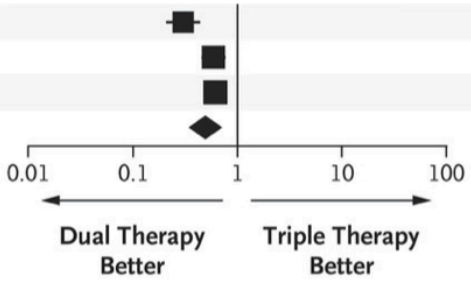
PIONEER-AF-PCI:
eine Gruppe Warfarin/Aspirin/Clopidogrel;
eine Gruppe Rivaroxaban 15mg plus Clopidogrel
eine Gruppe Rivaroxaban 5mg 2xtgl plus Clopidogrel/Aspirin

REDUAL-PCI: Warfarin/Aspirin/Clopidogrel vs. Dabigatran 110mg oder 150 mg 2xtgl plus Clopidogrel;
gepowert um Unterschiede in Stroke/Stentthrombose/ Herzinfarktrate nachzuweisen

Meta-Analyses of Results from Three Major Trials of Dual Therapy versus Triple Therapy.

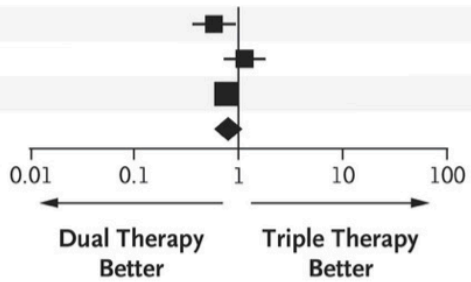
A Safety: Major and Minor Bleeding Events

Trial	Dual Therapy	Triple Therapy	Odds Ratio (95% CI)	z Score	Relative Weight	P Value
	no. of events/total no.					
WOEST	54/279	126/284	0.30 (0.21–0.44)	–6.22	29.1	<0.001
PIONEER AF-PCI	109/696	167/697	0.59 (0.45–0.77)	–3.86	34.1	<0.001
RE-DUAL PCI	305/1744	196/764	0.61 (0.50–0.75)	–4.68	36.8	<0.001
Overall			0.49 (0.34–0.72)	–3.70		<0.001
I^2=82.06						



B Efficacy: Major Adverse Cardiovascular Events

Trial	Dual Therapy	Triple Therapy	Odds Ratio (95% CI)	z Score	Relative Weight	P Value
	no. of events/total no.					
WOEST	31/279	50/284	0.58 (0.36–0.95)	–2.18	25.5	0.03
PIONEER AF-PCI	41/694	36/695	1.15 (0.72–1.82)	0.59	27.0	0.55
RE-DUAL PCI	239/1744	131/764	0.77 (0.61–0.97)	–2.23	47.47	0.03
Overall			0.80 (0.58–1.09)	–1.40		0.16
I^2=51.17						



Piccini JP, Jones WS. N Engl J Med 2017;377:1580-1582.

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Bewertung

1. **Bei Patienten mit Vorhofflimmern, die eine PTCA/Stentimplantation erhalten, ist die Kombination eines NOAK mit Clopidogrel ausreichend, um eine Stentthrombose bzw. einen Schlaganfall zu verhindern**
2. **Der Verzicht auf Aspirin senkt das Risiko für Blutungskomplikationen erheblich**

2.) Stent bei stabiler Angina pectoris

Ketzerische Frage:

Was bringt das dem Patienten?

ORBITA-Studie

Percutaneous coronary intervention in stable angina: a double-blind, randomised controlled trial

Lancet, November 2, 2017

ORBITA-Studie: Methoden

- 230 Patienten mit 1-Gefäss-Erkrankung > 70% Stenose,
- Vergleich PTCA/Stent vs. Placebo-Prozedur nach Koro
- Placebo-Prozedur: >15 min auf Korotisch mit Katheter im Herz und Dormicum-Sedation
- Vor und 6 Wochen nach der Prozedur: Ergometrie, Dobutamin-Stressecho und Fragebogen
- Vor PTCA/Placebo-Prozedur 6 Wochen lang Optimierung der antianginösen Medikation
- Primärer Endpunkt: Zunahme der Belastungsdauer im Belastungs-EKG bis AP, Ischämiezeichen im EKG oder Erschöpfung

Background

Over 500 000 PCIs per year for stable angina

- **Primarily for angina relief**

Size of angina relief beyond placebo unknown

- **Unblinded PCI +96 seconds** (NEJM 1992)
- **Single drug +55 seconds** (JACC 2004)

Principal hypothesis:
Symptom relief in stable angina

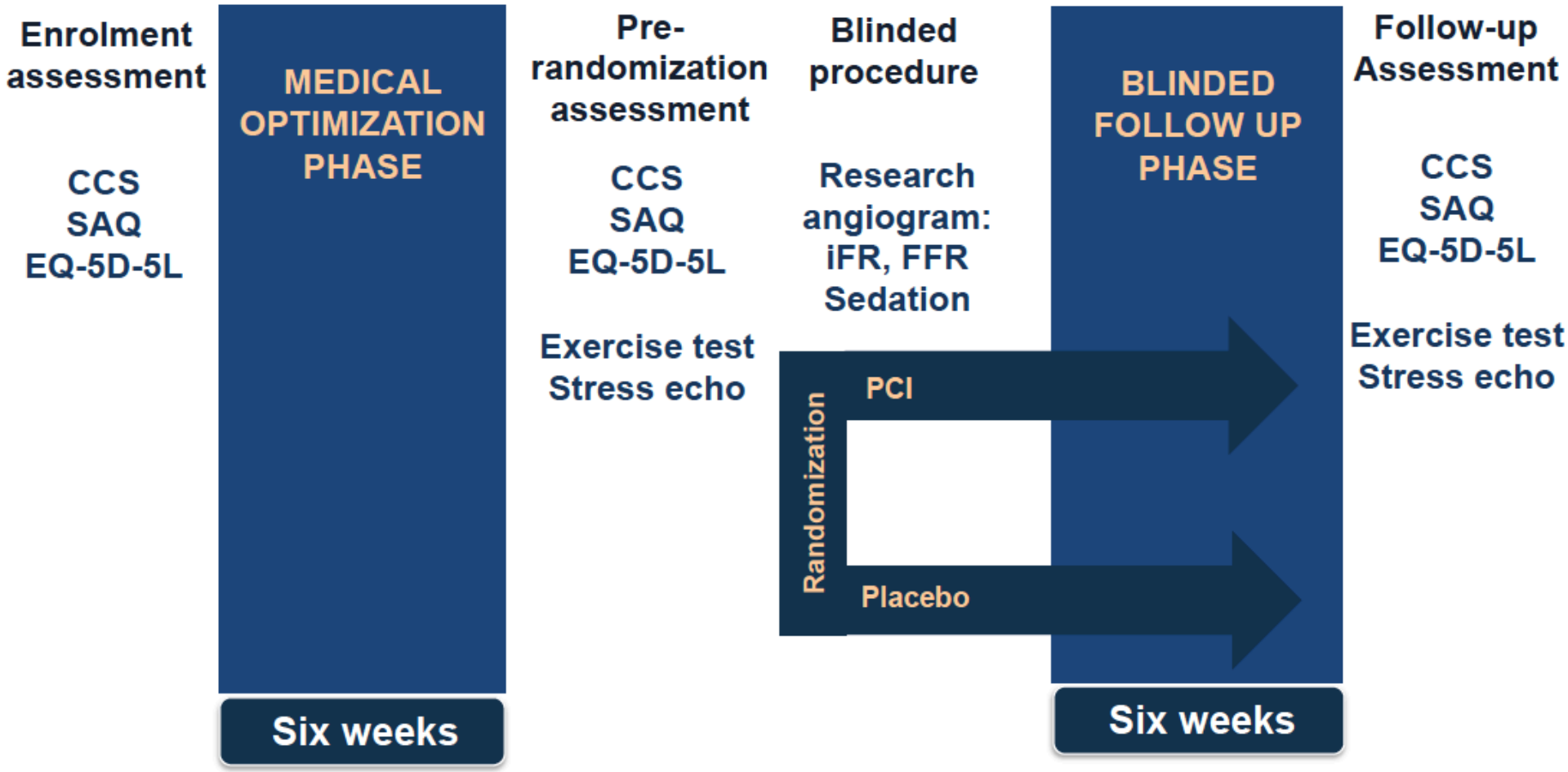
PCI increases exercise time more than placebo procedure

Primary endpoint

Difference in exercise time increment between the arms

For patients to be willing to participate in this first placebo-controlled trial of PCI, duration must long enough for full hemodynamic effect but not so long as to inhibit recruitment

Trial design



Sample size calculation

To detect 30 sec,

at 80% power,

within-arm SD 75 sec,

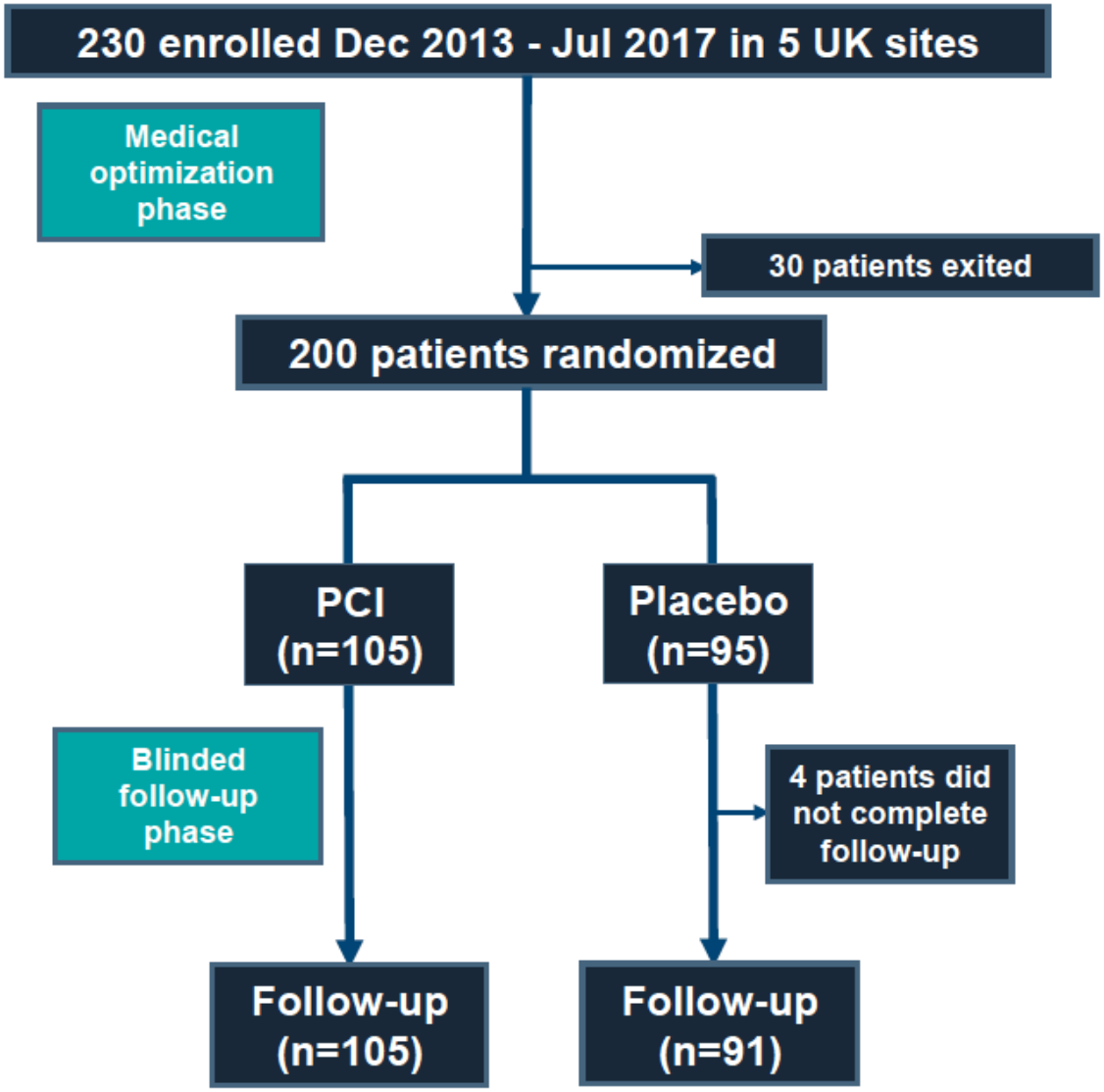
needs 200 randomized patients

This sample size is comparable to other trials assessing *this question*.

Inclusion criteria

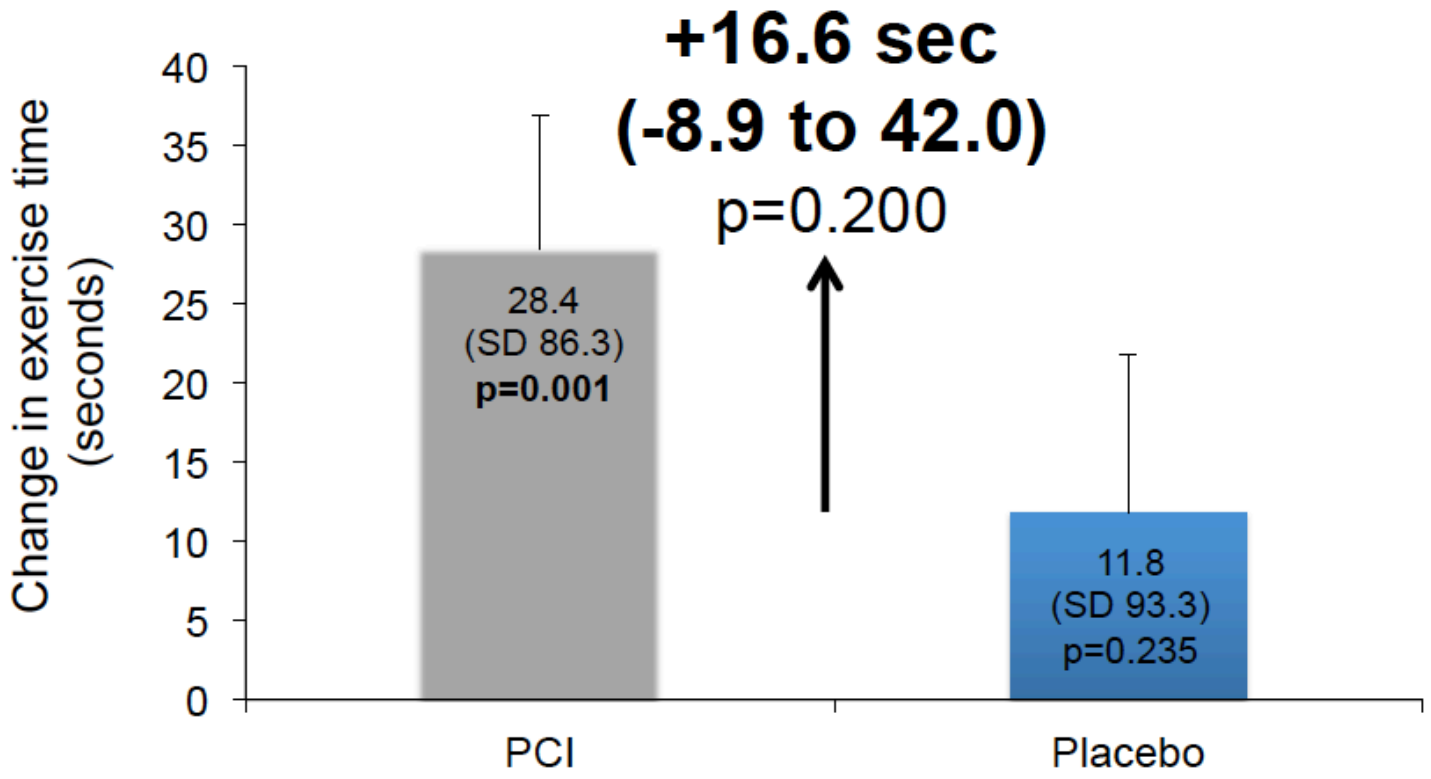
- **Stable angina**
- **One or more ≥ 70% stenosis in a single vessel**
- **Suitable for PCI**

ORBITA trial



Primary endpoint result

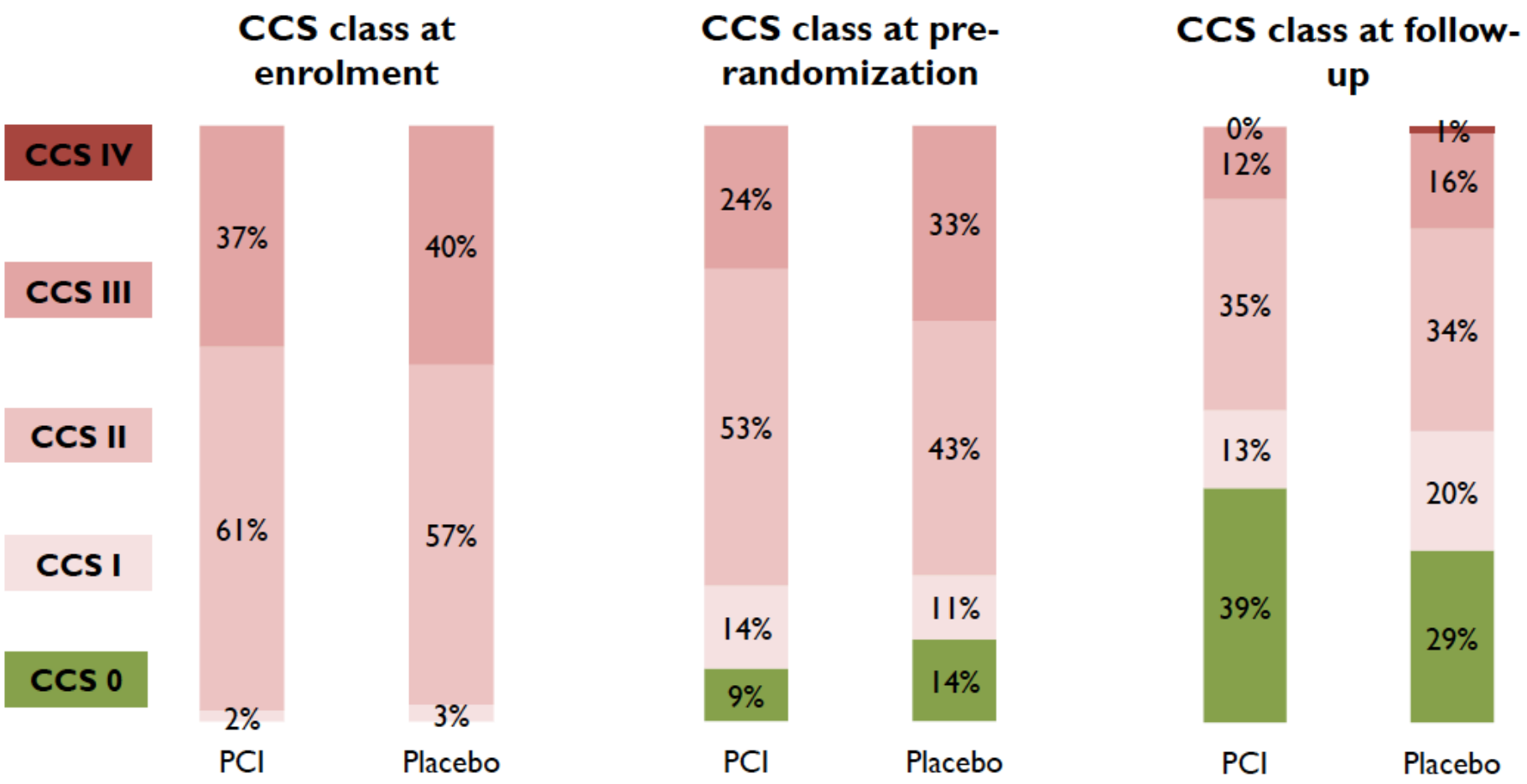
Change in total exercise time



Error bars are standard errors of the mean

Secondary endpoint results

CCS class improved in both groups



Secondary endpoint results

Blinded evaluation of ischaemia reduction

Peak stress wall motion index score	PCI n = 80	Placebo n = 57
Pre-randomization	1.11 (0.18)	1.11 (0.18)
Follow-up	1.03 (0.06)	1.13 (0.19)
Δ (Pre-randomization to follow-up)	-0.08 (0.17)	0.02 (0.16)
	p<0.0001	p=0.433
Difference in Δ between arms	-0.09 (-0.15 to -0.04) **p=0.0011**	

Conclusions

- ORBITA is the first placebo-controlled randomized trial of PCI in stable angina
- Area stenosis QCA 84.4%, FFR 0.69, iFR 0.76
- PCI was safe and physiologically effective
- PCI significantly reduced ischemic burden as assessed by stress echo
- In this single vessel, angiographically guided trial there was no difference in exercise time increment between PCI and placebo

Bewertung

Bewertung

1. **Ein PTCA führt nicht per se zu einer Verbesserung der körperlichen Leistungsfähigkeit, insbesonders nicht bei sedativen Patienten**
2. **Nur durch ein Stressecho kann geklärt werden, ob ein Patient eine induzierbare Myokardischämie hat. Die Beschwerdesymptomatik oder ein Belastungs-EKG sind nicht aussagekräftig**
3. **Nur durch die PTCA wird die induzierbare Myokardischämie beseitigt, nicht jedoch durch eine antianginöse Therapie, selbst wenn diese die Symptomatik verbessert**

Vielen Dank für Ihr Interesse!

Haben Sie Fragen, Kommentare?

Blinding techniques

Patient

Headphones and music
Sedation
Minimum 15 min wait

Both arms:
- DAPT
- Same post-procedural instructions
- Same discharge letter

Clinical team

Standardised handover
Ward team blinded

Both arms:
- Treated as if PCI
- No access to cath report
- Same discharge letter

ORBITA in context

- Single vessel
  - To allow complete revascularization
- PCI guided by angina + angiogram
  - In line with common practice
- Focus is on symptomatic relief
  - Not risk or events
- Intensive medical therapy
  - In line with Guidelines

Stenosis severity

	PCI n = 105	Placebo n = 95	P
Area stenosis by QCA (%)	84.6 (SD 10.2)	84.2 (SD 10.3)	0.781
FFR	0.69 (SD 0.16)	0.69 (SD 0.16)	0.778
iFR	0.76 (SD 0.22)	0.76 (SD 0.21)	0.751