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CLINICAL TRIAL UPDATES AND HOTLINE SESSIONS

Hotlines and clinical trial updates presented at the German Cardiac Society Meeting 2010: FAIR-HF, CIPAMI, LIPSIA-NSTEMI, Handheld-BNP, PEPCAD III, remote ischaemic conditioning, CERTIFY, PreSCD-II, German Myocardial Infarction Registry, DiaRegis

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Abstract This article summarizes the results of a number of clinical trials and registries in the field of cardiovascular medicine which were presented during the Hotline Sessions at the annual meeting of the German Cardiac Society, held in Mannheim, Germany, from 8th to 10th April 2010. The data were presented by leading experts in the field with relevant positions in the trials. It is important to note that unpublished reports should be considered as preliminary data, as the analysis may change in the final publications. The comprehensive summaries have been generated from the oral presentation and should provide the readers with the most comprehensive information on diagnostic and therapeutic development in cardiovascular medicine similar as previously reported (Maier et al. in Clin Res Cardiol 98:345–352, 2009; 98:413–419, 2009).

Keywords FAIR-HF · CIPAMI · LIPSIA-NSTEMI · Handheld-BNP · PEPCAD III · Remote ischaemic conditioning · CERTIFY · PreSCD-II · German Myocardial Infarction Registry (DHR) · DiaRegis

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FAIR-HF

Iron deficiency (ID) is associated with increased morbidity and mortality in patients with chronic heart failure (CHF). FAIR-HF is a multi-centre, randomized, double-blind, placebo-controlled study determining the effect of intravenous iron repletion therapy with ferric carboxymaltose (FCM) in patients with CHF and ID either with or without anaemia [1]. 459 patients with symptomatic CHF with NYHA functional class II or III, LVEF $\leq$45%, ID [ferritin $<$ 100 ng/mL or ferritin 100–300 ng/mL when transferrin saturation (TSAT) $<$20%], and haemoglobin 9.5–13.5 g/dL were randomized to receive FCM (Ferinject®) 200 mg or saline i.v. weekly until iron repletion (correction phase), then monthly until week 24 (maintenance phase). Patients were aged 68/67 years and had a mean left ventricular dysfunction with a LVEF of 32/33% in the FCM/placebo group. In 80%, left ventricular dysfunction was due to ischemic cardiomyopathy. Patients were under optimal CHF treatment (92% ACE-inhibitors/angiotensin receptor blockers; 86% beta-blockers). Primary endpoints were self-reported patient global assessment (PGA) score and NYHA class at week 24 (adjusted for baseline NYHA class). Key secondary endpoints included the 6-min walk test (6MWT) distance, the PGA-score at weeks 4 and 12, the Kansas City Cardiomyopathy Questionnaire (KCCQ) score and the European Quality of Life-5 Dimensions questionnaire (EQ-5D) score. Compared to placebo, iron repletion improved self-reported PGA-scores [odds ratio (OR) for improvement 2.51; 95% CI 1.75–3.61; $p < 0.0001$]. Among the patients assigned to FCM, 47% had a NYHA functional class I or II, as compared to 30% of the patients receiving placebo (OR for improvement by 1 class 2.4; 95% CI 1.55–3.71; $p < 0.0001$; adjusted for baseline; Fig. 1). Interestingly, the improvement of the primary endpoints could be observed independently of the presence

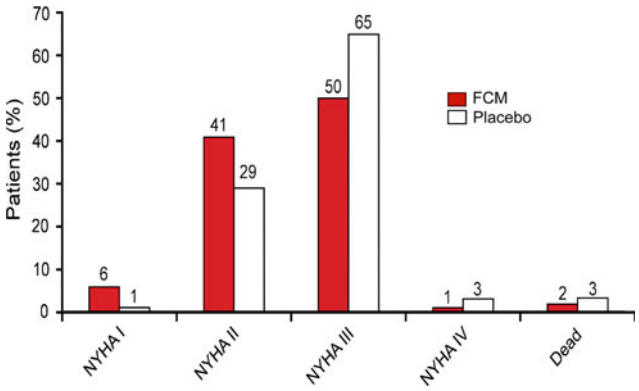

Fig. 1 FAIR-HF: improvement of NYHA functional class by FCM

of anaemia (two predefined subgroups with Hb <120 and >120 g/L). At all time points starting at week 4, FCM therapy significantly improved the 6MWT distance (treatment effect on walk distance shown as mean ± SEM, 21 ± 6/37 ± 7/35 ± 8 at weeks 4/12/24; $p < 0.001$) and quality of life assessments by the KCCQ score ($p < 0.001$) and the EQ-5D score ($p < 0.001$). Renal function was significantly improved in the FCM group. FCM was well tolerated, no severe or serious hypersensitivity reactions could be observed. In summary, in CHF patients with iron deficiency with and without anaemia, a 24-week treatment with FCM was well tolerated and improved self-reported health status, functional NYHA class, exercise capacity, quality of life measures and renal function (presented by Piotr Ponikowski, Wroclaw, Poland).

CIPAMI

In patients with ST-segment elevation myocardial infarction (STEMI), the main treatment goal is a prompt reperfusion of the infarct-related artery. In a meta-analysis including more than 8,000 patients with STEMI, pre-treatment with clopidogrel was an independent predictor of early reperfusion and improved clinical outcome [12]. However, there is still controversy about the optimal time point of initiation of clopidogrel therapy. CIPAMI is a randomized, controlled study determining the effect of pre-treatment with clopidogrel in patients with acute STEMI (onset of symptoms <6 h) with planned primary PCI. 337 patients were included. All patients were treated with aspirin and heparin and were prehospitally randomized to either pre-treatment with 600 mg clopidogrel ($n = 166$) or to standard therapy ($n = 171$). There were no differences between the groups regarding the patients' characteristics. The primary endpoint was the percentage of TIMI 2/3 patency of the infarct-related artery before PCI. Secondary endpoints were bleeding, death and reinfarction. There was no significant difference regarding the primary endpoint (percentage of TIMI 2/3 patency before intervention 49.3% in the pre-treatment vs. 45.1% in the standard therapy group) and regarding the ST resolution 1 h after PCI (62% in the pre-treatment vs. 61.4% in the standard therapy group). One possible explanation for these negative results could be the short clopidogrel to angiography time in the pre-treatment group of only 46 min (Table 1). Interestingly, the study showed a trend towards a reduction of clinical endpoints in the pre-treatment group (death 2.3% in the standard group vs. 0.6% in the pre-treatment group, reinfarction 1.7 vs. 0.6%, re-PCI 5.2 vs. 2.5%, death/reinfarction/re-PCI 7 vs. 3%, CABG). Unfortunately, the study was not powered for these endpoints. There were no differences in the occurrence of major bleeding events (8.6 vs. 8.7%). In summary, in patients with STEMI, pre-treatment with clopidogrel did not improve pre-PCI vessel patency but was safe and showed a clear trend towards a clinical benefit (presented by Uwe Zeymer, Klinikum Ludwigshafen, Germany).

Table 1 CIPAMI

	Prehospital clopidogrel (min)	Standard (min)	*p* value
Symptom onset to randomization	75	75	0.9
Randomization to angiography	50	51	0.8
Clopidogrel to angiography	46	7	0.001
Symptom to angiography	140	137	0.7

LIPSIA-NSTEMI

In the management of patients with NSTEMI, the optimal timing of PCI remains a controversy. LIPSIA-NSTEMI is a randomized, multicenter trial designed to test whether in patients with NSTEMI, an immediate invasive approach is superior to an early invasive approach or a selective invasive approach. All 603 included patients received a standard therapy with aspirin (500 mg i.v.), clopidogrel loading dose (600 mg p.o.), heparin (5,000 IE i.v. followed by continuous infusion, aPTT 50–70 s) and tirofiban (10 µg/kg bolus, followed by continuous infusion of 0.15 µg/kg per min). Subsequently, patients were randomized into three groups: immediate approach (timing to angiography <2.5 h, mean 1.1 h), early approach (12–48 h; mean 18.6 h) and selective approach (mean 67.2 h). All patients were concomitantly treated with tirofiban for 24 h, aspirin 100 mg/day and clopidogrel 75 mg/day for 12 months. The primary endpoint was the peak CK-MB value. Secondary endpoints were death and the composites death/re-MI, death/re-MI/rehospitalisation for unstable angina, death/re-MI/rehospitalisation for unstable angina and death/re-MI/rehospitalisation for unstable angina/refractory ischemia at 6 months.

Safety was assessed by severe bleeding complications according to the GUSTO definition. There was no significant difference between the three groups regarding the primary endpoint, the peak CK-MB value ($p = 0.14$; Fig. 2). Furthermore, there was no significant difference in the occurrence of secondary ischemic endpoints. Timing of angiography did not affect the incidence of bleeding complications (severe/life threatening bleeding 2.5% in immediate invasive approach vs. 2.5% in early invasive approach vs. 2.1% in the selective invasive approach, $p = 0.86$). The length of the hospital stay was significantly longer in the selective invasive group compared to the other two groups (5 days in the selective invasive approach group vs. 4 days in the early invasive and immediate invasive group, $p < 0.05$). In summary, in stable patients with NSTEMI, an immediate invasive strategy did not reduce the size of myocardial infarction and did not affect the occurrence of secondary ischemic events or safety outcomes (bleeding) compared with an early and a selective invasive strategy. However, it significantly shortened the length of the hospital stay (presented by Holger Thiele, Leipzig, Germany).

The Handheld-BNP Study

Patients with symptoms of heart failure usually present first to their general practitioner (GP). Based on patients' history, examination and electrocardiogram, the percentage of incorrect diagnoses is high. The Handheld-BNP Study investigated the diagnostic use and the prognostic value of point-of-care BNP testing and handheld echocardiography in diagnostic naïve patients. For this study, 44 GPs in two regions of Germany were trained in the practical use of handheld echocardiography and BNP point-of-care device. 852 patients were included and randomly assigned to four different groups: no additional tools/BNP/echocardiography/BNP and echocardiography. After diagnostic assessment by the GP, patients were referred to a cardiologist who was blinded to the GP diagnosis and BNP value. In 44% of all cases, the diagnosis of the GP was confirmed by a cardiologist. 74% of correct diagnoses were heart failure with preserved ejection fraction. In patients without heart failure the cardiologist attributed the cause of symptoms in 24% to pulmonary disease, in 12% to coronary artery disease, in 11% to obesity, and in 10% to hypertension. Addition of BNP or echocardiography raised specificity but decreased sensitivity in diagnosing heart failure compared to the reference standard. The cumulative survival after 36 months was 90.6% (95% confidence interval 88.2–93). In patients with a BNP concentration ≥60 ng/ml and diagnosis of heart failure by a cardiologist, the hazard ratio for all-cause death was 11.9 (3.6-39.9; $p < 0.001$). A BNP ≥60 ng/ml without diagnosis of heart failure was associated with a HR of 4.6 (1.2–17.9; $p < 0.05$). In summary, the addition of handheld echocardiography and point-of-care BNP testing provided diagnostic and prognostic information and thereby enabling the GP to identify patients at increased risk and in need for further diagnostic workup (presented by Christiane E. Angermann, Würzburg, Germany).

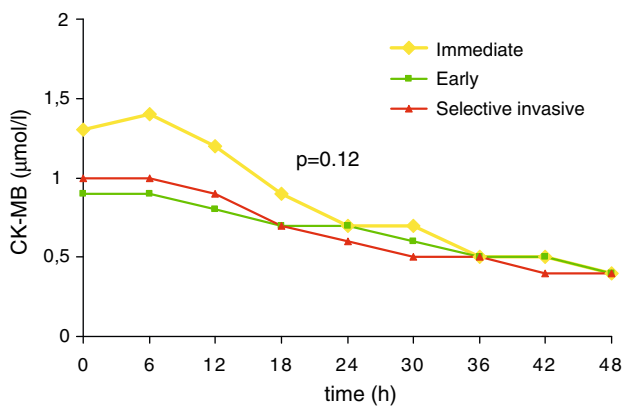

Fig. 2 LIPSIA-NSTEMI: CK-MB

PEPCAD III

Clinical trials on drug-eluting stents (DES) suppressing neointimal proliferation by sustained release of antiproliferative drugs have shown excellent results in reducing restenosis. Drug-coated balloon catheters (DCB) represent an alternative concept for local drug delivery not requiring stent implantation. Clinical trials on DCB based on the PACCOCATH technology have shown superiority of this new approach over conventional angioplasty and DES in the treatment of coronary in-stent restenosis [8, 9, 11]. Furthermore, promising clinical data are available for stand-alone use of DCB in coronary small vessel disease and bifurcation lesions [10]. The multicentric PEPCAD III trial investigated a new application of DCB, a bare metal stent (BMS) mounted on a DCB compared to the Cypher DES. $N = 637$ patients with stable or unstable angina were randomized at 24 sites all over Europe. The primary endpoint in a non-inferiority design was late lumen loss at 9 months angiographic follow-up. Secondary endpoints included MACE (death, myocardial infarction, and any revascularisation) at 9 months. Clinical endpoints were analysed intention-to-treat. For the per protocol analysis of the primary endpoint $n = 277$ patients (75%) were available. In-stent late lumen loss was significantly higher in the DCB + BMS group compared to the DES (0.41 ± 0.51 vs. 0.16 ± 0.39 mm, $p = 0.001$); however, in-segment measures were not significantly different (0.20 ± 0.52 vs. 0.11 ± 0.40 mm, $p = 0.07$). Total MACE rate was 18.5%

in the DCB + BMS group and 15.4% in the DES group ($p = 0.16$). The DES group presented with a lower incidence of myocardial infarction (3.8 vs. 0.6%, $p < 0.01$), and target lesion revascularization (8.1 vs. 3.1%, $p < 0.01$). Definite stent thrombosis rate was 1.3% ($n = 4$) in the DCB + BMS group versus 0.3% ($n = 1$) in the DES group ($p = 0.16$). Detailed analysis revealed that most cases of stent thrombosis and myocardial infarctions were not related to a study device failure but different reasons. In conclusion, this first DCB + BMS device did not meet the non-inferiority criteria versus the sirolimus DES presenting with exceptionally favourable results. However, late lumen loss in both groups was comparable to published data on different DES. Restenosis in the DCB + BMS group was predominantly focal. Therefore, further design evolution seems to be possible to improve this new approach. Currently, DCB are not a replacement for DES but a new platform in interventional cardiology and radiology to reduce the need for stents (presented by Bruno Scheller, Homburg/Saar, Germany).

Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction

Despite improved prognosis of reperfusion therapy in patients with myocardial infarction, reperfusion can also damage previously ischemic myocardium. In animal models, brief cycles of ischaemia and reperfusion are able to reduce this reperfusion injury. The presented study investigated the effects of remote ischaemic conditioning before hospital admission in patients with acute myocardial infarction. The study included 333 patients with first ST-elevation myocardial infarction who were randomized in a 1:1 ratio to receive primary percutaneous coronary intervention (PCI) either with or without remote ischemic preconditioning. The remote preconditioning procedure was performed by intermittent upper-arm ischaemia through four cycles of 5-min inflation of a blood-pressure cuff during transport to the hospital where PCI was performed. The primary endpoint was the myocardial salvage index at 30 days after PCI, estimated by single photon emission CT (SPECT). A large part of patients were excluded because they did not meet the inclusion criteria ($n = 82$), were lost to follow-up ($n = 32$) or did not complete the follow-up with data for salvage index ($n = 77$). In the remaining patients, the mean salvage index was 0.69 ± 0.27 in the remote conditioning group versus 0.57 ± 0.26 in the control group. No significant differences were recorded regarding biochemical markers of myocardial ischaemia, ST-segment resolution, and TIMI frame count (Table 2). Furthermore, left ventricular function and major cardiac events at 30 days after PCI did not significantly differ between both groups. In summary, the study offers a safe and simple tool for reducing the infarct size in patients with myocardial infarction. However, large clinical trials are urgently needed to investigate if remote conditioning has a clinical benefit and the potential to reduce morbidity and mortality [2] (presented by Hans Erik Bøtker, Aarhus, Denmark).

CERTIFY, subgroup analysis

The CERTIFY study compared the efficacy and safety of certoparin compared to unfractionated heparin (UFH) for thromboprophylaxis in acutely ill, non-surgical elderly patients [7]. 3,239 patients aged 78.6 ± 6.3 years were randomized to either certoparin 3,000 U anti-Xa once daily or UFH 5,000 IU three times daily. The incidence of the primary endpoint (deep venous thrombosis, pulmonary embolism or venous thromboembolism related death) was 3.94% in the certoparin group and 4.52% in the UFH group, with a difference in proportions of −0.59% (95% CI −2.09–0.92; $p < 0.0001$ for non-inferiority). Major bleeding occurred in 0.43% of certoparin and in 0.62% of UFH patients (OR 0.69; 95% CI 0.26–1.83). The subgroup analysis investigated the relevance of heart failure in this context. No significant differences were observed for the primary endpoint for therapy with certoparin versus UFH in patients with heart failure (OR 0.79; 95% CI 0.32–1.94) and without heart failure (OR 0.88; 95% CI 0.59–1.33). Bleeding complications were similar in both groups. In elderly patients, thromboprophylaxis with certoparin was non-inferior to UFH. The results of the sub study, however, should be interpreted with caution as no details on heart failure, e.g. echocardiography or clinical status, were presented (presented by Ulrich Tebbe, Detmold, Germany).

PreSCD-II-Registry

In Germany, almost 80,000 patients die every year from sudden cardiac death. Persons who survive a myocardial infarction (MI) are at highest risk for sudden death from ventricular tachyarrhythmia. Implantable cardioverter-defibrillators (ICD) reduce mortality in patients with a prior myocardial infarction and an advanced left ventricular systolic dysfunction [6]. The PreSCD-II-Registry (prevention of sudden cardiac death) was initiated to investigate mortality and treatment of patients after MI. 10,612 patients from 19 German rehabilitation clinics were included. The follow-up period was 36 months. Depending on the left ventricular ejection fraction (EF) ≥4 weeks

Table 2 Secondary endpoints

	PCI only ($n = 125$)	PCI + remote conditioning ($n = 126$)	p value
ST-segment resolution (%)	72	75	0.55
Troponin T (μg/l)	2.90 (1.43; 5.49)	1.46 (0.43; 3.84)	0.67
CTFC (frames/s)	15 (9; 25)	15 (9; 21)	0.64
MACE	3/1/0	3/1/0	1.0
LVEF (%)	53 (45; 58)	53 (47; 58)	0.73

Data are shown as median (interquartile range)

CTFC corrected TIMI frame count, *MACE* major cardiac events (death/myocardial reinfarction/stroke), *LVEF* left ventricular ejection fraction

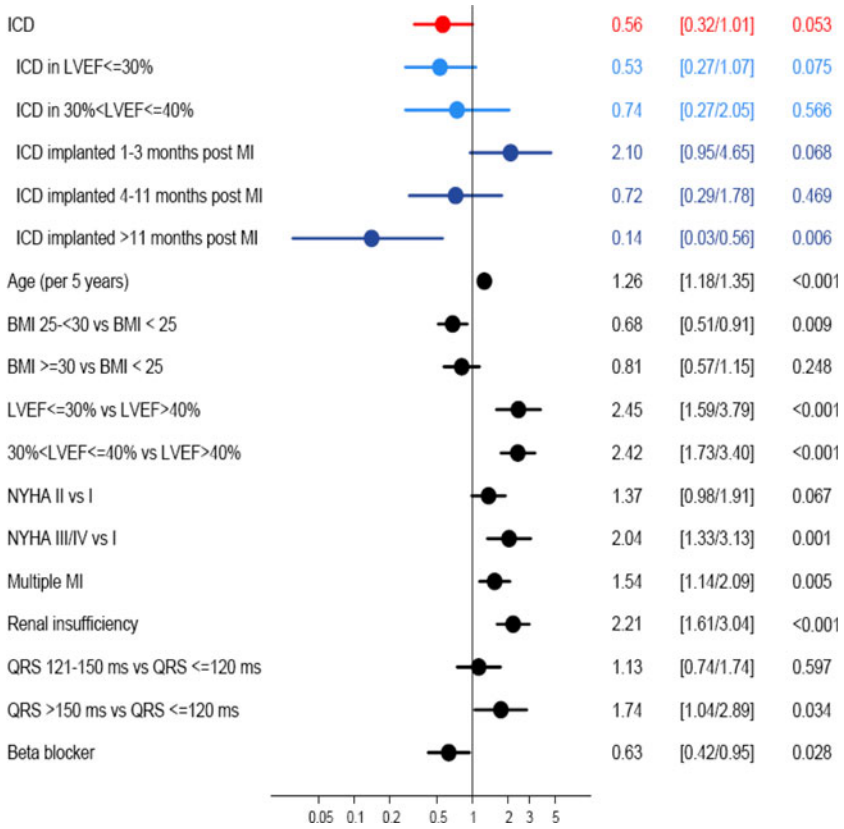

Fig. 3 PreSCD-II-Registry: parameters that influence survival after myocardial infarction during 3-year follow-up

post-MI, the patients were assigned to 3 groups: EF ≤30%, EF 31–40%, and EF >40%. As expected, the mortality rate increased with lower EF (EF ≤30%, 20.2%; EF 31–40%, 16.4%; EF >40%, 4.6%). In 90% of the patients, the medication was in accordance with the current guidelines. However, only 22% of the patients with highly reduced EF received an ICD during the first 4 months after the MI. Another 10% of the patients received the ICD later. The presenter discussed that this could be explained by the uncertainty about the optimal timing of ICD implantation. In the overall registry population, implantation of an ICD was associated with a borderline significant survival benefit ($p = 0.053$; Fig. 3). If patients received the ICD more than 11 months after MI, the implantation was associated with a significant improvement of survival (HR 0.14, CI 0.03–0.56, $p = 0.006$). However, when the ICD was implanted 1–3 months after MI, there was even a trend to a higher mortality (HR 2.10, CI 0.95–4.65, $p = 0.068$). This is in line with randomized studies demonstrating no survival benefit of ICD implantation during the first 4 weeks after MI [3, 5]. Therefore, the decision to implant an ICD in patients with severely impaired left ventricular function should be made between 3 and 11 months after MI (presented by Michael Block, München, Germany).

Results of the German Myocardial Infarction Registry (DHR): 1 year follow-up after STEMI

Two hundred and eighty PCI centers participated in the German Myocardial Infarction Registry. The 1-year follow-up data of 3,365 patients with ST-elevation myocardial

infarction (STEMI) were presented. Mean age of the patients was 63.5 years, 28% were women. More than 80% received a PCI as primary therapy. The in-hospital mortality was 6.8%, 5.3% of all patients died after discharge during the 1-year follow-up. 2.9% had another myocardial infarction, 1.2% had a stroke, 13.9% needed a Re-PCI, 3.3% underwent CABG surgery, and 2.7% received an ICD. 25% suffered from angina, 45% from dyspnea. In 90%, the medication was taken according to the current guidelines, with exception of the dual antiplatelet therapy. After 1 year, 95.5% of the patients were taking aspirin, whereas only 32.2% were taking clopidogrel. Only 31% had a combined antiplatelet therapy with aspirin and clopidogrel. The presenter emphasized that this dramatic underuse of dual antiplatelet medication is concerning (presented by Uwe Zeymer, Ludwigshafen, Germany).

DiaRegis

Recent studies revealed that in patients with type 2 diabetes an intensive glucose lowering strategy is not superior to a standard therapy. Moreover, targeting glycated haemoglobin (HbA1c) levels below 6.0% increases the rate of death from any cause. Both, low and high mean HbA1c values are associated with increased all-cause-mortality and cardiac events. Hypoglycemic events are discussed to be a main reason for the harm of intensive glucose lowering therapy. The Diabetes Registry (DiaRegis) is a prospective multicenter registry initiated to document the anti-diabetic therapy in ambulant patients. A special focus was to identify patients with severe hypoglycemic episodes. 3,447 patients with type 2 diabetes and failure of the initial oral medication were included. 24.2% had vascular disease (VD). The mean age was 71 years in the group with VD and 64 years in the group without VD. 90% of the patients were obese. As expected, the patients with VD had significant more comorbidities and more co-medications. The rate of hypoglycemia was 11.8% in the group with VD and 9.3% in the group without VD. A medication with sulfonylurea constituted an independent predictor of hypoglycemic events (2.58 times higher risk) whereas metformin was associated with less hypoglycemic events (factor 0.57) (presented by Anselm K. Gitt, Ludwigshafen, Germany).

The German Chest Pain Unit (CPU) registry

Since 2008, the German Cardiac Society certifies CPU to assure standard quality of care for patients presenting with chest pain. Shortly afterwards, the German Cardiac Society started a registry to continuously validate work in CPU in 19 university and rural hospitals throughout Germany. Data

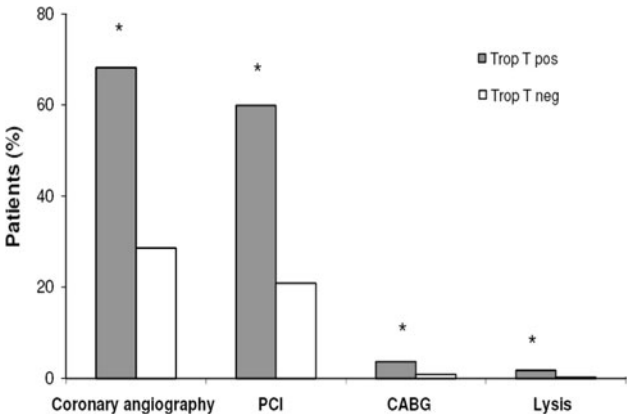

Fig. 4 CPU registry: diagnostic and therapeutic procedures in patients submitted to the CPU

on more than 5,500 patients who presented in CPU were shown. Patients with troponin T-positive myocardial infarction (20%) were compared to those without a rise in troponin levels (80%). Patients with elevated troponin levels were significantly older than patients with normal troponin levels (70 vs. 68 years) with 67% being male (vs. 58% in the normal troponin group). Compared to patients with normal troponin, significantly more patients with high troponin levels presented with chest pain (70 vs. 65%) and dyspnea (25 vs. 20%). Patients with normal troponin more often suffered from rhythm disturbances. 83% of the patients with elevated troponin where diagnosed with acute coronary syndrome (vs. 31% in the group with normal troponin). 68% underwent a coronary angiogram (vs. 29% in the group with normal troponin) with high incidence of PCI (60%/21% in the high/normal troponin group, Fig. 4). Surprisingly, in both groups, patients' medication was not optimal. Only 77% of the patients were treated with aspirin, 67% with clopidogrel, and about 60% with statins, ACE-inhibitors and β-blockers. In summary, the CPU registry showed that prospective data can be achieved of patients treated in CPU. It demonstrated differences between patients with elevated troponin and normal troponin levels. Further studies are on their way to investigate clinical endpoints (death, MI, stroke) (presented by Lars Maier, Göttingen, Germany).

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