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ORIGINAL PAPER

Gender differences in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial

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Abstract
Background Cardiogenic shock (CS) complicating acute myocardial infarction (AMI) is associated with high mortality. Previous studies regarding gender-specific differences in CS are conflicting and there are insufficient data for the presence of gender-associated differences in the contemporary percutaneous coronary intervention era. Aim of this study was therefore to investigate gender-specific differences in a large cohort of AMI patients with CS undergoing contemporary treatment.
Methods In the randomized Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial, 600 patients with CS complicating AMI undergoing early revascularization were assigned to therapy with or without intra-aortic balloon pump. We compared sex-specific differences in these patients with regard to baseline and procedural characteristics as well as short- and long-term clinical outcome.
Results Of 600 patients 187 (31 %) were female. Women were significantly older than men and had a significantly lower systolic and diastolic blood pressure at presentation ($p < 0.05$ for all). Diabetes mellitus and hypertension were more frequent in women, whereas smoking was more frequent in men ($p < 0.05$ for all). Women showed a higher mortality within the first day after randomization ($p = 0.004$). However, after multivariable adjustment this numerical difference was no longer statistically significant. No gender-related differences in clinical outcome were observed after 1, 6 and 12 months of follow-up.

K. Fengler and G. Fuernau contributed equally to this study.

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Conclusion In this large-scale multicenter study in patients with CS complicating AMI, women had a worse-risk profile in comparison to men. No significant gender-related differences in treatment as well as short- and long-term outcome were observed.

Keywords Cardiogenic shock · Gender · Sex-differences · Mortality · Myocardial infarction · Early revascularization

Abbreviations

AMI	Acute myocardial infarction
CABG	Coronary artery bypass grafting
CS	Cardiogenic shock
IABP	Intra-aortic balloon pump
LMCA	Left-main coronary artery
PCI	Percutaneous coronary intervention
STEMI	ST-segment-elevation myocardial infarction

Introduction

Mortality in cardiogenic shock (CS) complicating acute myocardial infarction (AMI) is still unacceptably high [1, 2]. In AMI without CS inconclusive data regarding gender differences and clinical outcome exist. Women tend to have a higher mortality, especially in the setting of ST-segment-elevation myocardial infarction (STEMI) [3–7]. However, it was argued that this difference can rather be explained by a higher age and multimorbidity in women with AMI than by gender-related effects [8–11].There are only scarce data on gender differences in AMI complicated by CS. CS tends to be more frequent in women than in men [2, 9, 12–14]. There is also evidence that women have an age-independent lower cardiac power index, which has been shown to be the strongest hemodynamic predictor of mortality in CS patients [15]. Results on mortality itself so far are conflicting, as some studies found higher intra-hospital and even long-term mortality in women [3, 13, 16], while several others did not [14, 17–19]. Moreover, there are insufficient data for gender-associated differences in the present era of early revascularization by primary percutaneous coronary intervention (PCI).

The primary objective of this study was to determine gender-specific differences in a large cohort of AMI patients with CS undergoing contemporary treatment including early revascularization by PCI or coronary artery bypass grafting (CABG).

Methods

In the open-label, multicenter randomized Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial, 600 patients with CS complicating AMI undergoing early revascularization were assigned either to therapy with or without intra-aortic balloon pump (IABP). The exact design, inclusion and exclusion criteria of the trial as well as short- and long-term outcomes have been published previously [20–22]. Briefly, patients with AMI and CS were enrolled and randomized in a 1:1 ratio to one of the two study groups. CS was defined by a systolic blood pressure <90 mmHg for >30 min or inotropes required to maintain a systolic blood pressure >90 mmHg in the absence of hypovolemia, signs of pulmonary congestion and signs of impaired organ perfusion with at least one of the following: altered mental status, cold, clammy skin, urine output <30 ml/h or serum lactate >2 mmol/l. All patients were planned to undergo early revascularization using primary PCI or CABG and to receive optimal medical treatment according to current guidelines. Follow-up was performed at 1, 6 and 12 months. Safety-assessment included ischemic events, sepsis and bleeding. No significant differences in clinical outcome at short- and long-term follow-up were observed between the two groups. In the present substudy, we compared sex-specific differences in these patients with regard to baseline and procedural characteristics as well as short- and long-term clinical outcome.

Statistics

Most variables showed a non-normal distribution; therefore, all continuous variables are presented as median with interquartile range. Differences between men and women were investigated by Chi-square test for dichotomous variables and with Student's *t* test or Mann–Whitney *U* rank sum test according to the distribution for continuous variables. Differences in acute mortality (death within the first day after randomization) were analyzed by Chi-square test. For short- (30 days) and long-term (1 year) outcome

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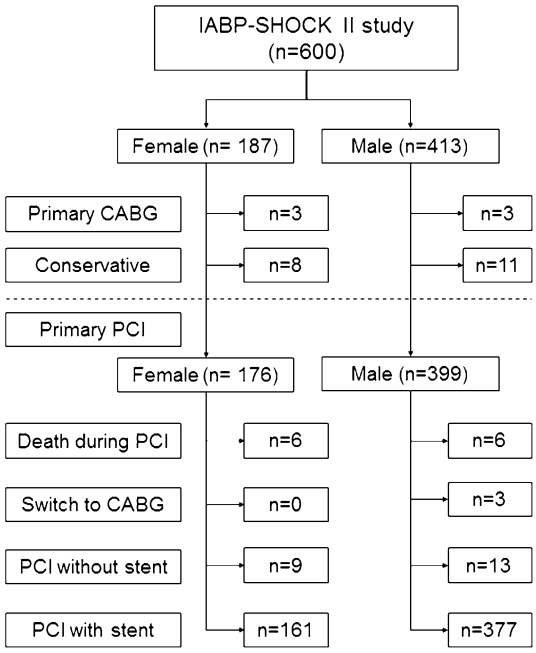

Fig. 1 Study flow

Chi-square testing as well as time to death analyses by Kaplan–Meier method with log-rank testing was used. To identify predictors of acute mortality a stepwise logistic regression model was used including the variables gender, age, IABP use, mechanical ventilation at admission, prior stroke, known chronic kidney disease, known peripheral artery disease, diabetes mellitus, impaired consciousness, cold and clammy skin, oliguria, arterial serum lactate, smoking status, hypertension, prior use of aspirin, beta-blockers, vitamin-K-antagonists or statins, serum creatinine, hemoglobin, hematocrit, ECG parameters (presence of left bundle branch block or ST-elevation), multivessel disease, and body temperature. For long-term outcome a stepwise Cox-regression model was built including all baseline variables with an association ($p < 0.1$) in univariable analysis. To test whether drug-eluting- or bare-metal-stent use was influenced by gender we created a logistic regression model including gender, age, atrial fibrillation at presentation, diabetes, known chronic kidney disease and presence of STEMI. p values <0.05 were considered significant. All statistical analyses were performed by an independent statistician at the Institut für Herzinfarktforschung, Ludwigshafen, Germany using SAS statistical package (Version 9.3).

Results

In total 600 patients were randomized in the IABP-SHOCK II trial. Of these, 187 (31 %) were female (Fig. 1). Further baseline characteristics are shown in Table 1. Women were significantly older than men and had a lower systolic and diastolic blood pressure at presentation. Diabetes mellitus and hypertension were more frequent in women, whereas a history of smoking was more frequent in men. Male patients were more likely to have undergone resuscitation before randomization and were characterized by a higher rate of mechanical ventilation at admission. Also, body temperature at admission was significantly lower in male than in female patients (Table 1).

Procedural characteristics

Of the 600 patients, 3 women and 3 men were planned for primary CABG (1.6 vs. 0.7 %; $p = 0.58$). In total, 19 patients (8 female and 11 male; 4.3 vs. 2.7 %; $p = 0.43$) were treated conservatively and received no PCI or CABG. Of the remaining patients in whom PCI and stent implantation were intended (see Fig. 1), 6 of each group died during the procedure (female vs. male: 3.4 vs. 1.5 %; $p = 0.25$), 3 male patients were switched to CABG after PCI was unsuccessful; 9 women and 13 men were treated with balloon angioplasty only (5.1 vs. 3.3 %; $p = 0.40$). Altogether 161 (86.1 %) female and 377 (91.3 %) male patients received a coronary stent (Table 2). Culprit lesion in the left-main coronary artery (LMCA) was seen significantly more often in men (Table 2). Rates of drug-eluting stent implantations were lower and a normal coronary flow in the culprit vessel after PCI was less often achieved in female patients. In a multivariable model for prediction of drug-eluting stent use (Table 3), age and the presence of STEMI were found to be negative predictors of drug-eluting stent implantation; female gender was not a significant predictor.

Adverse events

Adverse event rates were comparable in the two groups, with no significant differences in major bleeding (GUSTO definition), use of renal replacement therapy, sepsis and vascular complications until day 30. However, there was a significantly higher rate of minor or moderate bleeding events in women within the first 30 days (Table 2).

Mortality

In an unadjusted analysis women showed a significantly higher mortality within the first day after randomization. However, this numerical difference was no longer statistically significant after multivariable adjustment. Age, known peripheral artery disease and pH <7.36 remained significant predictors of acute mortality (Table 4). After 1 and 6 months no significant mortality differences between

Table 1 Baseline characteristics

	Overall ($n = 600$)	Female ($n = 187$; 31.2 %)	Male ($n = 413$; 68.8 %)	p value
Age (years)	70 (58; 77)	74 (63; 81)	68 (57; 75)	<0.001
Body mass index (kg/m^2)	27.3 (24.7; 30.0)	27.6 (25.0; 31.3)	27.0 (24.7; 29.4)	0.03
Heart rate at admission (bpm)	92 (75; 110)	93 (75; 110)	92 (75; 110)	0.85
Atrial fibrillation, *n* (%)	76 (13)	27 (14)	49 (12)	0.38
Systolic blood pressure at admission (mmHg)	90 (80; 109)	88 (80; 101)	90 (80; 110)	0.04
Diastolic blood pressure at admission (mmHg)	58 (49; 69)	53 (45; 60)	60 (50; 70)	<0.001
Baseline serum lactate (mmol/l)	3.9 (2.2; 7.6)	3.9 (2.3; 7.5)	3.8 (2.1; 7.8)	0.67
Baseline serum creatine kinase (ukat/l)	114 (92; 147)	106 (82; 141)	118 (97; 149)	0.001
STEMI, *n* (%)	373 (63)	119 (64)	254 (62)	0.66
Smoking, *n* (%)	204 (34)	46 (25)	158 (39)	<0.001
Hypertension, *n* (%)	412 (69)	142 (76)	270 (66)	0.02
Hypercholesterolemia, *n* (%)	227 (38)	66 (35)	161 (40)	0.32
Diabetes mellitus, *n* (%)	195 (33)	75 (40)	120 (29)	0.009
Known peripheral artery disease, *n* (%)	73 (12)	20 (11)	53 (13)	0.45
Prior myocardial infarction, *n* (%)	132 (22)	29 (16)	103 (25)	0.009
Prior PCI, *n* (%)	115 (19)	28 (15)	87 (31)	0.07
Prior CABG, *n* (%)	32 (5)	6 (3)	26 (6)	0.12
Prior stroke, *n* (%)	44 (7)	16 (9)	28 (7)	0.44
Randomized to IABP, *n* (%)	95 (50)	45 (48)	50 (52)	0.66
Coronary 3-vessel disease, *n* (%)	308 (52)	88 (48)	220 (54)	0.20
Resuscitation, *n* (%)	270 (45)	66 (35)	204 (49)	0.001
Mechanical ventilation at admission, *n* (%)	341 (57)	95 (51)	246 (60)	0.04
Left ventricular ejection fraction (%)	35 (25; 45)	40 (25; 45)	35 (25; 45)	0.08
Body temperature (°C)	36.6 (35.1; 37.7)	36.8 (35.7; 37.4)	36.5 (35.0; 37.2)	0.02
SAPS II-Score	52 (37; 68)	52 (39; 72)	52 (37; 67)	0.32

STEMI ST-segment-elevation myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *IABP* intra-aortic balloon pump, *SAPS II-Score* Simplified Acute Physiology Score II

female and male patients were observed (analyzed by both Chi-square test and Kaplan–Meier estimates). In unadjusted analysis, a non-significant trend towards higher mortality in women was found for 1-year mortality by Kaplan–Meier estimates (see Figs. 2, 3). However, after multivariate Cox-regression analysis female gender was not found to be an independent predictor for long-term outcome (Table 5).

Discussion

The present subanalysis of the IABP-Shock-II-trial shows several important findings: (1) there were significant gender-specific differences at baseline suggesting a higher cardiovascular risk in female patients; (2) after multivariable adjustment there were no significant gender-specific differences in the treatment strategy (e.g. choice of revascularization method or stent type); (3) there were no significant differences in mortality between female and male patients up to 12 months of follow-up after multivariable adjustment.

First, our findings at baseline are similar to previously reported studies. In the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? (SHOCK)-trial registry including over 800 patients women were also found to be older, had more often a history of hypertension and diabetes mellitus, were less likely to be smokers and presented more often with first myocardial infarction [17]. This has been confirmed in several other trials [14, 18, 19]. In the present analysis, male patients were more likely to have undergone resuscitation and were characterized by a higher rate of mechanical ventilation at admission compared to females. According to previous research, cardiac arrest, infarct-related or of other origin, is significantly more frequent in men and associated with high mortality [5, 7, 23]. The authors of one study also hypothesized that a higher intra-hospital short-term

Table 2 Periprocedural characteristics and adverse events

	Overall ($n = 600$)	Female ($n = 187$; 31.2 %)	Male ($n = 413$; 69.8 %)	p value
Culprit lesion				
LMCA, *n* (%)	54 (9)	8 (4)	46 (11)	0.007
LAD, *n* (%)	253 (42)	85 (46)	168 (41)	0.27
RCA, *n* (%)	152 (25)	54 (29)	98 (24)	0.18
LCX, *n* (%)	112 (19)	33 (18)	79 (19)	0.67
Bypass, *n* (%)	15 (3)	1 (1)	14 (3)	0.04
Additional lesions other than culprit lesion, *n* (%)	505 (84)	150 (80)	355 (86)	0.07
Primary strategy				
PCI, *n* (%)	575 (96)	176 (94)	399 (97)	0.16
CABG, *n* (%)	6 (1)	3 (2)	3 (1)	0.32
Conservative, *n* (%)	19 (3)	8 (4)	11 (3)	0.30
PCI[e] attempted/performed, *n* (%)	560 (93)	170 (91)	390 (94)	0.15
Patients with stent implanted, *n* (%)	538 (90)	161 (86)	377 (91)	0.07
Drug-eluting stents used (% patients with stents)	249 (46)	60 (37)	189 (50)	0.006
TIMI flow 0 prior PCI, *n* (%)	348 (61)	107 (61)	241 (61)	0.96
TIMI flow 3 post PCI, *n* (%)	469 (82)	135 (77)	334 (84)	0.04
Severe or life-threatening bleeding, *n* (%)	23 (4)	7 (4)	16 (4)	0.94
Moderate bleeding, *n* (%)	100 (17)	48 (26)	52 (13)	<0.001
Renal replacement therapy, *n* (%)	110 (18)	34 (18)	76 (18)	0.95
Sepsis, *n* (%)	111 (19)	31 (17)	80 (19)	0.41
Peripheral vascular complications, *n* (%)	23 (4)	8 (4)	15 (4)	0.70

LMCA left main coronary artery, *LAD* left anterior descendant coronary artery, *RCA* right coronary artery, *LCX* left circumflex coronary artery, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *TIMI* thrombolysis in myocardial infarction

Table 3 Logistic stepwise regression analysis for prediction of drug-eluting stent use

	Chi^2	Odds ratio	95 % CI	p value
Female sex	2.6	0.72	0.48–1.07	0.11
Age per 10 years	16.3	0.73	0.62–0.85	<0.001
Atrial fibrillation	3.1	0.60	0.34–1.06	0.08
Diabetes	0.3	0.88	0.59–1.33	0.56
Known chronic kidney disease	3.1	1.55	0.95–2.50	0.08
ST-elevation	5.5	0.63	0.43–0.92	0.02

95 % CI 95 % confidence interval

mortality in women was outweighed by the higher pre-hospital mortality in men [5]. Notably, such difference has not been previously reported for the setting of CS. Also there is evidence for a shorter pre-hospital delay in male patients with acute coronary syndrome with and without CS indicating a better infarction-related prognosis [3, 14, 24]. Unfortunately, data for time from symptom onset to revascularization were only available in less than half of the patients included in the present cohort and could thus not be included in our analysis.

We also found an excessively high rate of LMCA-culprit lesions in male participants in the present study. Previous trials regarding this finding are inconclusive [4, 9, 25, 26]. In the published literature for CS, there were no significant differences in the prevalence of the LMCA as culprit lesion between men and women and its prognostic value is unclear [3, 17]. Due to the small absolute number of LMCA culprit lesions in women in the present study, its effect on mortality cannot be fully determined.

Second, our univariable findings suggested that drug-eluting stents were used less frequently in women. However, this hypothesis could not be confirmed in a multivariable analysis. Herein, female gender was no more significantly associated with the type of stent used. Koeth and coworkers [14] reported similar results in their study including >3,800 patients, even though the overall number of revascularization by PCI was low in their trial (PCI in <20 %). Surprisingly, the proportion of drug-eluting stents being used throughout the present study cohort is relatively low as compared to previous trials for STEMI [3, 9], non-STEMI [9] and also compared to one study including 103 patients with CS [27]. In comparison to these trials including the trial investigating patients with CS, our study population tended to be older possibly resulting in a higher rate of bare-metal stents. Furthermore, the rate of atrial

Table 4 Logistic stepwise regression analysis for mortality on day 1 (only statistically significant predictors and sex presented)

	Chi^2	Odds ratio	95 % CI	*p* value
pH <7.36	6.0	3.87	1.31–11.43	0.01
Known peripheral artery disease	4.0	2.47	1.02–6.00	0.045
Age per 10 years	4.0	1.45	1.01–2.10	0.047
Female sex	0.2	0.82	0.34–1.97	0.65

95 % CI 95 % confidence interval

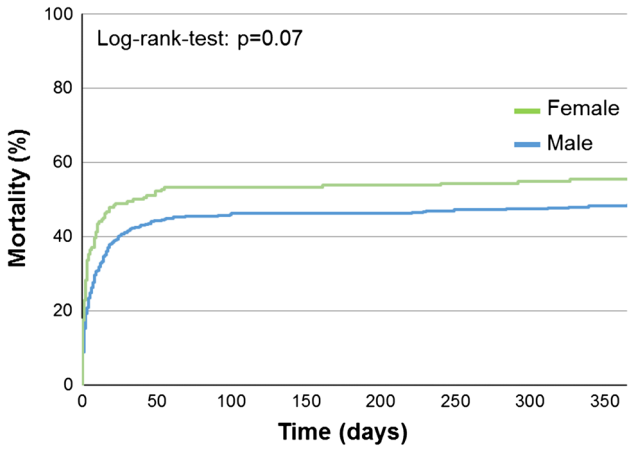

Fig. 2 Kaplan–Meier survival curve for long-term survival

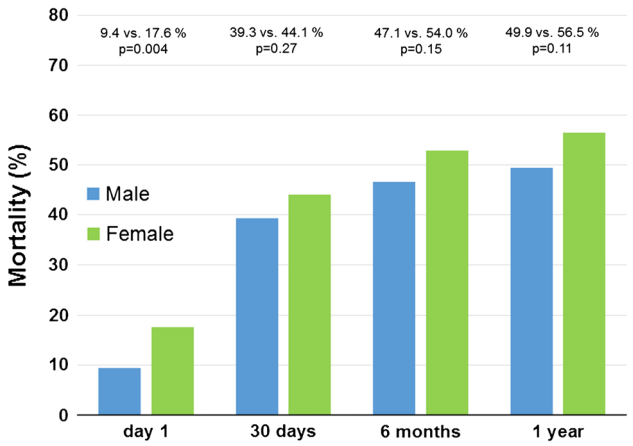

Fig. 3 Gender-related exact mortality by Chi-square test

fibrillation in our study in CS (13 %) seems to be higher than previously described in STEMI without CS also influencing the use of bare-metal stents [28].

Third, the lack of gender-specific differences in acute mortality is in line with the results of the SHOCK-trial [17], even though treatment has changed significantly. These results are also consistent with several other studies [14, 18, 19]. In contrast, 3 recent registry studies (including 227, 157,000 and 47,500 patients with CS, respectively)

Table 5 Multivariable stepwise Cox-regression analysis for 1-year mortality (only statistically significant predictors presented)

	Chi^2	Hazard ratio	95 % CI	*p* value
Baseline lactate per 10 mmol/l	45.8	1.31	1.17–1.48	<0.001
Age per 10 years	22.1	1.29	1.15–1.43	<0.001
TIMI flow 3 after PCI	15.3	0.54	0.40–0.72	<0.001
Baseline creatinine per 100 µl/l	15.6	1.27	1.12–1.45	<0.001
Cognitive impairment at admission	14.3	1.64	1.19–2.26	<0.001
Prior stroke	12.5	2.06	1.40–3.03	<0.001
pH <7.36	7.3	1.48	1.11–1.96	0.007

95 % CI 95 % confidence interval, *TIMI* thrombolysis in myocardial infarction, *PCI* percutaneous coronary intervention

found a worse outcome for women as compared to men, which persisted even after multivariable adjustment [3, 13, 16]. However, these studies included only CS-patients with STEMI, and rates of early revascularization were low (42.7 %) [13], or not reported [16]. Only the study by Velders and colleagues [3] had a PCI rate as recommended by present guidelines (>95 % treatment with stents). Interestingly, for AMI a meta-analysis by Berger et al. showed that after adjustment for angiographic severity of coronary artery disease, sex-related differences disappear [4]. Also in the latter analysis, no gender difference was found for the subset of patients undergoing cardiac catheterization. These findings in CS are also supported by a lack of difference in myocardial salvage in patients with STEMI without CS [29]. Similar observations were made in a study investigating stable patients undergoing CABG. Woman showed higher acute mortality which was not significant after multivariable adjustment [30].

Data for gender-specific long-term-survival in CS are scarce. Abdel-Qadir and colleagues [18] found no gender-related differences in adjusted mortality in a registry study of 9,750 patients (PCI rate 14.0 % in men and 10.6 % in women). In fact, there is only one contemporary observational study in 227 CS-patients providing long-term-data, in which female gender was an independent effect-modifier for 1-year mortality after CS complicating STEMI [3]. In contrast, in our larger cohort including also patients with non-STEMI-related CS, female gender was not an independent predictor for 1-year mortality.

Conclusion

Within the present cohort of patients with CS complicating AMI treated with early revascularization, there was no

significant difference in short- or long-term mortality between female and male patients.

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Conflict of interest Dr. Thiele reports receiving consulting fees from Eli Lilly, grant support on behalf of his institution from Eli Lilly and Terumo, and lecture fees from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, the Medicines Company, and Terumo; Dr. Zeymer, serving on the board of Daiichi Sankyo and Eli Lilly and receiving consulting and lecture fees from Daiichi Sankyo, Eli Lilly and the Medicines Company; Dr. Richardt, receiving lecture fees from Maquet Cardiovascular; Dr. Böhm, receiving consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Merck, Novartis, Pfizer, Sanofi Aventis, and Servier and lecture fees from AstraZeneca, AWD.pharma Dresden, Bayer, Berlin-Chemie, Boehringer Ingelheim, Daiichi Sankyo, Merck, Novartis, Pfizer, Sanofi Aventis, and Servier; Dr. Schneider, serving on the ethics committee of Landesärztekammer Baden-Württemberg, receiving payment for manuscript preparation from Biosense Webster, Grupo Ferrer, and Nycomed, and receiving money on behalf of the clinical research organization at his institution from Abbott Vascular, AstraZeneca, Bayer Schering, Bayer Vital, Biotronik, Bristol-Myers Squibb, Boehringer Ingelheim, Cordis, Daiichi Sankyo, Diagenics, Enverdis, Eli Lilly GlaxoSmithKline, Guidant, IKKF, Impulse Dynamics, Medtronic, Merck, Novartis, Roche Diagnostics, Sanofi Aventis, Schering-Plough, Siemens, St. Jude Medical, Takeda Pharma, Tromssdorff, and Vifor Pharma; and Dr. Werdan serving on the board of Biotest and Servier, receiving grant support on behalf of his institution from Biotest and Servier, and receiving lecture fees from Biotest, Brahms, Maquet Cardiovascular, and Servier. No other potential conflict of interest relevant to this article was reported.

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