Clinical Safetyy and Efficacy of the Coroflex Blue cobalt-chromium coronary stent system. Results of the Real world Coroflex Blue Registry

Wolfgang Bocksch[a] MD, Francisco Pomar[b] MD, Mieczyslaw Dziarmaga[c] MD, Tresukosol Damras [d], MD, Omar Ismail[e], MD, Bronislaw Janek[f] , Joerg Carlsson[g] and Jean-Philippe Simon [h] on behalf of the Coroflex Blue Registry Investigators

[a] Charité-Universitaetsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany

[b] Hospital General de Valencia, Valencia, Spain

[c] SPSK, Poznan, Poland

[d] Siriraj Hospital Bangkok, Thailand

[e] Penang General Hospital, Penang, Malaysia

[f] Central Hospital of Kalmar, Kalmar Sweden

[g] Clinique Pasteur, Essey Lès Nancy, France

Correspondence to:

Wolfgang Bocksch, MD, PhD, Head of Cardiac Catheterization Laboratories, Department of Cardiology, Universitaetsmedizin Berlin, Charité-Campus Virchow-Klinikum, Humboldt-Universität zu Berlin, Augustenburger Platz 1, 13353 Berlin, Germany , Phone: ++49-30-450653262, Fax.:++ 49-30-450553961, e-mail: wolfgang.bocksch@charite.de

Abstract

Background —The development of cobalt-chromium bare-metal stents (BMS) with thinner struts has lead to better deliverability and lower target lesion revascularisation rates compared to stainless steel BMS.

Aim- The Coroflex Blue Registry was an international, prospective, multicenter registry study to evaluate the clinical efficacy and safety of the Coroflex Blue cobalt-chromium stent in a real-world-setting.

Methods— The registry enrolled 2315 patients (mean age 64.3±11.1 years, 459 diabetics [19.8%), 598 STEMI [25.8%], 266 NSTEM [11.5%]) with symptomatic ischemic heart disease attributable to single de novo or restenotic nonstented lesions of a single vessel amenable to percutaneous stenting. The primary end point was clinically driven target lesion revascularisation (cTLR) 6 months after enrolment, secondary endpoints were technical/procedural success, in-hospital outcome, definite stent thrombosis and major adverse cardiac events (death, myocardial infarction, or cTLR) after 6 months.

Results— In a complex lesion cohort (60.3% Typ B_2/C-lesions), the technical success rate was 99.1%, the procedural success rate 98.5%. In-hospital complications were death in 14 (0.6%), myocardial infarction in 28 (1.2%), emergency bypass surgery in 2 (0.1%) and definite stent thrombosis in in 13 patients (0.5%). The incidence of cTLR after 6 months was 5.5% (cTLR elective patients 4.7%, STEMI/NSTEMI patients 6.9%) . The cumulative 6-month acute/subacute stent thrombosis rate was 1.6%. 6-month-event-free survival was 90.8% in all patients, 93% after elective PCI and 87% after PCI for NSTEMI/STEMI.

Conclusions — This registry demonstrated the safety and clinical efficacy of the Coroflex Blue thin-strut cobalt-chromium coronary stent platform in a real life scenario including acute

MI patients and raises the question if the use of DES for primary prevention of restenosis and cTLR is really justified.

Key Words: cobalt-chromium stent; percutaneous coronary intervention;

Introduction

Elective percutaneous coronary intervention (PCI) using bare metal stents (BMS) does not prolong life but results in relief of ischemic symptoms (1). Therefore persistent relief of angina pectoris without the need for clinical driven target-lesion revascularisation (cTLR) for a significant In-Stent-restenosis remains the primary goal of PCI. Compared to BMS, drug-eluting stents (DES) significantly reduce the risk for in-stent-restenosis and subsequent target-lesion revascularisation (2,3,4,5). Therefore DES are used as standard therapy for a large variety of coronary lesions in various patient subsets (6). Disadvantages of DES are limited flexibility/deliverability due to the stent/polymer design, increased cost (7) and , of course the continous risk of late stent thrombosis (8,9). On the other hand, improved design of BMS and reduced strut thickness results in better outcomes after BMS (10,11,12). The Coroflex Blue coronary stent system (B.Braun Vascular Systems, Berlin, Germany) is a new low-profile, nonferromagnetic stent with a strut thickness of 65µm for all stent sizes (Figure 1). The stent is made of a cobalt-chromium based alloy which is stronger and denser than 316L stainless steel, allowing for thinner struts, increased flexibility, and better deliverability without compromising radial strength or radiopacity. The Coroflex Blue Registry was designed to determine the safety and efficacy of the Coroflex Blue coronary stent system in a real life setting including patients presenting with an acute coronary syndrom.

Methods

Registry design

This was an all-comer prospective, multicenter registry study designed to evaluate the safety and efficacy of the Coroflex Blue coronary stent system (B.Braun Vascular Systems, Berlin, Germany). Patients were enrolled at 58 sites in Asia (6) and Europe (52). The primary end point was the rate of cTLR after 6 months, secondary endpoints were technical success, procedural success, in-hospital outcome, definite acute/subacute stent thrombosis and event-free survival (absence of major adverse cardiac events [MACEs]—death, myocardial infarction [Q wave and non–Q wave], or target lesion revascularization (TLR) by means of PCI or coronary artery bypass graft surgery [CABG])—6 months after the procedure.

Inclusion and exclusion criteria

Study participants aged > 18 years were required to have symptomatic ischemic heart disease and/or proven ischemia (positive stresstest) attributable to stenotic lesions of native coronary arteries that were amenable to percutaneous stenting. Patients with 3-vessel disease were permitted, however, only 1 lesion per patient could be treated in this registry. The target lesion could be de novo or restenotic in native coronary arteries, with a reference vessel diameter of 2.5 to 4.0 mm and a maximal lesion length of 25 mm; restenotic lesions must not have been previously stented or have had any previous treatment other than standard balloon angioplasty. Major exclusion criteria were cardiogenic shock, unprotected left main stenosis, saphenous vein and arterial graft lesions, and planned multi-lesion or multi-vessel-stenting.

Percutaneous Interventional Procedure

After obtaining vascular access, an introducer sheath of ≥5Fr in size was inserted using the standard femoral, brachial or radial approach. After catheter introduction, intravenous heparin (100 IU/kg, maximum 10.000 IU) was administered and supplemented as needed to maintain anticoagulation throughout the procedure. Patients who had received a glycoprotein IIb/IIIa inhibitor had their activated clotting time maintained at >225 seconds; all others had their activated clotting time maintained >250 seconds. The target lesion was pretreated with standard balloon angioplasty, direct stenting could be preferred. No more than 1 stent was used (except for a bailout procedure). Immediately after the procedure, antithrombotic therapy was performed in accordance with the hospital protocol. Vascular sheaths were removed according to usual hospital practice, and approved vascular closure devices could be used at the discretion of the investigator.

Data collection and analysis

Baseline and follow-up clinical data were collected on case report forms by local study coordinators at the study sites. Clinical follow-up was performed at 180 days after the procedure by the participating hospitals during office visits or via telephone. The primary end point of cTLR at 6 months was analyzed on an intent-to-treat basis. Categorical variables are depicted in absolute numbers including percentage, continuous variables are reported as mean values including standard deviation. Differences between groups were evaluated by using the χ^2test.

Definitions of clinical events

Technical success: The Coroflex Blue stent could be placed successfully within the target-lesion directly or using any percutaneous method for lesion preparation

Procedural success: Procedural success was defined as technical success plus attainment of <50% residual stenosis of the target lesion.

Death: All deaths were considered cardiac unless an unequivocal noncardiac cause could be established. Cardiac deaths included all events related to a cardiac diagnosis, a complication of the procedure, treatment for a complication of the procedure, or an unexplained cause. Unexpected death even in patients with coexisting and potentially fatal noncardiac disease (eg, cancer, infection) was classified as cardiac unless history related to the noncardiac diagnosis suggested death was imminent. Mortality was then reported as all-cause as well as cardiac mortality versus noncardiac (13).

Myocardial infarction: Q-wave myocardial infarction was defined as either (1) the presence of chest pain or other acute symptoms consistent with myocardial ischemia and new pathologic Q waves in =2 contiguous electrocardiographic leads, or (2) elevated cardiac enzyme levels >2 times the upper limit of normal associated with any elevation above the upper limit of normal in creatine kinase-MB levels in the presence of new pathologic Q waves. Non–Q-wave myocardial infarction was defined as an elevated creatine kinase =2 times the upper limit of normal associated with any elevation above the upper limit of normal in creatine kinase-MB levels in the absence of new pathologic Q waves.

Clinically driven target lesion revascularisation (cTLR): cTLR was defined as repeat percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery trigerred by clinically indicated repeat coronary angiography.

Stent thrombosis: Stent thrombosis was defined as an angiographically documented thrombotic occlusion of target lesion (0-24 h post-PCI acute, 1-30 days post-PCI subacute, 1-6 months post-PCI late stent thrombosis, [13]).

Major adverse cardiac event (MACE): Occurrence of either death, myocardial, infarction or target lesion revascularisation during follow-up.

Results

Baseline demographics and lesion characteristics:

Among the 2315 patients enrolled, baseline demographic and clinical characteristics (Table 1) showed a mean age of 64.3 years; 25.4% were women and 19.8% had a history of diabetes mellitus. 37.3% presented with acute myocardial infarction (STEMI 25.8%, NSTEMI 11.5%), 62.7% underwent PCI electively. Baseline lesion characteristics are listed in Table 2. 60.3% of target lesions were Typ B_2/C lesions, 32.3% were moderately to severely calcified , 13% were severely tortuous with an angle of more than 45%. Mean preprocedure percent diameter stenosis was 87.0±12.9%.

Technical and procedural success

Technical success was achieved in 99.1% of patients. In only 21 patients the stent could not be delivered to the target lesion (0.9%). These patients were handled with balloon angioplasty only. Procedural success was achieved in 98.5% of attempted lesions (2281/2315). In 13 patients a residual post-procedural stenosis of less than 50% could not be achieved (no reflow, untreatable distal dissection) after stent placement despite successful placement of the stent. In calcified lesions procedural success was 98.3% (734/747), in tortuous target vessels 93.7% (282/301). Mean percent diameter stenosis decreased from 87±12.9% to 21.1±8.2%. Direct stenting was done in 54.5% of lesions, the maximal inflation pressure was 13 ± 3.2 atm. The entire procedural data is depicted in Table 3.

In-Hospital outcome

During hospital course, 14 out of 2315 treated patients died (0.6%). 2 patients underwent emergency CABG (0.1%). Procedure-induced myocardial infarction occurred in 28 patients which was 1.2% of the entire study population and 1.9% after elective PCI. 13 acute/subacute stent thrombosis occurred during the hospital stay (0.6%).

6-month-cTLR

352 patients (15.2%) had a clinically-indicated post-PCI non-invasive workup by an internist or cardiologist including stress testing. 278 patients (12%) underwent control coronary angiography, indications were in most cases typical recurrent angina without proven ischemia (118/278, 42.5%) and acute coronary syndrome (n=72 [25.9%], unstable angina 44 [15.8%], NSTEMI 17 [6.1%], STEMI 11 [4%]). 88 patients (31.7%) had proven ischemia, respectively. By angiography, 132 patients had an in-stent- restenosis of more than 50% (binary restenosis rate 47.5%) , 103/132 were successfully treated by repeat-PCI , 25 underwent elective CABG. Therefore, the primary end point of the registry, the cumulative 6 month-cTLR rate, exceeded 5.5% (128/2315). cTLR-rates did not differ significantly between elective PCI (n=68/1451, 4.7%) and patients with NSTEMI (n=14/266, 5.3%) or STEMI (n=21/598, 7.7%). Patients with diabetes (n=30/459, 6.5%) had a slightly elevated cTLR of 6.5% compared to patients without diabetes (n=98/1856, cTLR 5.3%, n.s.).

Event-free survival

214 out of 2315 patients (9.2%) suffered a MACE within 6 months of follow-up. The MACEs were 59 deaths (2.6%), 52 myocardial infarctions (2.3%) and 128 cTLRs (5.5%). In patients undergoing elective PCI, 6-month mortality/MACE-rate was 2.2% (32/1451) and 7% (102/1451), in NSTEMI/STEMI patients 3.1% (27/864) and 13% (112/864). In conclusion, 6-month event-free survival was achieved in 90.8% of all patients after PCI, in 93% after elective PCI, in 87% after PCI for NSTEMI/STEMI (n.s.).

Stent thrombosis

The post-discharge stent thrombosis rate was 1.0% (23/2315), all stent thrombosis occurred before day 30 post-PCI. Afterwards, not any stent thrombosis was observed. The cumulative 6-month-stent-thrombosis rate including the 13 in-hospital stent thrombosis was 1.6% (36/2315).

Discussion

To our knowledge the Coroflex-Blue Registry is the largest all-comer registry study to document the efficacy and safety of a thin-strut cobalt-chromium bare-metal stent in a real-world-setting instead of selected study patients.

The major findings of the registry are as follows: (1) In a real-world patient population with a high proportion of complex Type B_2/C-lesions and ACS patients the Coroflex Blue stent can be placed with a high technical success rate even in tortuous and moderately to severely calcified vessels. (2) The 6-month-cTLR-rate of 5.5% is remarkably low and comparable to the cTLR-rates after implantation of DES.

Regarding the Coroflex Blue registry patient population, there is a remarkable high proportion of ACS patients (37.3%) and patients with complex lesions (60.3% Type B_2/C-lesions) . Nevertheless, the overall technical success rate of 99.1% and the procedural success rate of 98.5% compares favourably to other cobalt-chromium stents. Including less complex lesions (35.2% MI-patients, 34% TypB_2 lesions only), Xu et al. (14) reported in 429 patients for the cobalt-chromium Vision stent a technical success rate of 99.3%. Sketck et al (15) reported in 298 patients a 100% technical success rate for the cobalt-chromium driver stent, excluding patients with acute myocardial infarction and including only 50.7% type B_2/C-lesions, respectively. Especially among patient subgroups with complex lesion morphology as calcified lesions and tortuous vessel anatomy, the procedural success rate of 94.3 and 94% for the Coroflex Blue stent is remarkable.

The in-hospital outcome after stent implantation with a low in-hospital-mortality of 0.6% and a procedure-induced myocardial infarction rate of 1.2% is excellent. Again, this compares favourably with the reported data for the Vision stent (7) in the BMS-arm of the BASKET-

Trial (281 patients, death 0.4% and myocardial infarction 2.9%) and the data of the driver stent registry. Sketch et al. (15) who excluded ACS-patients reported no in-hospital deaths and a procedure related myocardial infarction rate of 1.7%.

Acute, subacute and late stent thrombosis is a major limitation of either DES or BMS implantation. In a meta-analysis of Kereiakes et al. (16) the incidence ranges between 0.9% and 2.8% for BMS and between 0.8% and 3.1% for drug-eluting stents. Especially in complex patients (diabetics, chronic renal failure) and in complex anatomic situations (bifurcations, unprotected left main stenosis) the risk of stent thrombosis rises to 3.3% (17). In light of the complex patient cohort and the complex lesion morphology, the 30-day stent thrombosis rate of 1.6% is within normal limits. Not any late stent thrombosis was observed. This , of course, is a general advantage of BMS compared to DES which have a life-long constant risk of late stent thrombosis (18) and the need for 6-12-month dual-antiplatelet therapy for all patients receiving DES (6).

The reduction of cTLR is the major goal of any innovation in PCI, this refers to BMS (19,20) and, of course, also for DES (2,3,4,5). TLR-rates have declined from 23.3% after balloon angioplasty to 13.5% after BMS-Implantation (21) and finally to 7-9% after DES-Implantation (2,3,4,5). Regarding BMS, stent material, stent design and stent thrut thickness has proven to have an important impact on in-stent-restenosis and on subsequent cTLR (10,11,12). Using stainless steel stents only-as it was the case in the PRESTO-trial (Prevention of REStenosis with Tranilast and its Outcomes, 22)-.the cTLR-rate for all the 1148 patients was 14% (22). In the PRESTO-trial, 17.9% of the 2684 diabetic patients and only 12.8% of the 8798 non-diabetic patients underwent clinically-driven target vessel revascularisation (23). Cobalt-chromium stents have shown lower TLR-rates than conventional stainless steel stents in a limited number of patients with selected indication for PCI. In registry studies the cTLR-rate for the driver stent in 298 selected patients was 8.8%

after 9 months (15). For the Vision stent, cTLR after 6 months was 7.8% (7). The Coroflex Blue registry including more than 2300 patients is so far the largest cobalt-chromium stent registry with an all-comer design. The cTLR-rate of 5.5% is one of the lowest ever documented cTLR-rates for a bare-metal stent so far. The high proportion of STEMI-patients with potentially non-viable myocardium does not explain the low cTLR-rate, because in patients undergoing elective PCI, the cTLR-rate of 4.7% is even lower than in the entire study population.

Comparison to DES

TLR-rates after DES-Implantation range between 4.4% and 6.0 % in randomised studies (2,3,4) and between 1.4% and 5.8% (23,24,25) in registry studies. In complex lesions the cTLR-rate exceeded 9.4% after Taxus Express stent implantation (24). The German Cypher registry (25) enrolling more than 1700 patients has shown a cTLR-rate of 9.2% for elective patients, for NSTEMI patients 7.8% and 5.9% for STEMI-patients. The difference between these results for DES and the results of the Coroflex Blue registry is minor. The important question rises if primary DES-implantation for de-novo-stenosis in coronary arteries is really necessary in the majority of patients. Taking our data, 94.5% of patients would have received a DES without needing it, but with a low, life-long risk of late stent thrombosis (18). At present, BMS-In-Stent-restenosis can be handled easily and effectively by either Re-PTCA for focal ISR (26), by brachytherapy (27) or by DES-in-BMS-implantation for diffuse ISR (26,28). In the future, the drug-eluting balloon might be a therapeutic alternative for BMS-ISR with a much higher clinical efficacy than a DES or brachytherapy and a need for only 4-week-dual antiplatelet therapy (29).

At present, we definitely need drug-eluting stents for complex multi-vessel procedures where CABG is a therapeutic alternative. Complex lesion subsets as unprotected left main stenosis (30), chronic total occlusions after successful recanalization (31) and complex bifurcation stenosis requiring techniques like T-stenting, Culotte-stenting, Crush-stenting,V-Stenting have inferior results using BMS (32). In a report of Park et al. (33) 12-month-TLR after unprotected left main stenting was significantly lower after DES-implantation (2%) than after BMS-implantation (17.4%). After successful recanalization of chronic total occlusions the use of DES had a significant better outcome with a cTLR of 6.3% than the use of BMS with a cTLR of 44.7% (31). Using DES in bifurcation lesions, Colombo et al (34) reported a cumulative 6-month TLR for either main or side branch between 6.3% for provisional T-stenting and 7.3% for crush stenting. This is much better than the reported cTLR-rates of 12.5% after BMS-T-Stenting and 33.3% after BMS Culotte stenting (32).

Limitations

The risk of In-Stent-restenosis and subsequent cTLR does not end 6 months after stent implantation. There might be an increase in cTLR after 9 and 12 months, respectively (35). Moreover the cTLR-rate might be influenced by the different availability of outpatient cardiac care and catheterization facilities in different national health care systems.

The major limitation of the Coroflex Blue registry is the fact that –per protocol- only one lesion per patient could be treated. If multiple complex lesions in different vessels were attempted in one patient, the cumulative risk of any cTLR might have been higher, as shows the 16.8% repeat vascularisation rate after stenting in the Arterial Revascularization Therapies Study (21). Even by use of DES for multilesion- and multi-vesssel-stenting, the cTLR-rate after 6 months exceeds 14.3% (36).

Conclusions and Clinical implications

Using thin-strut cobalt chromium stents in a real-world setting including acute myocardial infarction patients, 90.8% of patients survive event-free and 94.5% do not need clinically-driven re-intervention for in-stent-restosis. The stent thrombosis rate of 1.6% is remarkably low for an all-comer cohort, not any late stent thrombosis was observed within 6 months. The question raises if primary prevention of cTLR by means of DES is really justified in most patients. DES should be reserved for complex multi-vessel interventions with a high risk of any restenosis and cTLR.

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Table 1: Baseline characteristics of the patients

Patients		**%**
Age (mean ± SD) (yrs)	64.3 ± 11.1	
Men	1726	74.6
Women	589	25.4
Diabetes mellitus	459	19.8
End stage renal disease	64	2.8
Stable/unstable angina	1451	62.8
Stress-ECG performed	580	40 *
Positive stress-ECG	559	96.8**
STEMI	598	25.8
NSTEMI	266	11.5

Results are shown as mean ± SEM or n (%);

Table 2. Angiographic baseline characteristics of the patients.

Patients	n	%
Target vessel		
Left anterior descending (LAD)	852	36.8 %
Left Circumflex (LCX)	583	25.2%
Right coronary artery (RCA)	880	38.0%
ACC/AHA lesion classification		
A	186	8.1%
B_1	732	31.6%
B_2	947	40.9%
C	450	19.4%
Lesion morphology		
Eccentric lesion	954	41.2%
Angulation >45°	301	13.0%
Calcification (moderate to severe)	747	32.3%
Bifurcation	234	10.1%
Ostial lesion	116	5.0%
Intracoronary Thrombus	502	21.7%
Chronic total occlusion	80	3.5%
Restenosis after PTCA	53	2.3%

Results are shown as n (%)

Table 3. Procedural characteristics of the patients.

Patients		%
Stent diameter		
2.5 mm	852	36.8 %
3.0 mm	583	25.2%
3.5 mm	880	38.0%
Stent length (n=2367)		
8 mm	256	10.8%
13 mm	728	30.8%
16 mm	735	31.1%
19 mm	410	17.3%
25 mm	238	10.1%
Diameter stenosis (visual estimate)		
Before PCI	87±12.9%	
After PCI	21.1±8.2%.	
Implantation		
Predilatation	1053	45.5%
Primary stenting	1262	54.5%
Max. Implantation pressure	13 ± 3.2 atm	
Post-Dilatation	499	21.1%
Max. Post-dilatation pressure	14.0± 3.6 atm	
Medication		
GPIIB/IIIA	489	21.2%
Heparin	2215	95.7%
ASS	2037	88.0%
Thienopyridine (Clopidogrel/Ticlopidine	2045	88.3%

Results are shown as mean ± SEM or n (%)

Table 4. MACEs (death, myocardial infarction and cTLR after 6 nonths in all patients, patients after elective PCI and after emergency PCI for NSTEMI/STEMI

Patients	**All**	**Elective PCI**	**STEMI/NSTEMI**
n	2315	1451	864
All-cause death	59 (2.6%)	32 (2.2%)	27 (3.1%)*
Myocardial infarction	52 (2.3%)	25 (1.7%)	27 (3.1%)*
cTLR	128 (5.5%)	68 (4.7%)	60 (6.9%)*
Any MACE	214 (9.2%)	102 (7%)	112 (13%)*

Results are shown as n (%) , * non-significant

Legend to the Figure

Figure 1: The Coroflex Blue cobalt chromium alloy coronary stent system

Appendix

Participating Centers (with more than 20 patients included in the registry)

Cyprus: Costas Zambartas, MD, National Principal investigator, Nicosia General Hospital, Cyprus
Czechia: Bronislav Janek, MD, , National Principal investigator ,IKEM, Praque, Pavel Cervinka, MD, Masaryk Hospital, Ústí nad Labem, Ladislaw Groch, MD, St. Anna Uni- Hospital, Brno
France : Jean Philippe. Simon, MD, National Principal investigator Polyclinique Pasteur, Essey Lès Nancy, Bruno Huret, MD, Jean-Francois Morelle, MD Pascal Richard, MD,Clinique St. Martin, Caen, Hakim Ben Amer, MD,Hôpital Européen de Paris –La Roseraie, Aubervilliers
Germany : Wolfgang Bocksch, MD, National Principal investigator , Kathrin Dittkrist, RN, Charité Campus Virchow, Berlin, Matthias Leschke, MD, prof., Staedt. Kliniken Esslingen, Martin Spieker, MD, Prof.St. Josef-Hospital, Klinikum der Ruhr-Universität Bochum, Günter Pothoff, MD, Gemeinschaftspraxis Kardiologie/Pneumologie im Elisabeth KKH, Moenchengladbach, Jürgen Stumpf, MD, Praxisklinik Dresden, Ulrich Tebbe, MD, Prof. ,Klinikum Lippe GmbH, Detmold, Conrad Pfafferott, MD, Prof. , Klinik Ingolstadt, Christian Hengstenberg, MD, Prof., Universitaet Regensburg, Dieter Horstkotte, MD, Prof., Herz- und Diabeteszentrum NRW, Roland Brueckl, MD, KH Landshut-Achdorf
Malaysia: Omar Ismail, MD, , National Principal investigator ,Penang General Hospital, Penang, Zurkurnai Yusof, MD, Hospital University Sains Malaysia, Sim Kui Hian, MD, Prof., Sarawak Umum Hospital/ Kuching GH
Netherlands: J. Vainer, MD, , National Principal investigator , Akademisch Ziekenhuis, Maastricht
P. Den Heijer, MD,Thoraxcentrum Breda, Breda, T.J. Gin, MD, Rijnstate Ziekenhuis, Arnheim
Norway: Jan Mannsverk, , National Principal investigator , Unversity Hospital, TromsØ,
Poland: Mieczyslaw Dziarmaga, MD, , National Principal investigator , SPSK, Poznan, Adam Kern, MD, WSS, Olsztyn , Piotr Kardaszewicz, MD, WNP, Czenstochowa, Zbigniew Krolikowski, WSS, Bytom, Stanislaw Buda, MD,, WSS ul. Grunwaldzka, Piotr Achremczyk, RSS ul. Tochtermana, Milosz Marc, MD, WSS ul. Lwowska , Waldemar Dorniak, SP Al. Jana Pawla
Portugal: António Leitão Marques, MD, , National Principal investigator ,Centro Hospitalar de Coimbra, Coimbra
Ricardo Santos, MD, Bernardo, MD, Setubal
Slovakia: Viliam Fridrich, MD, National Principal investigator, Institute for Cardiovasc. Disease, Bratislava
Spain: Francisco Pomar, MD , National Principal investigator , & Emilio Perez, MD, Hospital General de Valencia, Valencia, José Ramón, MD, López Mínguez, MD,Infanta Cristina,MD, Bajadoz, Luis Insa, MD ,Juan Sanchís, MD, Clínico de Valencia, Jaime Pey Illena, MD, Ramón y Cajal, Madrid, Jaime Pey Illena, MD, Clínica La Zarzuela, Ricardo García, MD, General de Elche, Elche, Javier Portales, MD, Clínica Nª Sª de Guadalupe, Cáceres, Francisco Picó, MD, Clínica San Carlos, Murcia, Luis Andrés, MD,Hospital La Fé, Valencia , José Díaz Fdez, MD, H. Juan Ramón Jiménez, MD, Huelva, Angel Sánchez, MD, V. del Rocío, MD, Sevilla, Fina Mauri, MD, Germans Trias i Pujol, Badalona, Bassaganya, MD, Josep Trueta, MD, Tarragona Adrián Beloscar, MD, Joan XXIII, MD, José Calabuig, MD, Clínica Universitaria de Navarra, Pamplona, Eduardo García Jiménez, MD, Hospital Univ. Guadalajara, Alvaro Merino, Clínica Rotger, Las Palmas, Vicente Palacios, MD, Hospital de la Ribera, Alzira
Sweden: Joerg Carlsson, MD, National Principal investigator, Central Hospital of Kalmar,Kalmar
Werner Puskar, MD, Central Hospital of Jönköping, Joenkoeping
Thailand: Tresukosol Damras, MD, National Principal investigator, Siriraj Hospital, Bangkok
Wasan Udayachalerm, MD, General Hospital, Chulalongkorn
Wirash Kehasukcharoen, MD,Central Chest Hospital