Comparison of Outcomes Up to Six Months of Heparin-Coated With Noncoated Stents After Percutaneous Coronary Intervention for Acute Myocardial Infarction

Eli I. Lev, MD, Abid R. Assali, MD, Igal Teplisky, MD, Eldad Rechavia, MD, David Hasdai, MD, Ofer Sela, MD, Nurit Shor, RN, BA, Alexander Battler, MD, and Ran Kornowski, MD

We prospectively followed 238 patients who underwent percutaneous coronary intervention for acute ST-elevation myocardial infarction and compared the outcomes of patients who received heparin-coated stents (n = 124) with those of patients who received noncoated stents (n = 114). The clinical characteristics and adjunctive medications of the 2 groups were similar. The use of heparin-coated stents was associated with improved 30-day outcome but had no significant effect on 180-day outcome. ©2004 by Excerpta Medica, Inc.

(Am J Cardiol 2004;93:741–743)

Clinical trials with heparin-coated stents (HCSs) have shown relatively low rates of acute and subacute stent thrombosis.[1–3] Most of these trials were not designed to compare the effect of coated versus noncoated stents, nor did they focus on patients with acute myocardial infarction (AMI). One direct comparison between coated and noncoated stents was performed with a wide array of patients.[4] Although this trial showed no benefit from heparin coating, few patients had undergone percutaneous coronary intervention (PCI) for AMI.[4] Our aim was to prospectively compare immediate, 30-day, and 180-day outcomes of HCS with noncoated stents implanted during PCI for AMI.

• • •

We prospectively followed all patients who underwent PCI for ST-elevation AMI at the Rabin Medical Center between January 2000 and November 2002. In-hospital, 30-day, and 180-day clinical outcomes as well as clinical characteristics and angiographic data from the AMI intervention were obtained. Routine angiography was not performed at 30 or 180 days. AMI was defined as the presence, for ≥30 minutes but <12 hours, of symptoms attributed to ischemia and the presence of ST-segment elevation in ≥2 contiguous leads or left bundle branch block. Patients admitted with cardiogenic shock and those with contraindications to aspirin, heparin, or clopidogrel were excluded from the study. A total of 238 patients were followed, of whom 202 underwent primary PCI and 36 underwent rescue PCI, defined as PCI following failed thrombolytic treatment. Clinical outcomes at 30 and 180 days were obtained by outpatient clinic follow-up and serial telephone interviews. Cardiac events (death, recurrent AMI, repeat coronary angioplasty, or bypass surgery) were confirmed by accompanying hospital documentation. The diagnosis of recurrent AMI was based on recurrent chest pain accompanied by reelevation of cardiac enzyme levels to ≥2 times the upper limit of normal ≥48 hours from PCI. Also, the appearance of new infarct-related electrocardiographic changes was required. The primary end point of the study included death, recurrent AMI, or target vessel revascularization within 30 days.

Coronary angioplasty and intracoronary stent implantation were performed using standard percutaneous techniques through the femoral artery. Of the 238 patients included in the study, 124 received HCSs (HCS group) and 114 received non–heparin-coated stents implanted (non-HCS group). The choice of stent type was at the discretion of the operator, and the patients were not randomly assigned to the 2 groups. In all patients in the HCS group, the stent implanted was HepaCoat BX Velocity type (Cordis, Johnson & Johnson, New Brunswick, New Jersey). The patients in the non-HCS group underwent implantation of noncoated stents: 51% AVE (Medtronic, Minneapolis, Minnesota), 21% NIR-Elite (Medinol Ltd., Jersualem, Israel), 7% PENTA Multi-Link (Guidant, Santa Clara, California), and others. Direct stenting was performed in 20% of cases in both groups. When suboptimal stent expansion was observed, angiographic optimization was performed by using high-pressure balloon dilation to achieve <20% residual stenosis. Each operator relied on his own visual estimation or on other objective measurements, such as quantitative coronary analysis, to assess PCI results.

All patients received unfractionated heparin intravenously during the procedure (70 U/kg bolus) that was adjusted to achieve an activated clotting time of 225 to 300 seconds. Glycoprotein IIb/IIIa inhibitors were administered during the procedure to 76.5% of the patients in both groups and continued for 12 to 18 hours. Most patients received aspirin before the PCI (Table 1). After the procedure, all patients received aspirin (200 mg once daily) and clopidogrel (300 mg loading dose orally, followed by 75 mg/day) for 1 month followed by aspirin alone at 100 mg/day.

Angiographic films were reviewed using the MD-View Quantitative Angiographic System (Medcon Telemedicine Technology, Tel-Aviv, Israel). An experienced cardiologist who was unaware of clinical outcomes and

From the Cardiology Department, Rabin Medical Center, Petah-Tikva, Israel. Dr. Kornowski's address is: Cardiology Department, Rabin Medical Center, 39 Jabotinski Street, Petah-Tikva 49100, Israel. E-mail: rkornowski@clalit.org.il. Manuscript received July 22, 2003; revised manuscript received and accepted November 19, 2003.

0002-9149/04/$–see front matter
doi:10.1016/j.amjcard.2003.11.067

TABLE 1 Use of Adjunctive Medications Before the Percutaneous Coronary Intervention

Medication	HCS Group (n = 124)	Non-HCS Group (n = 114)	p Value
Aspirin	118 (95%)	101 (89%)	0.1
β blockers	48 (39%)	51 (45%)	0.5
Angiotensin-converting enzyme inhibitors	53 (43%)	52 (46%)	0.6
Statins	45 (36%)	42 (37%)	1
Thrombolysis	17 (14%)	19 (17%)	0.5

TABLE 2 Demographic and Clinical Characteristics

Characteristic	HCS Group (n = 124)	Non-HCS Group (n = 114)	p Value
Age (yrs)	60 ± 13	61 ± 13.5	0.5
Men	100 (81%)	81 (71%)	0.06
Diabetes mellitus	36 (29%)	32 (28%)	0.9
Hyperlipidemia*	60 (48%)	57 (50%)	0.7
Systemic hypertension	56 (45%)	49 (43%)	1
Smoker	67 (54%)	55 (48%)	0.4
Prior-PCI	14 (11%)	13 (11%)	1
Prior AMI	14 (11%)	12 (10.5%)	0.6
Renal failure	10 (8%)	9 (8%)	1
Stroke	6 (5%)	10 (9%)	0.3
Peripheral vascular disease	4 (3%)	7 (6%)	0.2
Primary PCI	107 (86%)	95 (83%)	0.6
Anterior myocardial infarction	63 (51%)	54 (47%)	0.8
Killip class 1–2 at presentation	111 (90%)	107 (94%)	0.2
Systolic blood pressure (mm Hg)	131 ± 24	132 ± 25	0.8
Diastolic blood pressure (mm Hg)	75 ± 14	76 ± 13	0.6

The results of continuous variables are presented as mean ± standard deviation.
*Hyperlipidemia = diagnosis previously made by physician or receiving lipid-lowering therapy.

TABLE 3 Angiographic Characteristics and Procedural Factors

Characteristic/Factor	HCS Group (n = 124)	Non-HCS Group (n = 114)	p Value
Two-3 vessel coronary disease	63 (51%)	65 (57%)	0.5
AHA type B2/C	112 (90%)	91 (80%)	0.6
Thrombus	112 (90%)	87 (76%)	0.008
Pre-TIMI 0/1 flow	96 (77%)	77 (68%)	0.08
Post-TIMI 3 flow	120 (97%)	111 (97%)	1
Reference vessel diameter	3.08 ± 0.5	2.93 ± 0.6	0.04
Lesion length (mm)	14.2 ± 7.4	12 ± 3.5	0.02
Stenosis before (%)	95 ± 11	92 ± 13	0.001
Stenosis after (%)	5.4 ± 9.6	6.7 ± 11.9	0.4
Preminimum luminal diameter (mm)	0.20 ± 0.6	0.21 ± 0.42	0.9
Postminimum luminal diameter (mm)	2.96 ± 0.7	2.8 ± 0.6	0.06
Stent diameter (mm)	3.13 ± 0.4	3.06 ± 0.4	0.1
No. of stents per patient	1.1 ± 0.3	1.2 ± 0.4	0.04
Procedural success	122 (98%)	111 (97%)	0.8

The results of continuous variables are presented as mean ± SD.
AHA = American Heart Association; TIMI = Thrombolysis for Myocardial Infarction.

stent types performed the analysis. The criterion used for the diagnosis of coronary thrombus was the presence of a discrete, intraluminal filling defect with defined borders seen in multiple angiographic views, or, if the vessel was occluded, a convex margin, when stained with contrast, that persisted for several cycles. Using the guiding catheter as the calibration standard, reference and minimum luminal diameters were determined using an automated edge-detection algorithm. Based on these measurements, percentages of diameter stenosis were determined before and after PCI as were Thrombolysis In Myocardial Infarction flow grades.

Continuous variables are presented as mean ± SD. Chi-square tests and Fisher's exact tests were used for analysis of categorical variables when appropriate, and the Student's *t* test was used for analysis of continuous variables. Multivariate logistic regression analysis was performed to determine significance of variables related to 30-day recurrent AMI and the primary end point. The model included all variables for which p was <0.1 in the univariate analysis. Statistical analysis was performed using STATISTICA software (StatSoft, Inc., Tulsa, Oklahoma), and $p \leq 0.05$ was considered significant.

As shown in Table 2, the clinical characteristics were similar for the 2 groups, except for a trend of more men in the HCS group. The average times that elapsed from chest pain to arrival at the emergency room and from the emergency room to PCI were also similar (4.4 ± 5.2 hours in the HCS group vs 5.0 ± 9.0 hours in the non-HCS group, p = 0.5; and 2.4 ± 4.1 hours vs 2.4 ± 5.6 hours, p = 0.3, respectively). Medications administered before and during the procedure were also similar for the 2 groups (Table 1). Angiographic characteristics are given in Table 3. There were no significant differences between the groups in the infarct-related artery. Patients treated with HCS were more likely to have angiographic visible thrombus and tended more often to have preinterventional Thrombolysis In Myocardial Infarction 0/1 grade flow. Also, the average culprit vessel stenosis was more severe in the HCS group and the average lesion length was higher, but the reference vessel diameter was larger.

As demonstrated in Table 4, in-hospital death and recurrent AMI rates were significantly lower in the HCS group compared with the non-HCS group (0% vs 4.4%, p = 0.02, and 1.6% vs 7%, p = 0.02, respectively). Thirty-day complication rates were also lower in the HCS group, especially stent thrombosis and recurrent AMI rates (0.8% vs 6.1%, p = 0.03, and 4.0% vs 10.5%, p = 0.05, respectively). By multivariate analysis, the use of a HCS was associated with an odds ratio of 0.1 (95% confidence interval 0.01 to 0.73, p = 0.02) for 30-day recurrent AMI and an odds ratio of 0.2 (95% confidence interval 0.04 to 1.1, p = 0.07) for the primary composite end point. Complete follow-up at 180 days was available for 93% of the

TABLE 4 In-Hospital, 30-day, and 180-Day Outcomes

Outcome	HCS Group (n = 124)	Non-HCS Group (n = 114)	p Value
In-hospital			
Death	0	5 (4.4%)	0.02
Recurrent AMI	2 (1.6%)	8 (7%)	0.02
Stent thrombosis	1 (0.8%)	5 (4.4%)	0.1
Bleeding requiring blood transfusion(s)	2 (1.6%)	3 (2.6%)	0.7
Large groin hematomas	3 (2.4%)	3 (2.6%)	1
30 d			
Death	3 (2.4%)	5 (4.4%)	0.5
Stent thrombosis	1 (0.8%)	7 (6.1%)	0.03
Recurrent AMI	5 (4%)	12 (10.5%)	0.05
Composite end point*	7 (5.6%)	14 (12.3%)	0.07
180 d			
Death	7 (5.6%)	5 (4.4%)	0.7
Recurrent AMI	15 (12.1%)	17 (14.9%)	0.5
Target vessel revascularization	13 (10.5%)	17 (14.9%)	0.3
Composite end point*	20 (16.1%)	24 (21.1%)	0.3

*Composite end point = death/myocardial infarction/target vessel revascularization.

patients. There were no statistically significant differences in clinical outcomes of the 2 groups at 180 days.

• • •

This is the first study to directly compare HCS with noncoated stents in the setting of AMI. We prospectively followed patients with ST-elevation AMI treated by early PCI, which was either primary or rescue PCI. This study demonstrates that employing HCS during the PCI may improve short-term clinical outcome, mainly by reducing the rates of recurrent AMI and stent thrombosis. The use of HCSs was not associated with a reduction in clinical adverse events at 180 days.

The low rates of stent thrombosis and recurrent AMI at 30 days in the HCS group (0.8% and 4%, respectively) is in accord with previous HCS trials.[1,2,4–7] However, the differences we have found in short-term clinical outcomes for the groups disagree with the results of Wohrle et al[4] and Haude et al.[8] Possible reasons for the conflicting findings may be the different patient groups studied and differences in the HCS employed. Our study was limited to patients with AMI, a highly thrombogenic state, whereas in the other 2 studies, only few or no AMI patients were included.[4,8] The HepaCoat BX stent used in our study is coated with covalently bound, end point–attached heparin fragments, whereas the Jostent used in the other 2 studies is coated with covalently bound heparin without end point attachment. Use of end point attachment ensures that all antithrombin III binding sites remain functionally intact and, according to in vitro studies, offers higher antithrombin-binding capacity.[3]

In contrast to the HCS group, the non-HCS group in our study had an unexpectedly high rate of stent thrombosis (4.4% in-hospital and 6.1% at 30 days). A recent meta-analysis of coronary stent trials has shown that the rate of clinical stent thrombosis is only around 1%.[9] However, this meta-analysis excluded patients with suspected AMI or angiographic evidence of thrombus. Other stent trials have shown that acute coronary syndromes and a recent AMI are risk factors for the development of stent thrombosis.[10,11] Therefore, stent thrombosis rates in a highly thrombogenic state such as AMI may indeed be substantially >1%, as seen in the non-HCS group.

Our study is limited in that it was nonrandomized and routine angiographic follow-up was not performed. Furthermore, several bare metal stent types were used in the non-HCS group and the HepaCoat BX stent was not compared with an uncoated BX stent. However, this study reflects a "real-life" scenario in which stents were chosen at the discretion of the operator (e.g., HCS vs noncoated stents). Moreover, the groups had similar baseline characteristics and received similar adjunctive treatment. In summary, use of HCS during AMI coronary interventions may improve short-term clinical outcomes. Larger randomized controlled trials are needed to support these results and extend them to other thrombogenic settings.

1. Serruys PW, Van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, et al. Randomized comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998;352:673–681.

2. Vrolix MC, Legrand VM, Reiber JH, Grollier G, Schalij MJ, Brunel P, Martinez-Elbal L, Gomez-Recio M, Bar FW, Bertrand ME, et al. Heparin-coated Wiktor stents in human coronary arteries (MENTOR trial). *Am J Cardiol* 2000;86:385–389.

3. van Der Giessen WJ, van Beusekom HM, Eijgelshoven MH, Morel MA, Serruys PW. Heparin-coating of coronary stents. *Semin Interv Cardiol* 1998;3:173–176.

4. Wohrle J, Al-Khayer E, Grotzinger U, Schindler C, Kochs M, Hombach V, Hoher M. Comparison of the heparin coated vs the uncoated Jostent—no influence on restenosis or clinical outcome. *Eur Heart J* 2001;22:1808–1816.

5. Shin EK, Son JW, Sohn MS, Jin DK, Park GS, Koh KK, Ahn TH, Choi IS. Efficacy of heparin-coated stent in early setting of acute myocardial infarction. *Catheter Cardiovasc Interv* 2001;52:306–312.

6. Stone GW, Brodie BR, Griffin JJ, Costantini C, Morice MC, St Goar FG, Overlie PA, Popma JJ, McDonnell J, Jones D, et al. Clinical and angiographic follow-up after primary stenting in acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction (PAMI) stent pilot study. *Circulation* 1999;99:1548–1554.

7. Madduri J, Assali A, Teplizky I, Shor N, Battler A, Kornowski R. Acute and intermediate-term clinical outcomes following heparin coated BX coronary stent implantation in patients with thrombus containing lesions (abstr). *Am J Cardiol* 2002;90(suppl):H75.

8. Haude M, Konorza TF, Kalnins U, Erglis A, Saunamaki K, Glogar HD, Grube E, Gil R, Serra A, Richardt HG, et al. Heparin-coated stent placement for the treatment of stenoses in small coronary arteries of symptomatic patients. *Circulation* 2003;107:1265–1270.

9. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AL, Cohen DJ, Carrozza JP, Chauhan MS, Rodriguez O, Kunz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001;103:1967–1971.

10. Reynolds MR, Rinaldi MJ, Pinto DS, Cohen DJ. Current clinical characteristics and economic impact of subacute stent thrombosis. *J Invasive Cardiol* 2002;14:369–370.

11. Singh B, Isser HS, Sapra R, Sudan D, Kachru R, Kaul U. Coronary stent thrombosis: time course and clinical outcome. *Indian Heart J* 2000;52:554–558.