DOI: 10.1111/j.1540-8183.2008.00385.x

Differences in the Inflammatory Response between Patients with and Those without Diabetes Mellitus after Coronary Stenting

MARIA SANALI M. O. PAIVA, M.D.,[1,2,3] CARLOS V. SERRANO, JR., M.D., PH.D., F.A.C.C.,[1] JOSÉ CARLOS NICOLAU, M.D., PH.D., F.A.C.C.,[1] BRUNA O. JALBUT, M.S.,[1] JULIANO L. FERNANDES, M.D.,[1,4] JAMES A. DE LEMOS, M.D., F.A.C.C.,[5] MARIA HELOÍSA S. L. BLOTTA, PH.D.,[4] RÔMULO T. D. DE OLIVEIRA, B.S.,[4] ITAMAR R. DE OLIVEIRA, M.D.,[2,3] LUDMILLA DA A. R. R. DE OLIVEIRA, M.D.,[2,3] and JOSÉ ANTÔNIO F. RAMIRES, M.D., PH.D., F.A.C.C.[1]

From the [1]Heart Institute (InCor), Medical School, University of São Paulo, Brazil; [2]Onofre Lopes Hospital, Medical School, University of Rio Grande do Norte, Brazil; [3]Promater Hospital of Natal, Rio Grande do Norte, Brazil; [4]Department of Clinical Pathology, Faculty of Medical Sciences, State University of Campinas, Brazil; and [5]University of Texas Southwestern Medical Center, Dallas, TX, USA

Background: *Patients with diabetes mellitus who undergo coronary stenting are at increased risk of restenosis. It is known that inflammation plays a crucial role in restenosis.*
Objective: *We assessed the inflammatory response to elective coronary stent implantation (CSI) in stable diabetic and nondiabetic patients.*
Methods: *C-reactive protein (CRP), soluble (s) P-selectin, and soluble intercellular adhesion molecule (sICAM)-1 plasma levels were determined in diabetic ($n = 51$) and nondiabetic ($n = 56$) patients before and 48 hours and 4 weeks after bare metal stenting (BMS).*
Results: *Diabetic patients presented significantly higher inflammatory marker levels before and after CSI. Nonetheless, diabetic and nondiabetic patients had postintervention peak of markers attained within 48 hours. At baseline, diabetic and nondiabetic patients presented CRP levels of 5.0 ± 20.1 ($P \leq 0.04$) and 3.8 ± 9.4 μg/ml and, at 48 hours postintervention, 22.0 ± 20.2 ($P = 0.001$; $P = 0.002$) and 12.6 ± 11.3 ($P \leq 0.0001$) μg/ml. Regarding sP-selectin, diabetic and nondiabetic patients obtained levels of, at baseline, 182 ± 118 ($P \leq 0.04$) and 105 ± 48 ng/ml and, at 48 hours, 455 ± 290 ($P = 0.001$; $P \leq 0.01$) and 215 ± 120 ($P \leq 0.04$) ng/ml. For diabetic and nondiabetic patients, sICAM-1 levels were, at baseline, 248 ± 98 ($P \leq 0.04$) and 199 ± 94 ng/ml and, at 48 hours, 601 ± 201 ($P = 0.001$; $P \leq 0.01$) and 283 ± 220 ($P = 0.001$) ng/ml. At 4 weeks, for all patients, markers returned to preprocedural levels: versus before PCI: $^{*}P = 0.001$, $^{\S}P \leq 0.0001$; versus nondiabetic patients: $^{\#}P \leq 0.04$, $^{\P}P = 0.002$, $^{\Upsilon}P \leq 0.01$.*
Conclusions: *Diabetic and nondiabetic patients exhibited a temporal inflammatory response after an elective BMS. However, diabetic patients present higher preprocedural levels of CRP, sP-selectin, and sICAM-1 and reveal a further exacerbated inflammatory response after intervention. The differences in inflammatory response may have implications in restenosis within these two sets of patients.* (J Interven Cardiol 2008;21:403–409)

Introduction

Patients with diabetes mellitus who undergo percutaneous coronary intervention (PCI) are at increased risk of early and late complications, including restenosis.[1,2] Previous studies have supported a critical role of inflammation in the atherosclerotic[3] and restenotic processes.[4] Several markers are known to represent the systemic inflammatory status, among them C-reactive protein (CRP), soluble(s) P-selectin, and soluble intercellular adhesion molecule (sICAM)-1.

Arterial injury caused by coronary intervention results in the induction of several inflammatory

Address for reprints: Carlos V. Serrano Jr., M.D., Heart Institute (InCor HCFMUSP), Av. Enéas de C. Aguiar, 44 Building II, 2nd Floor, Room 12, São Paulo, SP 05403-901, Brazil. Fax: +1-409-356-4441; e-mail: carlos.serrano@incor.usp.br

components.[5] Several clinical studies have shown that the baseline levels of systemic inflammatory markers such as CRP are independent prognostic indicators for subsequent cardiac events and clinical restenosis.[6,7]

This study was based on the hypothesis that diabetic patients present a higher degree of inflammatory response to coronary stenting than nondiabetic patients. The aim of this study was to assess the inflammatory response to coronary stenting in stable angina patients with and without diabetes. Plasma concentrations of CRP, sP-selectin, and sICAM-1 were determined for this purpose.

Methods

Study Population. Between August 2003 and July 2004, 214 patients with stable angina underwent elective coronary stenting for clinical indications. A total of 107 patients were eligible for this study and had indication of coronary stenting independent of this study. The study protocol was approved by the Ethics in Research Committee and all patients gave informed consent before blood donation.

The present study population consisted of 107 stable angina patients, divided according to the presence (n = 51) or not (n = 56) of diabetes mellitus.

The diagnosis of stable angina was based on the presence of chest pain greater than 2 months of onset with a positive stress test, and/or provoked by exertion.[8] Diagnosis of diabetes mellitus was based on repeated fasting plasma glucose levels ≥126 mg/dL previous to the study.[9] These patients had blood glucose levels reversed nearly to 126 mg/dL with treatment with insulin and/or oral hypoglycemic agent for at least 1 month before the coronary intervention.

The patients' baseline characteristics—including demographic, laboratory, clinical, and angiographic features—are shown in Table 1. As seen, patients with diabetes were younger, had a greater incidence of arterial hypertension, presented more left ventricular dysfunction, and possessed smaller vessels to be treated.

Patients were excluded if one or more of the following situations were present: acute coronary syndrome within 3 months before coronary intervention; hemodynamic impairment; need of urgent revascularization; acute or chronic infection or inflammatory state; cancer; contraindication to the use of aspirin, heparin, or

Table 1. Baseline Characteristics of the Study Population

	With Diabetes (n = 51)	Without Diabetes (n = 56)	P
Demographic, laboratory, and clinical characteristics			
Age (years)	60.8	67.0	0.006
Men (%)	43.9	69.6	0.016
Hypertension (%)	78.0	52.2	0.01
Current smoker (%)	7.3	17.4	NS
Hypercholesterolemia (%)	68.3	45.7	0.07
Fasting glucose levels immediately before procedure (mg/dL)	116.0 ± 7.0	84.0 ± 5.0	0.01
White cell count (per mm^3)	7.7 ± 1.8	7.6 ± 2.0	0.48
Platelets (per mm^3)	244 ± 62	239 ± 63	0.16
Creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.2	NS
Previous MI (%)	12.2	19.6	NS
History of CABG (%)	9.8	10.9	NS
Angiographic findings			
LVEF < 0.40 (%)	0.0	4.3	NS
Multivessel disease (%)	36.6	41.3	NS
Treated vessel			
LMA (%)	2.4	0	NS
LADA (%)	40.0	56.9	NS
LCA (%)	24.0	17.2	NS
RCA (%)	28.0	24.1	NS
Restenotic lesions (%)	0.0	0.0	
Vessel size (reference diameter, mm)	2.7 ± 0.6	3.1 ± 0.7	0.02
MLD of stenosis preprocedure (mm)	0.8 ± 0.7	1.0 ± 0.7	NS
MLD of stenosis immediately postprocedure (mm)	2.5 ± 0.6	2.9 ± 0.7	0.005
Bare metal stent type			
Express (%)	94.0	89.7	NS
Lekton (%)	6.0	10.3	NS
Length of implanted stents (mm)	17.8 ± 8.0	15.3 ± 7	NS
Most common hospital medications			
Aspirin (%)	87.8	95.7	NS
Clopidogrel (%)	100	100	NS
Insulin (%)	12.2	0	NS
Oral hypoglycemic agent (%)	87.8	0	NS
Beta blockers (%)	41.5	43.5	NS
ACE inhibitors (%)	48.8	39.1	NS
Statins (%)	22.0	26.1	NS

Hypercholesterolemia was defined as total cholesterol levels >200 mg/dL. MI = myocardial infarction; CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; LMA = left main artery; LADA = left anterior descending artery; LCA = left circumflex artery; RCA = right coronary artery; MLD = minimal luminal diameter; ACE = angiotensin-converting enzyme. Data expressed in mean ± SD. NS = not significant.

clopidogrel; clear indication of glycoprotein IIb/IIIa inhibitor treatment.

Stent Placement and Adjunctive Therapy. The stent placement technique was according to the American College of Cardiology/American Heart Association[10] and Brazilian Society of Cardiology[11] Guidelines. Bare metal stents (BMS) were employed in this series. At the moment of the procedure, all patients were on aspirin (100 mg/day) and clopidogrel (loading dose of 300 mg followed by 75 mg/day)—these medications were initiated once coronary intervention was recommended based on the diagnostic coronary angiography, and at least 12 hours before the procedure. The usual waiting interval between diagnostic coronary angiography and the elective PCI was 1 week. During the intervention, the patients received heparin intravenously according to their coagulation time.

Patients with diabetes taking metformin had this agent discontinued for at least 48 hours before the procedure, and reinitiated 48 hours later. During the period without metformin the diabetes control was done with insulin.

Experimental Protocol. For all patients, peripheral venous blood samples were obtained after a 12-hour overnight fast, immediately before the loading dose of clopidogrel and initiation of coronary stenting procedure. Additional samples were collected over the 24 hours, 48 hours, and 4 weeks after coronary stenting. Ethylenediaminetetraacetic acid was used as an anticoagulant. All blood samples were processed within 2 hours of collection.

CRP was immediately measured with a high-sensitivity assay that had an analytic sensitivity of 0.175 μg/mL (Dade Behring, Marburg, Germany). The intra-assay variability for the lower assay range was $<$0.165 μg/mL. CRP levels above 3.0 μg/mL were defined as increased.

For measuring the adhesion molecule P-selectin and ICAM-1 concentrations, plasma was separated by centrifugation of the blood samples from each patient and was stored at –70 °C. Commercial enzymatic immunoassays (ELISA) and multiplex assays (R&D Systems, Minneapolis, MN) were used. In order to avoid platelet activation, an important source of P-selectin, care was taken on blood sampling for sP-selectin ELISA measurements. The first 2 ml of blood, drawn by venipuncture through a 21-gauge needle, were discarded. Then, blood was collected and subsequently centrifuged at 1,500*g* for 20 minutes.

Soluble P-selectin and sICAM-1 were measured, in duplicate, at the same time by the same ELISA, to avoid variation of assay conditions. Plasma levels expected for healthy subjects of ELISA assays for sP-selectin[12] and sICAM-1[13] were, respectively, 51–113 and 115–306 ng/mL. The lower limits of detection for these inflammatory markers and the coefficient of variation for these measurements for sP-selectin and sICAM-1 were, respectively, 0.5 and 15.6 ng/mL.

Follow-Up. The study follow-up protocol consisted of a clinical visit at 4 weeks and a telephone interview at 1 year. Information on the subsequent adverse clinical events was obtained: occurrence of angina, fatal and nonfatal myocardial infarction, cardiovascular death, stroke, and hospitalization for coronary bypass graft surgery.

Statistical Methods. The number of participants required to test our hypothesis was based on prior studies[3,6] reporting the relation between CRP increase and coronary intervention in a patient population. These studies indicate that 50 patients with stable angina and diabetes were needed to detect a 20% increase in CRP and adhesion molecule expression, based on a power of 0.90 and an alpha of 0.05. We, therefore, recruited diabetic and nondiabetic patients until we had 50 individuals in each group and then exceeded it for extra confidence.

Means, standard deviation, and percentages were used to describe the variables under study. Comparisons in baseline characteristics of patients with diabetes and without were analyzed using Student's t-test for continuous variables or Fisher's exact test for categoric variables. SAS programs were employed for statistical analysis.[14] The preprocedural concentrations of CRP, sP-selectin, and sICAM-1 in patients with diabetes and those without were compared using Wilcoxon's rank sum test. Differences between baseline and each time point were calculated for each patient with and without diabetes and marker and the mean differences were compared to zero using repeated measure analysis of variance of the log-transformed data.

A P value of $<$0.05 was considered significant for all statistical analysis.

Results

Angiographic and Procedural Results. A summary of the coronary angiographic and interventional

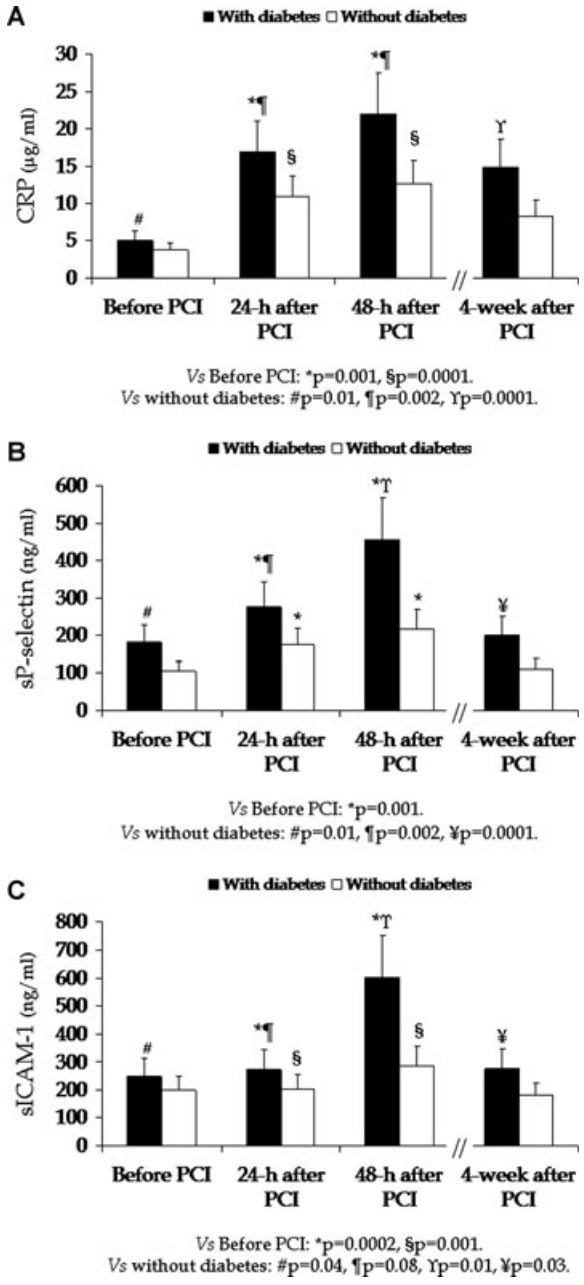

Figure 1. (A–C) Levels of inflammatory markers before and after (24-hour, 48-hour, and 4-week) PCI in patients with (n = 51) and without diabetes (n = 56). (A) C-reactive protein (CRP). (B) Soluble (s) P-selectin. (C) Soluble (s) intercellular adhesion molecule (sICAM)-1.

characteristics is shown in Table 1. All subjects enrolled in the study underwent successful stent implantation. Five patients had an asymptomatic postprocedural increase in their creatinine kinase-MB to greater than threefold the upper limit of normal—three were diabetic patients.

Also as seen in Table 1, patients with diabetes had a lesser diameter stenosis. After the procedure, diameter stenosis increased similarly for diabetic and nondiabetic patients: 2.54 ± 0.58 mm and 2.92 ± 0.70 mm, respectively; $P < 0.005$ for both diabetic and nondiabetic patients, when compared to preprocedural diameters.

Periprocedural Concentrations of Inflammatory Markers. As shown in Fig. 1A–C, CRP, sP-selectin, and sICAM-1 concentrations were determined throughout the study. Three findings are of interest. First, all markers presented a similar pattern of changes during the serial blood samples taken after the PCI. Regarding diabetic and nondiabetic patients, the peak of postintervention for all markers was attained within 48 hours after the procedure. Second, at 4 weeks postprocedure, all markers had returned close to baseline levels.

Finally, patients with diabetes, at all measurements, presented significantly higher inflammatory marker levels than those without diabetes—including at baseline.

Clinical Outcome. At 4 weeks, one patient with diabetes presented ischemic symptoms and needed to repeat PCI. Patients without diabetes did not develop adverse events at this time period.

Complete 1-year follow-up data were available in 49 (96%) of the diabetic patients and 53 (95%) of the nondiabetic patients. Table 2 shows that, after 1 year, 11 diabetic patients had suffered an adverse

Table 2. Adverse Clinical Events at the 1-Year Follow-up Period of Coronary Stenting

	With Diabetes (n = 49)	Without Diabetes (n = 53)	P
N	11 (22.0)	3 (6.0)	0.03
Recurrence of angina	3 (6.0)	0	NS
AMI* (%)	1 (2.0)	0	NS
Nonfatal (%)	1 (2.0)	0	NS
Fatal (%)	0	0	
Cardiovascular death (%)	1 (2.0)	2 (3.7)	NS
Stroke (%)	1 (2.0)	0	NS
Need for repeated PCI* (%)	6 (12.0)	0	NS
Need for CABG* (%)	1 (2.0)	1 (1.9)	NS

Data expressed in n and (%). AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery. *Adverse clinical events related directly to the PCI-treated artery. NS = not significant.

clinical event compared to three nondiabetic patients ($P = 0.03$). Three diabetic patients needed to repeat coronary stenting—clinical restenosis (angina) and angiographic restenosis (diameter stenosis $\geq 50\%$) were confirmed in these patients.

Discussion

The current study is based on the hypothesis that patients with diabetes may present different levels of systemic inflammation as a response to elective coronary stenting when compared to nondiabetic patients. In fact, the inflammatory response could explain, at least partially, the differences in clinical and angiographic outcome found between diabetic and nondiabetic patients that undergo contemporary coronary stenting for stable angina.[15,16]

The main findings of our study verify similarities and distinctions between patients with diabetes and those without in the inflammatory response related to elective coronary stenting. Both diabetic and nondiabetic patients presented temporal increases in CRP, sP-selectin, and sICAM-1 values after coronary intervention. However, at preprocedural conditions, patients with diabetes comprised higher levels of markers than those without diabetes. In addition, patients with diabetes presented a higher degree of inflammatory response than nondiabetic patients following coronary stent implantation (CSI)—even at 4 weeks where levels are close to preprocedural levels. Highest postintervention levels of markers were at least at 48 hours—since later time periods were not assessed.

Moreno et al.[17] have published data indicating that atherectomy specimens from patients with diabetes have an increased concentration of macrophages in atheromatous plaques, suggesting increased inflammation. These data, to a certain extent, corroborate with our study where patients with diabetes, before coronary manipulation, possessed superior levels of CRP, sP-selectin, and sICAM-1 than patients without diabetes—reflecting a higher inflammatory status among diabetic patients. Nevertheless, it is important to point out that macrophages are not a direct source of CRP, sP-selectin, and sICAM-1.

After vascular intervention, cell adhesion molecules such as P-selectin and ICAM-1 are fundamental in inflammatory processes, specifically in the early stages of leukocyte recruitment.[18] In particular, P-selectin expression has been reported in platelets, endothelial cells, and vascular smooth muscle cells (SMCs) in response to vascular injury or diseased arterial walls, and recently, in macrophages.[19] Regarding ICAM-1, this adhesion molecule is also strongly expressed within macrophage-rich areas in atherosclerotic lesions.[19] Due to the fact that macrophages are abundantly present in spontaneous atherosclerotic plaques from diabetic patients, we judge that a potential source of both sP-selectin and sICAM-1 observed in our study may well be arterial macrophages—activated after stent implantation. As reported by Li et al.,[19] macrophage expression of P-selectin and ICAM-1 may modulate a number of cellular functions related to vascular injury, including macrophage production of proinflammatory mediators and growth, apoptosis, and inflammatory activation of vascular SMCs and endothelial cells.

Recent studies[20,21] from both our laboratory and others demonstrated an increase in circulating levels of markers of inflammation, denoted by CRP, interleukin (IL)-6, IL-8, tumor necrosis factor-alpha, and of cell-mediated immunity, represented by serum-soluble IL-2 receptor, after CSI. Furthermore, there is evidence that the magnitude of the increase in CRP and IL-8 levels after coronary stenting is related to clinical restenosis.[21] However, to our knowledge, no other clinical investigation has shown such noticeable changes on inflammatory markers, such as soluble adhesion molecules P-selectin and ICAM-1, after coronary stenting within diabetic patients.

Our findings are in contrast to the ones presented by Aggarwal et al.,[22] who noted that patients without diabetes had a relatively greater but absolutely comparable peak activation of inflammation after stenting compared to those with diabetes. We believe that the mechanical plaque rupture provoked by coronary stenting on extremely macrophage-rich atheromatous plaques of patients with diabetes results in a superior inflammatory burst than observed within plaques of nondiabetic patients.

A variety of investigations have found that post-PCI inflammation is powerfully related to the pathogenesis of intimal hyperplasia after arterial injury and subsequent late lumen loss.[23,24] In diabetes, evidence is mounting that after coronary stenting, an exaggerated inflammatory response within the blood vessel wall contributes to restenosis.[25,26] The magnitude of vascular inflammatory response to injury after coronary stenting may play a central role in the degree of neointimal proliferation and be correlated with adverse late

clinical outcomes.[27] Clinical studies in support of the anti-inflammatory effects of abciximab and statins by modulating atherosclerotic plaque stability have been reported.[28] We judge, based on the findings of our study, that the degree of the inflammatory response to coronary stenting, as assessed by the changes of CRP, sP-selectin, and sICAM-1, may participate in the mechanisms implicated in in-stent restenosis in patients with diabetes.

It is important to point out that the interpretations of the findings of this study may present some limitations—in part due to the sample size, which decreases statistical power and the predictive value with regard do clinical outcome. Also due to the sample size, the effects of different hypoglycemic strategies, glycoprotein IIb/IIIa inhibition, statins, and drug-eluting stents (DES) on the inflammation status of patients with diabetes were not clearly determined. Additionally, any expressive insights into clinical events are restricted since no systematic angiographic follow-up was performed.

Our observations are also restricted by the detail that no DES were employed. A favorable impact of DES, compared to BMS, on the management of diabetic patients with stable obstructive coronary artery disease is well acknowledged by most interventionalists.[29]

Conclusions

The present study for the first time demonstrates that patients with diabetes, compared with those without diabetes, possess higher preprocedural levels of CRP and of soluble adhesion molecules P-selectin and ICAM-1 and reveal a further exacerbated inflammatory response after intervention. The differences in inflammatory response may have implications in restenosis within these two sets of patients.

Acknowledgments: We gratefully thank Hans J. Rapold, M.D., PH.D. for editorial assistance.

References

1. Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcomes after percutaneous transluminal coronary angioplasty. Circulation 1995;91:979–989.
2. The BARI Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996;335:217–225.
3. Ascer E, Bertolami MC, Venturinell ML, et al. Atorvastatin reduces proinflammatory markers in hypercholesterolemic patients. Atherosclerosis 2004;177:161–166.
4. Hong SJ, Kim MH, Ahn TH, et al. Multiple predictors of coronary restenosis after drug-eluting stent implantation in patients with diabetes. Heart 2006;92:1119–1124.
5. Serrano Jr CV, Ramires JA, Venturinelli M, et al. Coronary angioplasty results in leukocyte and platelet activation with adhesion molecule expression: Evidence of inflammatory responses in coronary angioplasty. J Am Coll Cardiol 1997;29:1276–1283.
6. Buffon A, Liuzzo G, Biasucci LM, et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. J Am Coll Cardiol 1999;34:1512–1521.
7. Farb A, Weber DK, Kolodgie KD, et al. Morphological predictors of restenosis after coronary stenting in humans. Circulation 2002;105:2974–2980.
8. César LAM. Diretriz de angina estável. Arq Bras Cardiol 2004;83(suppl II):1–44.
9. Bloomgarden ZT. Achieving glycemic goals in type 2 diabetes. Diabetes Care 2007;30:174–180.
10. Feldman TE, Hirshfeld JW, Jacobs AK, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. Available at: http://www.americanheart.org/downloadable/heart/1131740149971PCI_Final%20Final%20Clean%20Revision_AHA.pdf.
11. Saad JA. Diretriz para realização de exames diagnósticos e terapêuticos em hemodinâmica. Arq Bras Cardiol 2004;82(suppl I):1–6.
12. Linden MD, Furman MI, Frelinger AL 3rd, et al. Indices of platelet activation and the stability of coronary artery disease. J Thromb Haemost 2007;5:761–765.
13. Gearing A, Newman W. Circulating adhesion molecules in disease. Immunol Today 1993;14:506–512.
14. SAS Institute Inc. SAS Procedures Guide for Personal Computers. Version 6 ed. Cary, NC: SAS Institute Inc., 1985.
15. Moreno PR, Fuster V. New aspects in the pathogenesis of diabetic atherothrombosis. J Am Coll Cardiol 2004;44:2293–2300.
16. Van Belle E, Bauters C, Hubert E, et al. Restenosis rates in diabetic patients: A comparison of coronary stenting and balloon angioplasty in native coronary vessels. Circulation 1997;96:1454–1460.
17. Moreno PR, Murcia AM, Palacios IF, et al. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. Circulation 2000;102:2180–2184.
18. Rao RM, Yang L, Garcia-Cardena G, et al. Endothelial-dependent mechanisms of leukocyte recruitment to the vascular wall. Circ Res 2007;101:234–247.
19. Li G, Sanders JM, Phan ET, et al. Arterial macrophages and regenerating endothelial cells express P-selectin in atherosclerosis-prone apolipoprotein E-deficient mice. Am J Pathol 2005;167:1511–1518.
20. Caixeta AM, Brito FS Jr, Costa MA, et al. Enhanced inflammatory response to coronary stenting marks the development of clinically relevant restenosis. Catheter Cardiovasc Interv 2007;69:500–507.
21. Brunetti ND, Munno I, Pellegrino PL, et al. Inflammatory cytokine imbalance after coronary angioplasty: Links with coronary atherosclerosis. J Interv Cardiol 2007;20:248–257.

22. Aggarwal A, Schneider DJ, Sobel BE, et al. Comparison of inflammatory markers in patients with diabetes mellitus versus those without before and after coronary arterial stenting. Am J Cardiol 2003;92:924–929.
23. Salgado Fo W, Martinez Fo EE, Horta P, et al. Intracoronary inflammatory markers after percutaneous coronary interventions. Arq Bras Cardiol 2005;85:128–136.
24. Welt FGP, Rogers C. Inflammation and restenosis in the stent era. Arterioscler Thromb Vasc Biol 2002;22:1769–1776.
25. Iijima R, Ndepepa G, Mehilli J, et al. Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era. Am Heart J 2007;154:688–693.
26. Sukhija R, Aronow WS, Sureddi R, et al. Predictors of in-stent restenosis and patient outcome after percutaneous coronary intervention in patients with diabetes mellitus. Am J Cardiol 2007;100:777–780.
27. Douglas JS Jr. Pharmacologic approaches to restenosis prevention. Am J Cardiol 2007;100:10K–16K.
28. Flaherty JD, Davidson CJ. Diabetes and coronary revascularization. JAMA 2005;293:1501–1508.
29. Kirtane AJ, Ellis SG, Dawkins KD, et al. Paclitaxel-eluting coronary stents in patients with diabetes mellitus: Pooled analysis from 5 randomized trials. J Am Coll Cardiol 2008;51:708–715.