

## Unstable Angina Patients Treated with Percutaneous Coronary Intervention in the New Millennium: What Characterizes Them?

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**Objective:** To identify clinical and angiographic profiles of patients with unstable angina seen at a tertiary hospital and treated with percutaneous coronary intervention (PCI).

**Methods:** Study of a consecutive series of 1413 patients, selected from a computerized database, who underwent percutaneous revascularization in the three-year period of 2002-2004. There were no inclusion/exclusion criteria.

**Results:** Systemic arterial hypertension (74%) and hypercholesterolemia (65%) were the classical risk factors for coronary disease most frequently observed. Coronary artery bypass grafting and history of myocardial infarction were found in 24% and 28% of the cases, respectively. The subgroups most commonly treated were the IIB (48%) and IIIB (28%). Clopidogrel was prescribed for 51% of the patients and glycoprotein IIb/IIIa inhibitors, for 7%. Multivessel disease evidenced by coronary angiography was detected in 42% of the cases. Type B2 or C lesions were treated in 64%, 94% of which in native vessels. Restenotic lesions were dilated in 5% of the patients. All interventions were performed using coronary stents, the majority of which (67%) were standard bare-metal stents.

**Conclusions:** 1) Subgroups IIB and IIIB were the most frequently treated (76%); 2) Clopidogrel was the most prescribed antithrombotic agent (51%); 3) Multivessel coronary artery disease was found in 42% of the cases, most of which were complex target lesions located in native vessels; 4) Coronary stent implantation was the chief dilation technique used.

**Key words:** Unstable angina, coronary angioplasty.

Unstable angina (UA) is one of the most important medical emergencies because of its high frequency and expressive morbidity and mortality<sup>1,2</sup>. For example, in the United States, approximately 1.3 million patients (p) are hospitalized for this condition each year<sup>3</sup>, a figure that underscores the need for providing the best available treatment for this population.

In the second half of the last decade, three randomized clinical trials have proved the superiority of invasive strategy involving coronary angiography and early myocardial revascularization, whenever possible, over the conservative approach<sup>4-6</sup>. In this context, percutaneous coronary intervention (PCI) is the revascularization method most widely used. This has been made possible by the development of adjunctive antithrombotic drug therapy (fractionated heparin, glycoprotein IIb/IIIa inhibitors and clopidogrel) and the advent of coronary stents, after which procedural outcomes have become safer and more predictable<sup>4-6</sup>. More recently, the introduction of drug-eluting stents has resulted in a significant drop in late clinical events, by considerably reducing angiographic and clinical restenosis rates<sup>7,8</sup>.

This investigation sought to identify the main angiographic/clinical features related to the percutaneous procedure in a

consecutive series of patients (p) who underwent PCI in the presence of unstable angina in a very busy tertiary hospital.

### Methods

A retrospective analysis was conducted on all unstable angina patients admitted to our Service and treated by PCI between 01/01/2002 and 12/31/2004. In this period, 1413 UA patients were treated, a number corresponding to 25% of all dilated cases.

Patients were selected from a computerized database, in which they were consecutively included. There were no inclusion/exclusion criteria. The different UA subgroups were classified according to Braunwald's proposal<sup>9</sup>. Information related to electrocardiographic and/or biochemical risk markers at hospital admission were not provided, because they were not specified in the database.

Percutaneous coronary interventions with coronary stenting were performed using the conventional technique of optimal deployment, with direct implantation or predilation, which was left to the discretion of the interventional cardiologist.

The adjunctive pharmacological regimen consisted of the following: 1) unfractionated heparin at 200 IU/kg of body

weight administered immediately before the procedure in order to reach an activated clotting time (ACT) of 250 seconds or more; 2) aspirin (200 mg/day), initiated at least one day prior to the intervention and maintained indefinitely; 3) clopidogrel (loading dose of 300 mg, followed by 75 mg/day) or ticlopidine (500 mg/day), both with at least one day of pretreatment. This association was maintained by a period ranging from 30 days to one year. Glycoprotein IIb/IIIa inhibitors were used at the usual doses, when indicated.

With respect to preprocedural angiographic analysis, lesions with diameter stenosis greater than 50% were considered significant; target lesions were classified according to the American Task-Force proposal<sup>10</sup>. Left ventricular function was evaluated globally by left ventricular ejection fraction analysis (LVEF).

**Definitions** - 1) residual stenosis less than 50%, in the absence of major complications (death, myocardial infarction or emergency CABG), was considered successful; 2) myocardial infarction was characterized by the presence of new-onset Q-waves on a 12-lead electrocardiogram and/or a rise in CK-MB levels higher than three times the upper limit of normal.

## Results

Table 1 shows the primary baseline clinical characteristics. Among the classical risk factor for coronary artery disease, the most commonly observed were systemic arterial hypertension and hypercholesterolemia. Among the diabetic, 233 (57%) were treated with oral hypoglycemic agents 62 (15%) and were insulin-dependent.

According to Braunwald's classification (Tab. 2), most cases fell into subgroups IIB and IIIB.

As to adjunctive clinical therapy, clopidogrel was prescribed for 51% of the patients and ticlopidine, for 49%, whereas glycoprotein IIb/IIIa inhibitors were administered to 7%. All patients were medicated with aspirin and a thienopyridine.

Males	62%
Mean age	61 years
Family history of CHD	53%
Arterial hypertension	74%
Smoking	57%
Diabetes mellitus	29%
Hypercholesterolemia	65%
CRF	6%
Previous CABG	24%
Previous PCI	29%
Previous AMI	28%

CAD = coronary artery disease; CRF = chronic renal failure; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; AMI = acute myocardial infarction.

Table 1 - Baseline clinical characteristics

<ul style="list-style-type: none"> <li>Class I                             <ul style="list-style-type: none"> <li>- B - 12%</li> <li>- C - 1%</li> </ul> </li> </ul>	13%
<ul style="list-style-type: none"> <li>Class II                             <ul style="list-style-type: none"> <li>- B - 48%</li> <li>- C - 2%</li> </ul> </li> </ul>	50%
<ul style="list-style-type: none"> <li>Class III                             <ul style="list-style-type: none"> <li>- A - 2%</li> <li>- B - 28%</li> <li>- C - 7%</li> </ul> </li> </ul>	37%

Table 2 - Clinical subgroups, according to Braunwald's classification.

Left ventricular function was preserved (LVEF > 55%) in most patients (856 - 61%). As for the extension of heart disease, 824 patients (58%) had single-vessel disease, 370 (26%) had two-vessel disease, and 188 (16%) had three-vessel disease. Target lesions of greater complexity (B2 or C) were the most frequently treated (62%); angiographic evidence of intracoronary thrombi was found in 13% of the cases. In the overwhelming majority of patients, dilation was performed in native vessels (94%). Restenotic lesions were treated in 5% of the cases.

Complete revascularization was achieved in 73% of the cases. All patients received endovascular stents, 63% of whom by direct implantation. Drug-eluting stents were used in 33%, most of them (80%) were sirolimus-eluting stents. Multivessel PCI comprised 18% of the cases.

Ninety-six percent of the procedures were successful. Major in-hospital complications included: post-PCI myocardial infarction in 1% and death in 0.1%. No emergency surgeries were required.

## Discussion

The marked frequency and significant morbidity and mortality associated with unstable angina have prompted a series of clinical trial in the last decade. These trials concluded that invasive strategy, based on routine and early indication for coronary angiography and myocardial revascularization, yields consistent benefits to patients<sup>4,6,11,12</sup>. In these circumstances, recent clinical trials<sup>4,6,11-13</sup> have demonstrated that PCI accounts for around two-thirds of the revascularizations. Despite this observation, in both Brazilian and international literature, contemporary papers addressing this subject specifically are scant. For example, in the PCI-CURE<sup>14</sup> clinical trial, an exception to this rule, none of the 30 references discusses this subject in particular. In addition, it should be emphasized that the PCI-CURE study itself is, in fact, a subgroup analysis, rather than a specific larger investigation.

The present study, which assessed 1413 consecutive cases treated with PCI in a single center, demonstrated the following: 1) patients' mean age range was slightly over 60 years; 2) there was a high prevalence of classical risk factors for coronary disease, particularly hypercholesterolemia and systemic arterial hypertension; 3) approximately one-third of

the patients had past history of myocardial revascularization; 4) subgroup III of Braunwald's classification, an isolated inclusion criterion found in all contemporary studies<sup>4-6,12,13</sup>, was diagnosed in one-third of the treated cases.

Table 3 compares our data with that of the main UA clinical trials, including a recently published meta-analysis involving 9212 participants in seven studies, among them FRISC II, TACTICS-TIMI 18 and RITA III. Age and gender were observed in similar manner. However, the presence of classical risk factors for coronary disease and history of percutaneous or surgical revascularization was notably higher in our study. This observation may reflect the distinction between the so-called real world, of which our material is a reflex, and the more strict universe of scientific investigations limited by preestablished inclusion and exclusion criteria. The difference in subgroup III of the Braunwald's classification, found in 37% of the dilated cases in our Service and contrasting with the 100% reported by all aforesaid studies, is explained by the fact that these clinical trials included only anginal patients seen within the past 24 to 48 hours, unlike our cohort, which included also cases treated in the mentioned period, regardless of subgroup. It is found, therefore, that patients belonging to subgroups I and II of Braunwald's classification, probably the majority in the real-world setting, were poorly evaluated in recent international literature.

The association of aspirin and thienopyridines was prescribed for all patients not only because of their clinical condition itself<sup>15</sup>, but also because all of them had undergone coronary stenting<sup>16</sup>. The current pretreatment approach<sup>16,17</sup>, with either clopidogrel or ticlopidine, allowed glycoprotein IIb/IIIa inhibitors to be used in only 7% of the patients, with favorable clinical results in more than 95%. Another fact that may have accounted for the low use of abciximab or tirofiban was that most UA diagnoses indicated Braunwald's class II, that is to say, cases of relatively less urgency.

With regard to angiographic data, more complex target lesion (B2/C) was prevalent, usually with preserved left ventricular function. This is consistent with previous literature reports<sup>18,19</sup>, in which significant obstructive atherosclerosis predominates.

Because coronary stents treat these morphological types of stenosis more effectively, safely and predictably than the other dilation devices, they became the treatment of choice when PCI is considered<sup>7,8,10</sup>. In this study, all patients were treated with this technique, a figure approaching the 84% reported by the PCI-CURE study<sup>14</sup>. The high success rates and rare major complications of the in-hospital outcomes corroborate this statement. More recently, both in UA and other clinical presentations of coronary disease, drug-eluting stents, used in 33% of the patients in our investigation, yielded significant improvement in late clinical outcome, based on a marked decrease in additional revascularizations secondary to coronary restenosis<sup>20,21</sup>. Nevertheless, a recent European investigation on the cost-effectiveness of drug-eluting stents demonstrated that UA cases are among those that do not offer significant benefit when used routinely<sup>22</sup>. Of note is that the relatively small percentage of drug-eluting stents used in our study was especially due to the fact that the Sistema Único de Saúde (Brazilian national health care system), the chief financial source of the procedures performed in our hospital, does not authorize the implantation of these devices.

*Limitations* - This study evaluated a cohort of 1413 patients treated with PCI in a tertiary hospital in the presence of UA. Although it presents a clear profile of these cases, the characteristics observed do not necessarily express the clinical/angiographic profile of all the cases presenting non-ST segment elevation acute coronary syndromes in this kind of institutions. As already stated, similar studies providing a more accurate comparison are scarce. Accordingly, our data were compared with those of larger normative clinical trials, in which only part of the cases were treated with PCI.

## Conclusions

This investigations identified the following characteristics in the UA cases evaluated: 1) male patients, with high prevalence of classical risk factors for coronary disease; 2) of the clinical forms of unstable angina presented, subgroups IIB and IIIB of

Variables	Present Study	Meta-analysis	ISAR-Cool12	ICTUS13	PCI-Cure14
Age (years)	61	62	70	62	62
Men (%)	62	69	66	74	70
Diabetes mellitus (%)	29	19	26	14	19
Previous AMI (%)	28	33	22	25	27
Dyslipidemia (%)	65	NR	NR	35	NR
SAH (%)	74	NR	86	37	NR
Smoking (%)	57	NR	24	42	NR
Previous CABG (%)	24	NR	10	10	13
Previous PCI (%)	29	NR	21	13	13
Unstable angina III B/C (%)	37	100	100	100	100

AMI: acute myocardial infarction; NR = non-reported; SAH = systemic arterial hypertension; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

Table 3 - Comparison of baseline clinical characteristics of this analysis and the major normative studies.

Braunwald's classification predominated; 3) thienopyridines were administered to all patients, whereas glycoprotein IIb/IIIa inhibitors were used in 7%; 4) target lesions of greater

complexity, located in native vessels, predominated; 5) all patients were treated with coronary stent implantation, one-third of whom with drug-eluting stents.

## References

1. Theroux P, Fuster V. Acute coronary syndromes unstable angina and non-Q-wave myocardial infarction. *Circulation*. 1998; 97: 1195-206.
2. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. Guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. *J Am Coll Cardiol*. 2000; 102: 1193-209.
3. Unstable angina: diagnosis and management. Guideline overview. Agency for Health Care Policy and Research. *J Natl Med Assoc*. 1994; 86: 649, 710-2.
4. Wallentin L, Lagerqvist B, Konny F, Stahle E, Swahn E. Outcome at one year after an invasive compared with a non-invasive strategy in unstable-coronary artery disease: the FRISC II invasive randomized trial. *Lancet*. 2000; 356: 9-16.
5. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001; 344: 1879-87.
6. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation Rita 3 randomized trial. *Lancet*. 2002; 360: 743-51.
7. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002; 346: 1773-80.
8. Stone GW, Ellis SG, Cox DA, Hermiller J, Oshaghnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004; 350: 221-31.
9. Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation*. 2000; 102: 118-22.
10. Smith SC, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines) – executive summary: a report of the American College of Cardiology / American Heart Association task force on practice Guidelines. (Committee to revise the 1993 guidelines for percutaneous Transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Intervention. *Circulation*. 2001; 103: 3019-41.
11. Mehta SR, Cannon CP, Fox KAA, Wallentin I, Boden WE, Spacek R, et al. Routine versus selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA*. 2005; 293: 2908-17.
12. Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, et al. Evaluation of prolonged antithrombotic pretreatment ("Cooling-Off" strategy) before intervention in patients with unstable coronary syndromes. A randomized controlled trial. *JAMA*. 2003; 290: 1593-9.
13. de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, et al. Early invasive versus selective invasive management for acute coronary syndromes. *N Engl J Med*. 2005; 353: 1095-104.
14. Mehta SR, Yusuf S, Peters RJC, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001; 358: 527-33.
15. CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001; 345: 494-502.
16. Steinhubl SR, Lauer MS, Mukherjee DP, Moliterno DJ, Lincoff AM, Ellis SG, et al. The duration of pretreatment with ticlopidine prior to stent is associated with the risk of procedure-related non-Q-wave myocardial infarctions. *J Am Coll Cardiol*. 1998; 32: 1366-70.
17. Steinhubl SR, Berger PB, Mann JT3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002; 288: 2411-20.
18. Cianflone D, Ciccirillo F, Buffon A, Trani C, Scabbia EV, Finocchiaro ML et al. Comparison of coronary angiographic narrowing in stable angina pectoris, unstable angina pectoris and in acute myocardial infarction. *Am J Cardiol*. 1995; 76: 215-9.
19. Pinheiro MG, Rabelo Júnior A, de Jesus RS, Nascimento LC, Costa UM. Acute coronary syndromes in the absence of significant coronary artery disease. *Arq Bras Cardiol*. 2005; 84: 24-8.
20. Sabaté M, Jiménez-Quevedo P, Angiolillo DJ, Gomez-Hospital JA, Alfonso F, Hernandez-Antolin R, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation*. 2005; 112: 2175-83.
21. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare-metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA*. 2005; 294: 1215-23.
22. Kaiser C, Brunner-La Rocca HP, Buser PT, Buser PT, Bonetti PO, Osswald S, et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real world setting: randomized Basel Stent KostenEffektivitäts trial (BASKET). *Lancet*. 2005; 366: 921-9.