And the Answer Is, It Doesn’t Much Matter

David R. Holmes, Jr, MD; Bernard J. Gersh, MBChB, DPhil

There has been widespread interest in defining optimal treatment strategies for patients with unstable angina. Within the penumbra of this diagnosis is a wide spectrum of patients, ranging from those with non–ST-segment elevation myocardial infarction to those who have had recent onset of progressive angina without electrocardiographic changes or evidence of myocardial necrosis. A great deal of interest in the former group of patients has been stimulated by the most recent trials, Fragmin and Fast Revascularization During Instability in Coronary Artery Disease (FRISC II), Validation of Immediate angioplasty in Non–Q-wave myocardial infarction: an Open randomized multicenter study (VINO), and Treat Angina With Aggrastat and Determine Costs of Therapy With Invasive or Conservative Strategies (TACTICS).1–4 which support an aggressive approach for the majority of patients. Seventy-five percent of the patients in the TACTICS trial fell into the categories of intermediate or high risk on the basis of the TIMI grading system, and in these subsets there was a clinically significant improvement in outcomes in the invasive arm, a finding heartily applauded by interventional cardiologists.

Nonetheless, it should be emphasized that a sizable minority of patients with a history strongly suggestive of unstable angina have neither ECG changes nor elevated serum biomarkers, and in these subgroups the benefit of an aggressive approach is less evident. Although percutaneous coronary intervention has frequently been used in this group of patients, it has not been without problems, with the potential for increased complications particularly when angiographic thrombus was present.5 In addition, during follow-up, subsequent restenosis rates were found to be increased. Of interest, as far back as 1984,6 the initial National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angiography (NHLBI PTCA) registry found unstable angina to be a risk factor for the development of subsequent restenosis. As stents were added to the therapeutic equation, outcomes changed, both from the standpoint of short-term and long-term.

On a parallel tract, surgeons have also struggled with unstable angina.7–9 Early series demonstrated a higher perioperative mortality and morbidity in unstable angina patients, particularly in the setting of a recent myocardial infarction. Nonetheless, as has been the case with percutaneous coronary intervention, surgical techniques and perioperative management have changed, with a corresponding improvement in outcomes. In regard to current approaches to coronary revascularization for both stable and unstable angina, surgeons and cardiologists are both painting on a very different canvas from that which was available 10 to 15 years ago.

These observations form the backdrop for the article by de Feyter et al,10 which studies the importance of unstable versus stable angina within the randomized Arterial Revascularization Therapies Study (ARTS) trial of patients with multivessel disease who were randomized to either stent implantation or coronary bypass graft surgery. The definition of unstable angina is crucial in any such analysis and included Braunwald IB, C to IIIB, and C (Table).11 whereas all other categories came under the rubric of stable angina. Importantly, this was a prespecified sub-analysis, which minimizes the potential for bias. The goals of this analysis were to study clinical outcomes, costs, and cost-effectiveness. During this trial from 1997 to 1998, the interventional and surgical techniques used reflected the current state of the art at that time. It is important to remember that interventional cardiology, however, has advanced further since that time, with the widespread use of glycoprotein IIb/IIIa receptor antagonists. The results of the main ARTS trial have been published elsewhere12 and demonstrated that for the overall group of patients with multivessel disease deemed suitable for either coronary bypass graft surgery or percutaneous coronary intervention with a stent, the 1-year outcomes in terms of rates of death, myocardial infarction, or stroke were not significantly different. At 1 year, 90.7% of the patients in the stent group were alive and had not had a stroke or myocardial infarction versus 91.2% of the patients in the surgery group (95% CI 1.07, 0.75 to 1.52).

There was an imbalance in need for subsequent repeat revascularization procedures. The percutaneous coronary intervention patients needed to have more repeat procedures during follow-up, 16.8% versus 3.5% in the surgery group.

The current analysis by de Feyter et al10 focuses on the essential question, namely whether, with the then-current techniques (1997 to 1998), does the presence of unstable angina still matter in terms of the outcome of revascularization with either a catheter or a bypass operation. The answer is that it does not; there were no significant differences in either early or 1-year major adverse cardiac event (MACE) rates between unstable or stable angina patients undergoing either treatment modality. For the surgical group, event-free survival from MACE, which was defined as death, stroke, nonfatal infarction or repeat revascularization by either percutaneous coronary intervention or coronary bypass graft surgery, was 89.2% for stable angina patients and 85.3% for unstable angina patients.
unstable angina patients. Death was infrequent, at 3.2% and 2.2%, respectively, and myocardial infarction at 2.9% and 5.8%, respectively. In the percutaneous coronary intervention group, there was also no difference in MACE rates at 1 year, with 73.5% of stable and 74.3% of unstable angina patients free of major adverse cardiac event. Death occurred in 2.4% and 2.7% of patients, respectively, and myocardial infarction occurred in 5.1% and 5.8%, respectively. Although there was no difference in 1-year MACE rates between stable and unstable angina patients within each treatment modality, there was an obvious difference between the 2 therapeutic groups, with the percutaneous coronary intervention patients having more MACEs at 1 year. This was, as has been reported in the main trial,12 related not to differences in death or myocardial infarction but to the continued problem of an increased need for repeat percutaneous procedures, which occurred in 13.9% of stented stable angina patients and 10.6% of stented unstable angina patients, or coronary surgery, which was performed in 3.7% of stented stable angina patients and 6.2% of stented unstable angina patients.

The final endpoint assessed in this trial was that of "dollars and cents." Measured in US dollars, there was no significant cost difference between stable angina and unstable angina in each group. There was a significant difference in the incremental cost-effectiveness ratio between groups in favor of stenting compared with bypass surgery, which was $16,300 for patients with stable angina compared with $32,983 for patients with unstable angina.

As with any randomized, controlled trial, one has to place the results into the perspective of clinical practice in the community. Patients entered into the ARTS trial were highly selected, in that both cardiologists and surgeons agreed on the suitability of the patient for either procedure. Secondly, it should be appreciated that there are degrees of "instability" that no formal classification scheme can account for in its entirety. For example, a patient requiring an intra-aortic balloon pump for post-myocardial infarction unstable angina and left ventricular dysfunction poses a very different set of problems and risks than a patient with rest angina and mildly increased serum biomarkers in the setting of a normal ECG. Moreover, there is a difference between a patient with unstable angina who is pharmacologically stabilized before angiography and a patient with refractory ongoing chest pain. Despite the very encouraging results of this study, we should not automatically assume that the risk of intervention in all patients with unstable angina is identical to that in all patients with stable angina.

This trial must be put in the context of our current knowledge and database. At the time it was performed, there were no studies comparing the relative merits of modern surgical revascularization versus percutaneous revascularization techniques for the treatment of multivessel disease patients with both unstable and stable angina. Since that time, treatment strategies have continued to evolve. An enduring principle that emanated from the trials of bypass surgery and medical therapy remains; the "sicker" the patient, the greater the benefit of surgery over medical therapy on survival. Perhaps in the current era we can extrapolate to the situation in patients undergoing percutaneous coronary intervention versus medical therapy alone. Patients with unstable coronary syndromes are in general "sicker" than those with stable disease, at least in regard to factors such as plaque stability, endothelial dysfunction, and the frequency of current events. However, the marked improvement in outcomes of both coronary bypass graft surgery and percutaneous intervention, as documented in this study,10 shifts our focus toward recognizing the fact that unstable angina provides "a window of opportunity" rather than an "open window from an upper floor." Moreover, these encouraging data from the ARTS trial12 suggest that the inherent risk posed by "instability" is much less than previously thought. The bottom line is that in the past, unstable angina was a bad actor; with current approaches, revascularization cares not whether the diagnosis is unstable or stable angina. In general, it does not matter nearly as much anymore.

### References


2. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomized multicenter study.


**KEY WORDS:** Editorials  ■  angioplasty  ■  stents  ■  surgery
And the Answer Is, It Doesn't Much Matter
David R. Holmes, Jr and Bernard J. Gersh

Circulation. 2002;106:11-13
doi: 10.1161/01.CIR.0000024293.71103.3A
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/1/11

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/