Unstable Angina

Current Concepts and Management

Editors:
P. G. Hugenholtz
B. S. Goldman

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Proceedings from a Conference held in
Rotterdam, May 23–25, 1985

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There is an almost nostalgic ring to this title, for "Unstable Angina Revisited" is the aphorism for the conference held in Rotterdam, The Netherlands, May 23–25, 1985, and from which "happening" has come this book "Unstable Angina, Current Concepts and Management". Scientific investigation, clinical experience and understanding of the current limits in medical care, all expressed at the meeting, have generated this forceful and practical clinical guide to therapy.

Any physician intimately involved in the care of patients with coronary disease knows from his experience that the toughest cases, those who require the most difficult decisions, are found in those patients who are temporarily on the watershed between angina and myocardial infarction. Many therapeutic approaches have been advocated; literally hundreds of articles have been written; many carefully constructed trials have been carried out; yet the truth concerning the actual cause and the best therapy, continues to elude us. This is the principal reason why, after almost 20 years of investigation and modern research, we are still unclear how to best manage this problem or to optimally direct our therapeutic attack. Unstable angina continues to cause unnecessary death and infarction in too many patients when unexpected and yet, strangely enough not in others, when anticipated. Why? Are we not clever enough or does the disease defy our means?

A major reason for these discrepancies in clinical outcome must be that the disease is multifactorial, and that within the same patient, different pathophysiological mechanisms may occur at different times and in succession. Unstable angina presents itself to us as a continuous spectrum of ischemic syndromes. Therefore, each physician treating a patient with unstable angina must be aware of the many factors that may be causative at that particular moment of the disease process. He needs also to be aware that the very next moment, a different mechanism may prevail or spontaneous improvement can occur. Consequently, there will never be *one* therapy for *every* case of unstable angina, nor will there *ever* be the *best* therapy for unstable angina. There will only be the *optimal* therapy for that *particular stage* of the disease at that particular *moment* in time *for that patient.*

What is in 1985 the significance of the syndrome of unstable angina? It marks the boundary between the manageable syndrome (by the patient) of exertional angina, and the unmanageable loss of tissue (by the doctor) that ensues once myocardial infarction has taken place. Unfortunately, the boundary is indistinct and blurred in the temporal sense. While it is true that not every case of unstable angina will lead to myocardial infarction or prolonged ischemia or sudden death, it is not clear how many symptoms or singns of the unstable syndromes have actually preceded sudden death. In fact, we are still woefully short of real understanding of the natural history of unstable angina, within and outside the hospitals walls, no matter what some of the reported clinical series would lead one to believe. In fact, it is the uncertainty of outcome in a specific patient that obliges us, urges us and indeed forces us to provide maximal treatment to all. This in turn should result in the prompt (i. e. within 24 hours or less) relief of symptoms with the absence of sequelae, such as subsequent infarction or death. It is my firm belief and aim that any attack of unstable angina, provided it is properly recognized and properly treated, should *never* result in myocardial infarction or death.

Five years ago in Toronto, Canada, a similar conference was organized from which a successful and much discussed book "Unstable Angina" resulted. Therefore, the organizers of the present meeting felt that it would be wise to provide completed manuscripts at the actual time of the meeting in another book, and in the form of a sequential text, rather than the usual collection of abstracts or delayed proceedings. We are most grateful to the autors for their intense effort in providing a completed manuscript even before they have uttered a word! The importance of providing such a book, in which the summaries replace abstracts and serve the role of messengers in introducing the speakers, cannot be underestimated. For it is the written word that eventually and ultimately seals the meaning which the investigator has meant to

give to his investigation; it is at the quiet of his desk where he puts his most fundamental thoughts to paper and formulates the "essence" of his message. In this rapidly changing world of numerous medical meetings, postgraduate teaching courses and audiovisual aids, none can challenge the quality and timelessness of a well written book. It is our conviction that a manuscript is truly original and best written when it must be sumitted before the oral presentation rather than after when one's memory may have been "edited" by discussion and aftertought.

The clinician who possesses knowledge may be an asset, but the one who can communicate knowledge is indeed a treasure. To enhance the reality and liveliness of this text and the meeting, an unedited "live" tape cassette record of the panel discussion held at the end of the conference will be available to the readers of this book. It is our fervent hope that these two works, the text and the tape, assembled by all those presenting at this conference on "Unstable Angina Revisited" will serve as a guide-line for the current management of patients with unstable angina with the expectation that still better approaches will become available in the next five years. May we meet then again, in good health and good spirit with new ideas, results and challenges or, perhaps, confirm that this book already contains most of the answers we seek.

Rotterdam, May 23, 1985

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ntroduction

Unstable angina revisited, a surgeon's perspective

In the fall of 1979, a symposium on Unstable Angina was held in Toronto, Canada, sponsored by the Toronto General Hospital, the University of Toronto and the Ontario Heart Foundation. The invited participants were from major centres in Canada, the United States and Europe. The purpose was to create an international forum, an environment wherein concepts and clinical practice could be discussed and debated and a consensus developed. The meeting was timely, occurring as it did almost a full decade after the introduction of coronary artery bypass graft surgery.

At the time, the term "unstable angina" encompassed a wide variety of pain syndromes intermediate between stable effort angina and frank myocardial necrosis. Despite attempts at more precise clinical definitions, the "pre-infarct(ional) state" created anxiety in both patients and physicians and precipitated urgent therapy, often bypass surgery. Without general agreement concerning the clinical subsets that constitute "unstable angina", and with controversy concerning the natural history, prognosis and management, the demonstration of critical coronary stenosis by immediate angiography usually resulted in emotional crisis, of even intellectual chaos and the rapid deployment of either the intra-aortic balloon pump, coronary bypass surgery or both modalities. Thus, the availability of an (apparently absolute) diagnostic tool (angiography) and (apparently) effective interventions, created a self-

sustaining aura that "pre-infarctional angina" was indeed mortal and required urgent attention, thereby putting further excessive strain on at the time limited clinical and hospital resources.

In this same time period, numerous randomized and non-randomized studies on stable and unstable angina were being conducted. The National Cooperative Unstable Angina Pectoris Study Group in the U. S. carefully and clearly demonstrated that urgent surgical therapy after a study interval of 24 hrs had no advantage over urgent medical therapy in terms of early mortality; that surgery indeed had higher (peri-operative) infarction rates, but that medical patients were left with worse functional status often requiring later revascularization. While individual management of the patient with left main coronary stenosis seemed clear, the patient with tight proximal LAD stenosis was considered urgent in some centres, but classified as only "single vessel disease" in others. The demonstration of coronary vasospasm as a mechanism of rest angina, the recognition of cellular injury during prolonged ischemia (but beginning within 5 to 10 minutes) and the efficacy of high dose propranolol and intravenous nitroglycerin in ameliorating the pain and ECG changes of acute coronary insufficiency, all contributed immensely to our emerging understanding of the natural history, prognosis and medical treatment of unstable angina. Surgeons and anesthetists meanwhile were creating a safer environment for the bypass operation, with lesser use of the intra-aortic balloon pump, better haemodynamic monitoring during smoother inductions, more complete revascularization and better peri-operative myocardial protection with cold potassium cardioplegia.

It was clearly a good moment to pause, reflect, consolidate and share attitudes and experience. The symposium and later the text of the proceedings [1], allowed the invited clinicians from eight different institutions, to summarize and agree on definitions, mechanism and therapy. The urgency and anxiety of the status quo ante had been replaced by a more measured approach of incremental therapy in a C. C. U. setting, appropriately timed angiography and delayed surgery when deemed necessary. The status quo was considerably more relaxed than in the period preceding 1979.

Like the next act of a stage play, it is now some five years later and the scene is Rotterdam, The Netherlands. This book contains the presentations of many physicians who participated in "Unstable Angina Revisited" May 23–25, 1985. "No good was ever achieved without enthusiasm" (Ralph Waldo Emerson). Certainly the energy and enthusiasm of the Thoraxcenter faculty, with the support of Erasmus University and the Netherlands Inter-University Cardiological Institute, Utrecht, have once again created a superb international forum. The force vivandi was Paul Hugenholtz, Cardiologist in

Chief at the Thoraxcenter and currently President of the European Society of Cardiology.

One may question "Why another act? Why another symposion? Why so soon?" The simple answer is: our sense of complacency regarding unstable angina was very soon disturbed. The long waiting lists for elective angiography and/or surgery in many countries have resulted in numerous patients presenting urgently with "break through" symptoms, or deteriorating clinical status. Since most of these are already on full triple medical therapy (nitrates, Ca antagonists and β-blockers), they clearly represent unstable and urgent problems. Clinical reports of successful revascularization of acute myocardial infarction have brought increasing numbers of patients for consideration of bypass surgery who have unstable angina with "some" infarction, or infarct patients with "some" continued ischemia; obviously, both are challenging problems. The availability and widespread use of more selective β-blockers, calcium channel blockers or inhibitors, the advent of percutaneous intra-aortic balloon pump assist devices, the aggressive use of percutaneous transluminal coronary angioplasty for single and even multiple vessel disease in unstable patients, and the use of thrombolytic therapy in conjunction with angioplasty for unstable patients (before or) after myocardial infarction, have all resulted in new weapons with which to wage battle against unneccessary infarction and death. From the surgeon's viewpoint, the increasing ease of multiple bypass grafts for more complete revascularization, the efficacy of blood or Ca^{2+} antagonist cardioplegia in high risk patients, and the constant improvement in surgical results have acted as an agreeable and even desirable alternative to prolonged medical therapy. Lastly, there has been the emergence of a new clinical group, unstable patients with failed bypass grafts or new stenotic lesions with (some) patent grafts, a formidable challenge in timing, technique and peri-operative management. All in all the challenge in 1979 has remained in 1985.

Like time itself, accepted clinical practice and available therapeutic modalities do not stand still. There is a constant ebb and flow of ideas in medicine basess on observations of the past mixed with and welded to a changing armamentarium. The perceptive clinician blessed with intellectual curiosity, will question the status quo and carefully pursue a new management plan, objectively assessing results as they become evident. Thus, it was in this spirit that the present book was conceived. The "best and the brightest" of modern cardiology and cardiac surgery were once again invited to present their experiments, clinical practice, and results of reaffirm or challenge ideas generated in 1979, and to agree upon a consensus for the remainder of this decade. Such was the enthusiasm generated by Hugenholtz and the Thoraxcenter, that 38

clinicians from 11 countries contributed to this book and many more to the proceedings. Their toughtful and informative works indeed summarize current clinical and theoretical knowledge of unstable angina and form the actual basis for a rational approach to the management of this most interesting and challenging syndrome in cardiology in 1985.

Toronto, May 1, 1985

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Introduction Section A:

Pathophysiology and origin of unstable angina

In the first section of this book on pathophysiologic mechanisms, the role(s) of fixed occlusive disease, accelerated atherosclerosis, plaque rupture, thrombosis and spasm are described. Schaper in his introduction to the problem emphasizes the variations in the speed with which the different processes may proceed in turn influencing the progression in the vascular component of this disorder. Born in his chapter carries this theme further and expands on the role of platelet aggregation, vascular endothelium and thrombosis. From therapeutic observations with aspirin, a better pathogenetic concept emerges which stresses the obstructive component caused by (intermittent) thrombus formation on an abnormal endothelium. A further attractive proposition on the significance of the endothelial factor (or better the absence thereof) comes from Parratt. His hypothesis combines the various postulated mechanisms better than any other before and serves to explain why in some patients symptoms and signs can subside spontaneously while in others the process leads to (in)complete obstruction in a matter of hours. The observations by all 3 authors correspond to the increased acceptance of early desobstruction by PTCA or bypass surgery advocated from clinical experience reported in later chapters. Becker in his overview of (rare) pathologic specimens confirms the likelihood of rapid waxing and waning of the obstructive elements in that the eccentric proliferation caused by the smooth muscle cell is the underlying mechanism in all lesions; which factors control the smooth muscle cell remains as yet a mystery. In humans, it is difficult to confirm these hypotheses, yet Théroux through painstaking analysis of angiograms of the coronary arteries, repeatedly visualized in the same patients, has tried to emphasize the role of (intermittent) thrombosis in the waxing and waning of unstable angina. In particular, high grade stenosis could be shown to progress rapidly when intraluminal thrombi were present. Also such rapid progress in disease was shown to be reflected in more severe angina and more regional