How European cardiologists perceive the role of calcium antagonists in the treatment of unstable angina

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Physicians in the United States have recently published a guide to the definition and management of unstable angina pectoris. The guideline divides this condition into three main groups: 'rest', 'new onset' and 'increasing' angina. For the great majority of patients, medication involves heparin, acetylsalicylic acid, nitrates and beta-blockers. In some patient groups, calcium antagonists are appropriate treatment. These recommendations seem to be broadly supported by European cardiologists. Study of individual cases, however, reveals a continuing diversity of opinion. (Eur Heart J 1997; 18 (Suppl A): A117-A124)

Key Words: Unstable angina, diagnosis, treatment strategies, coronary angiography, case studies.

Introduction

The treatment of unstable angina pectoris remains a stimulating challenge to the medical profession. Recently, experts in the United States have attempted to formalize criteria for the diagnosis and treatment of this multi-faceted condition. Our recent survey suggests that European cardiologists broadly agree with these proposals. However, considerable individual differences in approach become apparent when case studies are deliberated in more detail.

The U.S. Clinical Practice Guideline ‘Unstable Angina: Diagnosis and Management’, and its assessment in Europe

In the United States as elsewhere, the healthcare system is under considerable financial pressure. Insurance funds, and other organizations which pay for services, are keen to reduce expenditure. Diagnosis of ‘unstable angina’ automatically qualifies doctors and patients in the U.S. for reimbursement of the ensuing costs. In 1991, some 570 000 Americans were admitted to hospital as unstable angina patients. The impression increasingly arose in some quarters that the diagnostic net was sometimes cast too wide for rigorous cost-containment. This led to the formulation of more sharply defined contours for patients’ identification and treatment.

The consensus reached by Braunwald et al. has been published in various forms. It includes the views of a large number of American cardiologists and other medical practitioners. Their proposals for the definition of unstable angina are summarized in Table 1.

The second major part of Braunwald and collaborators’ suggestions concerns the medical treatment of unstable angina. This is summarized in Table 2.
**Table 1 U.S. Clinical Practice Guideline — Unstable angina pectoris: definition**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
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<tr>
<td><strong>Rest Angina:</strong></td>
<td>Angina at rest, usually prolonged (&gt;20 min), developing within 1 week of presentation.</td>
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<tr>
<td><strong>New Onset Angina:</strong></td>
<td>Angina of at least Canadian Cardiovascular Society Class (CCSC) III severity; onset within 2 months of presentation.</td>
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<tr>
<td><strong>Increasing Angina:</strong></td>
<td>Previously diagnosed angina now distinctly more frequent, longer, or with a lower threshold (increase by at least 1 CCSC class within 2 months of presentation, reaching at least class III).</td>
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**Table 2 U.S. Clinical Practice Guideline — Unstable angina pectoris: medical treatment**

<table>
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<tr>
<th>Treatment</th>
<th>Description</th>
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<tr>
<td><strong>Acetylsalicylic acid (ASA), 80-324 mg day⁻¹</strong></td>
<td>when necessary — for all patients with unstable angina (In the case of the very small minority in whom ASA is contra-indicated, ticlopidine 250 mg twice daily is to be used).</td>
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<tr>
<td><strong>Heparin i.v., 80 units kg⁻¹</strong></td>
<td>— in the emergency department, for all patients at high or intermediate risk of death or non-fatal myocardial infarction</td>
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<tr>
<td><strong>Nitrates i.v., 5-10 μg min⁻¹,</strong></td>
<td>titrated to 75-100 μg min⁻¹ — for those in whom symptoms are not fully relieved by three sublingual nitroglycerine tablets and initiation of β-blockade.</td>
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<tr>
<td><strong>β-blockers,</strong> dosage dependent on specific agent — for all patients with unstable angina, except where contra-indicated. (Target heart rate 50-60 beats min⁻¹)**</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium antagonists,</strong> dosage dependent on specific agent — for unstable angina patients already receiving 'adequate' doses of nitrates and β-blockers, or for those unable to tolerate adequate doses of one or both, or for patients with variant angina.</td>
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again, European cardiologists seem in broad agreement with their transatlantic colleagues. About 80% of those polled agree completely with the five drug classes suggested. The remainder do so at least in part, with 78% believing that the patient groupings for each class are wholly correct; 22% partly concur.

According to the Clinical Practice Guideline for Unstable Angina (CPGUA), calcium antagonists should be avoided for patients with either pulmonary oedema or evidence of left ventricular dysfunction. European cardiologists support this limitation, with the provision that left ventricular dysfunction refers only to systolic dysfunction. However, the approximately 160 American authors and reviewers involved also stress the importance of detailed assessment of each drug. The CPGUA specifically recommends that choice of a particular calcium antagonist be based on the patient's haemodynamic state, as well as on the risk of adverse effects on contractility and atrioventricular conduction. A further important aspect, as the CPGUA points out, is the familiarity of the treating clinician with the agent in question.

This 'familiarity' comes not only from frequent use but also from study of the literature. Some recent findings have prompted the belief that short-acting nifedipine should not be used in unstable angina without concomitant beta-blockade[23]. The CPGUA strongly underlines this restraint on the use of the dihydropyridine. Almost all the polled European cardiologists agree. In general, U.S. practitioners consider it important to differentiate between dihydropyridine calcium antagonists, the phenylalkylamines like verapamil, and the benzothiazepines like diltiazem. A very sizeable majority of European poll participants concur. The remainder favour a two-class distinction between dihydropyridine and 'heart-rate-moderating' calcium antagonists.

**Views on two case studies in the light of the CPGUA**

Interestingly, the CPGUA does not mandate the use of coronary angiography in unstable angina patients. In order to stimulate European discussion in this and related issues, cardiologists were asked to consider two case studies. The patient characteristics are outlined in Tables 3 and 4.

When asked how they would have proceeded in case I, 80% of European cardiologists favour angiography. Despite the lack of evidence for ischaemia, it is felt that recent limited infarction in a prominent area warrants this step.

Angiography initially revealed no abnormalities. Further investigation, however, revealed a lengthy dissection of the right coronary artery. The treating physicians suspected that this had been caused by rupturing of a complex atheroma.

Professional opinion as to the best course of action in such cases clearly remains divided. Currently, about one quarter of those cardiologists questioned favours medication. A further half prefers percutaneous transluminal coronary angioplasty plus a right coronary artery stent. The remainder would tend to opt for surgical treatment.

After prolonged discussion and a number of complications, the patient in fact received percutaneous...
Calcium antagonists in unstable angina

Table 3 Unstable angina: patient characteristics case study I

Female, aged 52, with anteroseptal infarction. Smoker, triglyceride reading 300 mg \( \text{dl}^{-1} \). Transdermal oestrogen use.

Complained of atypical 5–10 min chest pain episodes, mainly at rest. Referring physician obtained no objective evidence of transient ischaemia.

Physical examination: negative.

Exercise test: negative (93% of maximum heart rate); developed hypertension during 12–13 min under Bruce protocol.

ECG: Q-wave leads 1 and 2, otherwise normal.

Echo: Mild antero-apical hypokinesia. Ejection fraction maintained.

Table 4 Unstable angina: patient characteristics case study II

Male, aged 54, smoker. Diabetic, like both parents. Mother suffered additionally from ischaemic heart disease.

Effort and cold angina in the 2 months before presentation


On admission: Echo normal; sinus bradycardia during resting ECG.

No ECG changes were noted in the coronary care unit. Holter monitoring (without treatment): revealed over 10 episodes of T-wave peaking, and nine of silent ST elevation lasting an average of 2.6 min each.


Echo hyperventilation test (without treatment): septal akinesia, T-wave peaking, no pain.

Exercise stress test (under treatment with verapamil, nitrates and aspirin): 100 W, DP 33.000, anterior T-wave peaking, no pain.

Echo hyperventilation test on same treatment: no changes or mechanical impairment.

transluminal coronary angioplasty and three coil stents. She left hospital 3 days later. Her discharge medication was aspirin (100 mg \( \cdot \text{day}^{-1} \)), ticlopidine (250 mg twice daily), atenolol (50 mg once daily) plus 10 mg once-daily amiodipine. This regimen may seem intriguing to many readers. No published benefit data are yet available from controlled comparisons of aspirin, ticlopidine and their combination.

Treatment with ticlopidine is sometimes associated with neutropenia. American practitioners have good reason to be cautious in the use of ticlopidine. It is, however, the CPGUA substitute for aspirin in aspirin-sensitive patients. The two drugs have different action mechanisms and time-courses. Whether these differences contribute to any therapeutically advantageous synergies requires further investigation.

On her long journey home, the patient suffered renewed chest pain. She was readmitted to hospital. The ECG showed no changes on the inferior wall. Leads V₁, V₂ and V₃ revealed only minor changes related to the patient’s inverted T waves. Echocardiography showed some worsening of the hypokinesia in the antero-apical wall. There was no rise in cardiac enzymes. The patient’s chest pain subsided within 45 min of i.v. nitrate application.

Opinion as to the appropriate next step varies considerably between our voting groups. Overall, about 50% supported re-angiography; 18% favour thrombolysis. Belief in the appropriateness of calcium antagonists varies particularly markedly. Somewhat at odds with their support for the U.S. guideline, only about a third of the European cardiologists would have given the patient a calcium antagonist at second discharge.

In the original case, the patient received both amiodipine and verapamil. These two, combined with aspirin and ticlopidine, kept the patient symptom-free throughout her recent one-month follow-up.

The patient characteristics of case II are summarized in Table 4. A little under half of our poll participants attribute the ST segment elevation to critical stenosis. The remainder almost all presume that the elevation was caused by exercise-induced vasospasm. A few considered that spasm occurred during exercise by chance. Over half attribute the apparent discrepancy between visual ECG and Holter monitoring to a confusing lack of symptoms and the brevity of ECG changes. About 35% ascribe the difference only to the latter.

Opinion is similarly divided on the negativization of the pre-medication stress test under drug treatment. 40% of those questioned believe that this indicates spasm. The reproducibility of ST segment elevation under exercise may well be indicative of exercise-induced spasm. This is the view of all the physicians involved in judgement of case II.

Bearing in mind that the U.S. Guideline authors do not mandate angiography in unstable angina, we asked European cardiologists for their views on its suitability for the patient. 100% would carry out angiography in such a case. This was indeed performed in the treating hospital. Angiography revealed 60% stenosis of the proximal left anterior descending segment. The appropriate response remains a matter of contention: one third of our participants would have carried out percutaneous transluminal coronary angioplasty in the patient, two thirds were opposed to this approach. Given the high risk of restenosis, the arguments against the use of PTCA in this case currently seem convincing. No published data as yet suggest a prognostic advantage for percutaneous transluminal coronary angioplasty in such a setting. The patient received verapamil (80 mg
t.i.d.), 5-mononitrate (20 mg t.i.d.) and aspirin (100 mg). This medication kept the patient symptom-free by suppressing vasospasm probably occurring at the stenosis level.

Discussion

The Clinical Practice Guideline for Unstable Angina has already begun to alter physicians' behaviour in the U.S.A. Notably fewer patients are now being admitted to hospitals there with a diagnosis of unstable angina (Pepine C., personal communication). As with most payer-driven trends in healthcare systems, such changes are not necessarily in the best interests of every patient. However, the CPGUA now provides terms of reference in place of probable uncertainty and inconsistency. It is therefore to be welcomed. In the United States, a shift is now visible away from coronary angiography towards non-invasive approaches. New guidelines for this area of medical practice are currently in preparation. We look forward with interest to their publication, conscious of the fact that such a framework is always no more than a set of proposals. Guidelines like the CPGUA do not legally bind, and they cannot hope to cover all patients in every situation. Fortunately, medical practice remains the care of individuals by individuals.

β-blockers and/or nitrates coupled with acetylsalicylic acid and/or heparin constitute first-line drug treatment in unstable angina. Calcium antagonists can be used as a second choice, or in patients unable to tolerate adequate doses of other drugs. Among calcium antagonists, those reducing heart rate and cardiac inotropism should be preferred, as they resemble the activity of beta-blockers. Dihydropyridines can be used, but only in combination with beta-blockers. As borne out strongly by our poll, the correct course of action is frequently a matter of refreshingly open debate.

The authors would like to acknowledge the assistance of Dr. Michael O'Donnell and Paul Castle in the preparation of the manuscript.

References

Case 1

Sex: Male
Age: 54 years
Family history: IHD (mother), Diabetes (both parents)
Risk factors: Cigarette smoker, Diabetes, Family history

History:
Effort and cold angina in the last two months

Exercise stress test without treatment
(performing one month before admission)
* 50 W DP 18,560
* ST segment elevation on anterior leads
* No pain

The ST-Elevation during exercise test is a sign of?

- Critical stenosis
- Coronary vasospasm induced by exercise
- Coronary vasospasm occurring by chance

Exercise stress test under treatment
(verapamil, nitrates, aspirin)
* 100 W DP 33,000
* Anterior T-wave peaking
* No pain

Is the negativization of the stress test performed under treatment reminiscent of a coronary spasm?

- Yes 40%
- No 60%

Is the reproducibility of ST-segment elevation during exercise indicative of exercise-induced spasm?

- Yes 100%
- No 0%
On a basis of these results would it be necessary to perform coronary angiography?

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<tr>
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<th>Yes</th>
<th>No</th>
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<tr>
<td>100%</td>
<td></td>
<td></td>
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<tr>
<td>0%</td>
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Is PTCA indicated to prevent coronary vasospasms?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>33%</td>
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<tr>
<td>67%</td>
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Unstable angina: U.S. clinical practice guideline

Rest Angina—angina occurring at rest and usually prolonged (>20 min) developing within one week of presentation

New Onset Angina—angina of at least Canadian Cardiovascular Society Class III (CCSC) severity with onset within 2 months of presentation

Increasing Angina—previously diagnosed angina distinctly more frequent, longer in duration or lower threshold (increased by at least 1 CCSC within 2 months of presentation to at least CCSC III)

Do European cardiologists agree with using the above three categories (rest angina, new onset angina, increasing angina) to define unstable angina?

Do European cardiologists agree with the specific definition provided for each category?

Medical treatment for unstable angina

**Aspirin**
(for all patients with unstable angina)

**Heparin**
(for unstable angina patients in high risk category)

**Nitrates**
(for those in whom symptoms are not fully relieved)

**Beta-blockers**
(for all unstable angina patients)

**Calcium antagonists**
(for unstable angina patients already receiving adequate doses of nitrates and beta-blockers, or in patients unable to tolerate adequate doses of one or both, or those with variant angina)

Do European cardiologists agree with the drugs recommended?
Do you agree with this recommendation?

U.S. practitioners feel that it is important to differentiate between various classes of calcium antagonists, particularly dihydropyridines (nifedipine-like), phenylalkylamines (verapamil-like), and benzothiazepines (diltiazem-like).

The U.S. Clinical Practice Guideline for Unstable Angina specifically recommends that nifedipine should not be used in the absence of concurrent beta-blockade therapy.