Angina: A Continued Challenge for the Cardiologist

Lead Article

Expert Answers to Three Key Questions

Fascinoma Cardiologica

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Angina: identifying and managing the patient at risk

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Stable angina, the most prevalent manifestation of coronary artery disease (CAD), has been under-researched, partly because it excites less interest among cardiologists than the more acute manifestations of CAD—where progress has been nothing less than brilliant—and partly because it is difficult to conduct studies sufficiently powered to demonstrate significant prognostic benefit in a population whose overall annual mortality rate is 1%-3%. Whether nitrates improve prognosis, for example, is still unknown. Yet, stable angina offers a perfect window of opportunity for identifying those exposed to future events and for developing novel therapies such as plaque-stabilizing drugs. At the entry level of the workup pyramid, simple clinical assessment aided by the ankle-brachial index remains as accurate as any measure or combination of measures yet devised. At the highest level, angiography supplemented by plaque studies using magnetic resonance angiography is a candidate gatekeeper to revascularization. Bypass has definite prognostic benefit in many well-selected patients. Tailoring a management plan to optimize event-free survival in the individual patient requires awareness of the precise prognostic impact, in both the overall angina population and specific groups, of lifestyle, prophylaxis (aspirin, statins, and, increasingly, angiotensin-converting enzyme inhibitors), specific antianginal drug therapy, and invasive intervention.

Coronary artery disease (CAD) has been the plague of industrialized nations since the latter half of the last century. Stable angina is the most prevalent manifestation of this menacing disease, which affects millions worldwide. The cost to society is enormous in terms of premature mortality and reduced quality of life, in addition to a significant economic burden caused by inflationary medical costs and loss of employment. Tremendous strides have been made where the immediate risk of mortality is greatest. In the field of acute myocardial infarction (MI), treatment directed at achieving infarct-related artery patency combining aspirin and thrombolytic agents or percutaneous interventional techniques, β-blockade, and secondary prevention have improved prognosis, and, in unstable angina, more advanced means of risk stratification, the use of antithrombotic and antiplatelet agents, and interventional approaches have also effected a significant improvement in outcome.

However, stable angina remains somewhat shaded by the brilliance of progress in other dimensions of CAD, in part because of the inherent difficulties in proving a significant prognostic benefit of a treatment or combination of treatments in a population in whom the overall annual mortality rate is 1% to 3%. Angina not only impairs quality of life, which may be improved either by medication or revascularization, but also identifies a population in whom a proportion are at increased risk of future cardiovascular events and mortality. In this high-risk group there is considerable room to improve prognosis. Stable angina is a period of clinical stability that provides an excellent window of opportunity to identify those at highest risk of future events and to intervene in an appropriate manner, either by lipid lowering, medical therapy, percutaneous intervention, or surgery to improve prognosis. The identification of those high-risk individuals remains a challenge, even with current risk prediction techniques, which will be outlined, but new methods of determining plaque vulnerability and susceptibility to acute

SELECTED ABBREVIATIONS AND ACRONYMS	
4S	Scandinavian Simvastatin Survival Study
ACME	Angioplasty Compared to MEdicine
APSIS	Angina Prognosis Study In Stockholm
ASIST	Atenolol Silent Ischemia Trial
AVERT	Atorvastatin vs Revascularization Treatment
BARI	Bypass Angioplasty Revascularization Investigation
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CARE	Cholesterol And Recurrent Events
CASS	Coronary Artery Surgery Study
CRP	C-reactive protein
DSE	dobutamine stress echocardiography
EBCT	electron beam computed tomography
ECAT	European Concerted Action on Thrombosis
ECSS	European Coronary Surgery Study
END	Economics of Noninvasive Diagnosis
EUROPA	EURopean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease
FACT	Fluvastatin Alone and in Combination Treatment
HOPE	Heart Outcomes Prevention Evaluation
IONA	Impact Of Nicorandil in Angina
IVUS	intravascular ultrasound
LIPID	Long-term Intervention with Pravastatin in Ischemic Disease
LVH	left ventricular hypertrophy
MASS	Medicine, Angioplasty, or Surgery Study
MI	myocardial infarction
MRA	magnetic resonance angiography
PEACE	Prevention of Events with Angiotensin-Converting Enzyme inhibition
PTCA	percutaneous transluminal coronary angioplasty
RITA-2	Second Randomised Intervention Treatment of Angina
RR	relative risk
SAPAT	Swedish Angina Pectoris Aspirin Trial
SoS	Stent or Surgery
TIBET	Total Ischemic Burden European Trial
VACS	Veterans Administration Cooperative Study

events hold promise for the future. The current armamentarium to reduce risk may need to expand to incorporate plaque-stabilizing agents if markers of plaque vulnerability are found to portend outcome.

The estimated annual death rate in stable angina ranges from 1% to 3.2%, depending on the population studied,[1-3] and whether patients considered for revascularization or patients with heart failure are included. Conventionally, subjects presenting with anginal symptoms have an initial clinical assessment and a form of provocative or functional assessment, either exercise electrocardiography (ECG), stress echocardiography, or myocardial perfusion scan, which allows stratification into high- and low-risk groups and influences referral for further invasive investigation by cardiac catheterization. The use of electron beam computed tomography (EBCT) to stratify patients presenting with chest pain into those who would benefit from further invasive assessment of their coronary anatomy and those who do not warrant further investigation has also been proposed.

The assessment of risk occurs at different levels of the workup pyramid, and the relative importance of individual items of information in prediction of outcome varies to reflect the prior probability of disease in the population, and also the other information available. For example, the prognostic importance of a single clinical factor, the presence of increasing frequency of chest pain, is far greater in a middle-aged man known to have significant three-vessel disease than in a woman in her twenties with no risk factors for CAD, or a patient known to have normal coronary arteries at coronary angiography.

CLINICAL ASSESSMENT

Clinical assessment, history, examination, resting electrocardiography (ECG), and, in some circumstances, chest radiography, constitute the initial step on the stair of management. From this point, it may be considered likely that the patient's symptoms are noncardiac in nature and further cardiac investigation unnecessary, or necessary to ascend to the next step and employ noninvasive testing to make a diagnosis. In cases where pretest probability is high, noninvasive testing is commonly employed to assess severity and prognosis prior to cardiac catheterization, which may not be undertaken if the results of the investigation predict a favorable outcome and symptoms can be controlled medically. If the coronary anatomy is known, functional assessment may assist in assessing prog-

nosis and planning further management, particularly revascularization. In a select group of subjects, the clinical presentation may be sufficiently compelling, eg, unstable symptoms associated with ECG changes, to refer for immediate cardiac catheterization with a view to revascularization. *Table I* lists the various parameters that predict prognosis in patients with known CAD.

	Incremental prognostic information*
Clinical data	+
Resting ECG	-
Conventional risk factors	?
Exercise ECG	+
Coronary calcification	-
Stress echocardiography	+
Myocardial perfusion imaging	+
CRP & other inflammatory and fibrinolytic markers	?
Homocysteine	?

*When combined with detailed coronary anatomy and left ventricular function.

Table I. *Parameters that may be used to predict prognosis in patients with known coronary artery disease.*

Clinical variables evaluated to determine prognostic influence may be grouped for convenience into factors relating to angina, indications of widespread vascular disease, prior MI, or heart failure, or conventional risk factors. Age and male sex, the course and frequency of chest pain, and indicators of severity of heart failure, including diuretic and digoxin usage, all ascertainable during the clinical history, are predictive of an adverse cardiovascular outcome. The presence of diabetes also has a strong negative impact on survival.

Clinical assessment, although considered by some to be subjective, may, if properly carried out, be a potent discriminator between groups at high and low risk of cardiac mortality. An initial assessment by a physician using information obtained from the history, specifically age, sex, the course and frequency of anginal pain, the severity of heart failure symptoms and prior history of MI or cerebrovascular or peripheral vascular disease, the examination, specifically, the presence of a ventricular gal-

lop or carotid bruit, the resting ECG and heart size on chest radiograph, was at least as accurate, and possibly superior (trend rather than statistically significant difference), than exercise ECG in isolation for the prediction of 3-year survival in patients referred for non-invasive testing for suspected CAD.[4]

When clinical and exercise data are combined, the relative importance of each factor in prediction of prognosis is altered, and when combined with angiographic data, the importance of certain clinical factors is obscured in the composite picture. In most studies, multivariate analysis yields angiographic variables as the strongest predictors of mortality,[5,6] reflecting the importance of coronary anatomy and ejection fraction on prognosis; however, simple clinical assessment remains a useful tool. Califf et al showed that the use of an angina score in the Duke database, combining the course of the angina (stable, progressive, or unstable), with frequency of symptoms and ST-segment/T-wave changes on the resting ECG, added significant independent prognostic information to the patients' age, sex, coronary anatomy, and left ventricular (LV) function *(Table II).*[7] It must be noted that in the absence of progressive symptoms, although not necessarily unstable, the frequency of angina did not add further prognostic information. Furthermore, the angina score does not contribute to long-term risk prediction, ie, beyond 3 years.

Clinical indications of widespread vascular disease, such as peripheral vascular disease or the presence of carotid disease, predict an adverse prognosis in patients with angina. Simple, inexpensive, and readily performed tests such as the ankle-brachial index can provide independent prognostic information in patients with known CAD. An ankle-brachial index <0.9 was associated with an event-free survival of 73% over 14 months versus 90% in patients with an ankle-brachial index of >0.9.[8] More detailed ultrasonographic assessment of femoral and carotid arteries such as carried out in the Angina Prognosis Study in Stockholm (APSIS) population does not necessarily improve prognostic information, although femoral and, to a lesser extent,

ANGINA PROGNOSIS SCORE		
Score (points) = angina course × (1+ frequency) + ST-segment/T-wave abnormalities		
stable = 0 progressive = 1 nocturnal pain = 2 unstable =3	(up to 5)	(6)

Table II. *Duke database angina prognosis score combining the course of angina, frequency of symptoms, and ST-segment/T-wave changes on the resting ECG.*[7]

carotid intima-media thickness was associated with cardiovascular death and MI in univariate analysis. When adjusted, only femoral intima-media thickness was a significant independent predictor of outcome, and then only of revascularization (odds ratio [OR] 2.6), not death or MI.[9]

The use of the resting ECG in predicting mortality in stable CAD is often underestimated. The prognostic value of pathological Q-waves was identified by Block et al[10] in the 1950s, and the presence of Q-waves and/ or ST-segment/T-wave changes has been used in many clinical prediction models. The predictive value is strongly related to the association with prior MI. The development of QRS scoring systems that have been shown to correlate with infarct size has allowed improved prognostic performance of the resting ECG. Although a very strong predictor of outcome in univariate analysis, when heart failure class, prior history of MI, and cardiomegaly are accounted for, the QRS score does not add independent prognostic information.[11]

ASSESSMENT OF CONVENTIONAL —AND SOME NONCONVENTIONAL— RISK FACTORS

Diabetes, hypertension, hyperlipidemia, and tobacco smoking are well established as risk factors for incident CAD, and unchecked, these risk factors contribute to progression of disease both in extent and severity. The presence of one or more of these risk factors increases the likelihood of significant CAD.[4] Many of the large prospective studies demonstrating the adverse effects of these risk factors on mortality have been population-based, and the results are not automatically directly applicable to a population with angina or documented CAD. However, high cholesterol levels have been demonstrated to be associated with an increased risk of cardiac death and nonfatal MI in a population with stable CAD,[12] as are hypertension and smoking.[13] More recently, statin-treated hyperlipidemia was actually associated with a reduction in cardiac mortality and MI.[14]

Of the conventional risk factors, diabetes mellitus carries the greatest prognostic weight in risk stratification of patients with CAD. In patients with type 2 diabetes, the risk of recurrent coronary events is approximately 6 times that of nondiabetics.[15] A large proportion of this excess risk is associated with the high prevalence of other risk factors, including hypertension, obesity, and dyslipidemia in the diabetic population, but when corrected for the presence of other conventional risk factors in multivariate analysis, diabetes remains a

strong independent predictor of adverse cardiac outcome. In patients with known CAD, diabetes is associated with almost double the risk of mortality even after adjustment for coronary anatomy.[14] Diabetes also adversely affects the outcome of intervention, both surgical and percutaneous.[16,17]

In a risk prediction score based on multivariate analysis of noninvasive strategies,[18] including clinical assessment, exercise ECG, and thallium scanning, in 8411 patients, the presence of diabetes (16 points) and hypertension (8 points) remained predictive of cardiac death, when the noninvasive tests were included in the analysis. The only other clinical factors that were also retained for the risk prediction score were prior MI (8 points) and congestive heart failure (43 points). The adverse impact of diabetes and hypertension on prognosis was also borne out in the subgroup analysis of the Angina Prognosis Study In Stockholm (APSIS) trial, a 686-patient study of metoprolol and verapamil in stable angina.[19] This is food for thought when one considers the high rate of undiagnosed diabetes and hypertension in stable patients.[20]

High triglycerides have gained increasing recognition as an independent risk factor for incident CAD and, furthermore, have been identified as an independent predictor of MI in a nested case-control study.[21,22] Treatment with fibrates reduces both triglyceride levels and the incidence of cardiovascular events, but also has beneficial effects on fibrinogen, which may be important in the reduction of events. Homocysteine is another risk factor for which there is increasing weight of epidemiological evidence for an association with CAD. Pathophysiologically, hyperhomocysteinemia is associated with a hypercoagulable state, which may increase the risk of MI and potentially increase cardiac death. This concept is supported by studies that have found an association between elevated homocysteine and increased risk of MI and death in patients with angiographically proven disease. The relative risk (RR) of death was 4.5 for patients in the patients in the highest levels compared with the lowest in the study of Nygard et al,[23] and 1.64 in the highest tertile compared with the others in the larger study (n=1412) by Anderson et al.[14] Homocysteine levels may be reduced by treatment with folic acid, and large-scale clinical trials investigating the effect of folic acid supplementation on cardiovascular outcome are under way.

The presence of left ventricular hypertrophy (LVH) is also a powerful predictor of adverse cardiac events. ECG evidence of LVH was associated with a 2- to 4-fold

increase in cardiovascular mortality compared with subjects without LVH in the Framingham study, similar to the risk associated with ECG evidence of MI.[24] In patients both with and without CAD, LVH is associated with poorer survival.[25] In stable angina patients, one study of over 200 patients showed LVH to be predictive of sudden death in the short term (2 years) in univariate analysis, but not over a longer 8-year period, and when adjusted for other factors in multivariate analysis, LVH no longer remained a significant independent predictor of sudden death.[26]

THE GAMUT OF INVESTIGATIONS FOR THE CAD PATIENT

Cardiac catheterization

Through documentation of LV function, and the extent and location of CAD, cardiac catheterization contributes significantly to prognostic assessment. Knowledge of LV function and the coronary anatomy allows not only discrimination of patient groups at high risk of cardiovascular death and MI, but also identifies those patients who benefit prognostically from revascularization. In the Seattle Heart Study,[6] ejection fraction, age, the extent of CAD, and ventricular arrhythmia were selected as the most useful predictors of mortality in the medically treated cohort. From this database, a model was constructed using three discrete values of ejection fraction, age, number of vessels with >70% stenosis, and presence or absence of ventricular arrhythmia on the resting ECG, to estimate 3-year survival probabilities. Using this model, a 40-year-old subject with single-vessel disease, normal LV function (ejection fraction >65%), and no evidence of ventricular arrhythmia on resting ECG would have a 97% probability of survival at 3 years, while, at the other end of the spectrum, a 60-year-old with three-vessel disease, poor LV function, and ventricular arrhythmia on the resting ECG would have a less than 50% chance of surviving 3 years. Ejection fraction and number of diseased vessels were also highlighted as the most potent predictors of survival in the medically treated cohort of the Coronary Artery Surgery Study (CASS).[5] In this study, 4-year survival of medically treated patients with single-, two-, and three-vessel disease was 92%, 84%, and 68%, respectively. Stratification by ejection fraction yielded an even starker contrast, with 4-year survival of 92%, 83%, and 58%, corresponding to ejection fractions of >50%, 35% to 49%,

and <35%, respectively. LV function impacted on prognosis at all levels of severity of CAD. The 4-year survival for single-vessel disease with an ejection fraction <35% was 74% (vs 95% with normal LV function), 57% for two-vessel disease and poor LV function (vs 93% with normal LV function), and 50% for three-vessel disease with poor LV function (vs 82% with normal LV function).

These results are similar to those in medically treated patients in several large-scale studies of cardiac surgery, such as the Veterans Administration Coronary Artery Study (VACS)[27] and the study of coronary artery bypass surgery in stable angina pectoris by the European Coronary Surgery Study (ECSS) Group.[28] The use of a prognostic index such as that proposed by Mark et al, modified in *Figure 1*, allows knowledge of the coronary anatomy to be readily translated into an estimated probability of 5-year survival.[29]

Provocative testing—ECG

Exercise ECG is a widely accepted, well-validated, and relatively inexpensive method of assessing prognosis in CAD, albeit with certain limitations. The majority of studies published on exercise testing focus on the exercise ECG in the diagnosis of CAD, and on risk stratification post-MI or post–unstable angina, but the prognostic value of exercise ECG in stable CAD has been addressed comprehensively by a number of studies. Two excellent reviews of the subject were published by
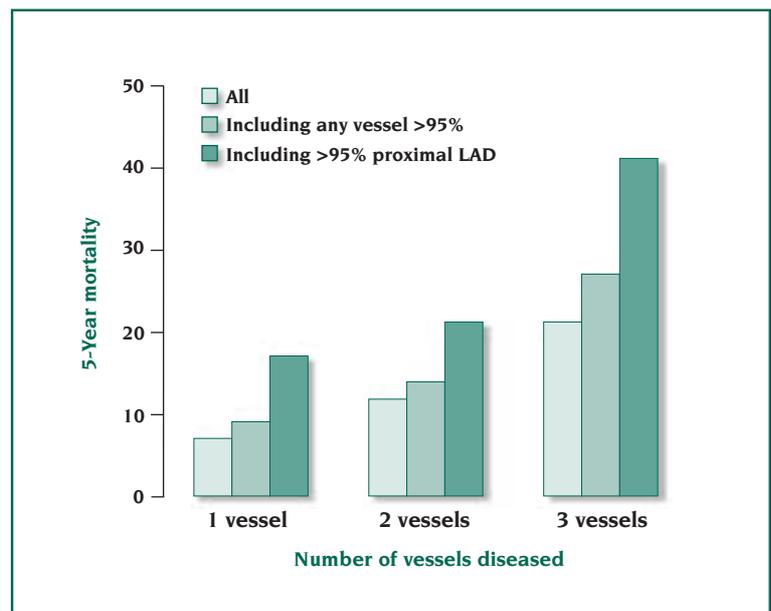

Figure 1. *Prognostic index (modified) proposed by Mark et al,[29] translating coronary anatomy into an estimated 5-year survival probability. LAD, left anterior descending coronary artery.*

Morris et al[30] and Gibson[31] In a more recent synthesis by Ashley et al,[32] the prognostic studies published in the last decade have been included to provide a comprehensive overview of the role of exercise testing in prognostic evaluation of heart disease.

The degree of ST-segment depression, although a useful indicator of the presence of CAD, is not as important in predicting mortality and cardiovascular events in a population with angina as exercise tolerance and chronotropic incompetence. In Ellestad and Wan's retrospective study of 2700 patients,[33] the presence of ≥1.5-mm ST-segment depression was associated with a 15% incidence of MI and 13.2% mortality compared with a 1% incidence of MI and 1.1% mortality in negative responders over a 4-year follow-up period, but the magnitude of ST-segment depression (>2-mm ST-segment depression) did not greatly influence prognosis. The time to achieve ST-segment depression, however, demonstrated a much more marked effect on prognosis, with patients with ST-segment depression within 3 minutes of exercise at highest risk of death or MI. The importance of history was also highlighted in this study as patients with a prior MI greatly increased the risk of future events even in nonresponders, and among those with a positive test, a history of prior MI indicated more than double the risk of future events.

Also in the 1970s, McNeer et al published a retrospective analysis of 1477 patients,[34] of whom 876 had angiographically proven disease. In this study, while a positive test indicated by ST-segment depression was predictive of prognosis, it was not the most discriminative index. More powerful prognostic information was afforded by exercise duration and maximum heart rate achieved. Exercise tolerance yielded greater discrimination between high- and low-risk groups in those with documented CAD than in the group as a whole. In the population with known CAD, survival at 2 years for those who achieved only stage I of the protocol was 59%, compared with 90% for those who achieved stage IV or greater.

Prospective analysis of exercise testing in 1852 patients with clinical evidence of CAD followed up over a 3-year period by Bruce et al[35] also found that short exercise duration was predictive of a higher incidence of sudden cardiac death in multivariate analysis of clinical and exercise data. The importance of exercise duration and maximum heart rate achieved in predicting future events found in these landmark studies was confirmed in the Duke University[36,37] database and CASS[38] populations.

Mark et al[36] devised a treadmill score *(Table III)* that included exercise time, ST-segment deviation, and the presence of angina on exercise in its calculation, which remained a significant independent prognostic factor

TREADMILL SCORE
Exercise time – (5 × ST deviation) – (4 × angina index)
0 = Absent 1 = Present 2 = Limiting

Table III. *Mark et al's exercise treadmill score.*[36]

even when clinical and angiographic factors were included in the model and could be used to categorize patients into low- (score of -11 or lower), moderate- (score of -10 to + 4), and high-risk (score of +5 or greater) groups with 5-year survival rates of 97%, 91%, and 72%, respectively. The usefulness of this scoring system in prediction of mortality and coronary events has been confirmed by subsequent prospective evaluation.[37]

In the CASS[38] population, ST-segment response and exercise stage were predictive of mortality in addition to LV size and heart failure score, and independently of angiographic extent of CAD. In those patients with the greatest burden of disease anatomically, exercise duration was an excellent discriminator between high- and low-risk individuals. Patients with three-vessel disease and normal LV function who achieved stage V or greater of the Bruce protocol, had a 100% survival at 4 years, compared with only 53% for those who had achieved only stage I or II. When follow-up of the CASS population at 16 years was carried out, two exercise variables, ST-segment depression and exercise duration, were selected to risk-classify patients. Based on this risk classification, the 16-year survival rates ranged from 38% to 61% in men and 44% to 79% in women.[39]

The magnitude of ST-segment depression does not closely predict mortality, as demonstrated by Podrid et al, who studied 142 patients with at least 2-mm ST-segment depression during exercise.[40] In this study, an annual mortality of only 1.4 % was observed, but it must be noted that 59% of the subjects had no symptoms associated with the ECG changes. Other studies have also concluded that painless ST-segment depression has a more favorable prognosis than ST-segment depression associated with pain.[41] Among patients with 2 or more mm ST-segment depression, it is again exercise capacity, determined either by duration or metabolic equivalents of the task (METs), that is the strongest predictor of prognosis. In patients with 2-mm

or more ST-segment depression, achieving a workload of >10 METs was associated with a 93% 8-year survival, but, in the subjects achieving <5 METs, the 8-year survival was only 45%.[40] In terms of exercise duration, such patients can be stratified into high-, (exercise <3 minutes) intermediate- (exercise 3 to 9 minutes), and low-risk (exercise >9 minutes) groups.[42]

In the APSIS study, ST-segment depression both during and after exercise, and low exercise capacity were independently predictive of adverse outcome after adjustment for risk factors and prior MI, a reminder to examine post–exercise ECG changes also, as they may add to risk stratification.[43]

Thus, in stable angina, exercise duration and maximum heart rate are the strongest predictors of prognosis, followed by ST-segment depression. Exercise testing may be combined in a very useful fashion with clinical and, if available, angiographic data, to stratify patients into prognostic groups.

Ambulatory ECG monitoring of ischemia

Ambulatory ECG monitoring to detect the total ischemic burden, including silent ischemia, has also been evaluated as a potential prognostic indicator in stable CAD, with conflicting reports of its usefulness in discriminating between high- and low-risk groups. Ambulatory ischemia has been identified as a risk factor for the development of cardiovascular events and an independent predictor of mortality in some,[44] but not all, studies. Mulcahy et al[45] demonstrated, in a 5-year follow-up study, that transient ischemia detected by ambulatory monitoring was not of clinically useful value in predicting adverse outcome in a stable angina population. This is supported by the findings of the Total Ischemic Burden European Trial (TIBET),[3] in 682 patients, in which ischemia during 24-hour ambulatory monitoring did not predict mortality, MI, unstable angina, or softer end points, such as treatment failure or the need for revascularization. APSIS,[43] a similar study with over 800 patients, reported a greater duration of ST-segment depression on ambulatory monitoring to be independently predictive of mortality, but when exercise testing was added to the model, ambulatory ischemia only carried prognostic power in patients with >2-mm ST-segment depression on exercise.

Stress echocardiography

As previously discussed, two important factors in predicting outcome in patients with CAD are LV function and inducible ischemia, both of which may be evaluated by stress echocardiography, making this technique an attractive candidate for prognostic stratification. Stressors include treadmill and bicycle exercise, dobutamine, and drugs such as adenosine or dipyridamole, which are particularly useful when the hemodynamic response to dobutamine is not desirable, for example, in poorly controlled hypertension or large aortic aneurysm.

Semiquantitative assessment of wall-motion abnormalities is obtained by using a scoring system to describe wall motion in each of 16 ventricular segments. The presence of new wall-motion abnormalities, the number of new defects or extent of ischemia, and the extent of regional wall-motion abnormality at rest, particularly in infarcted territory, have been shown to influence prognosis.[46] The location and extent of inducible ischemia may also be helpful in planning percutaneous coronary intervention. A new wall-motion abnormality remains predictive of future cardiac death for up to 5 years after multivariate adjustment for LV ejection fraction and other clinical factors.

Exercise echocardiography has a high negative predictive value (91% to 98%), but a relatively low positive predictive value for future cardiovascular events, including mortality in a stable angina population.[47] Dobutamine echocardiography also has been investigated in the setting of stable CAD, and these studies indicate that dobutamine echocardiography may be used successfully to stratify patients into low-, intermediate-, and high-risk groups. For patients who are unable to exercise for orthopedic or other reasons, pharmacological stress (dobutamine stress echocardiography [DSE]) is a useful method of provoking ischemia. Similarly to exercise echocardiography, the positive predictive value is low (10% to 43%), but the negative predictive value is high (81% to 99%).[47] DSE contributes additional prognostic information independent of clinical, exercise, and catheterization data, and, in some studies, is superior to exercise ECG and coronary angiography in attributing risk. It must be noted that an inadequate chronotropic response to dobutamine during infusion is associated with an unfavorable outcome, compromising the prognostic power of a negative DSE result in this circumstance. Populations who have negative submaximal tests (ie, <85% maximum predicted heart rate) have a higher incidence of cardiovascular events than those who achieve >85% maximal heart rate, and so negative DSE at submaximal heart rate is nondiagnostic.[48]

Nuclear scintigraphy

Myocardial perfusion imaging is also widely accepted as a means to assess prognosis in stable CAD. Planar or tomographic imaging techniques may be performed in association with exercise or pharmacological stress, dipyridamole, adenosine, or dobutamine. Single photon emission computed tomography (SPECT) has the advantage of acquiring images 180° around the patient and reconstruction of the heart in three dimensions, thus allowing separation of individual coronary territories. In the absence of a critical coronary stenosis, >90% of luminal diameter or MI resting regional myocardial blood flow is usually homogenous. With exercise or pharmacological stress, the corresponding increase in coronary blood flow may be limited by noncritical coronary stenoses (>50%) causing nonhomogenous uptake of radiolabelled tracer, which may then be imaged. Conventionally, thallium- or technetium-labeled sestamibi is used as perfusion radioisotopes. Reproducibility and interpretation of results is enhanced by graphic display of the relative distribution of the radiopharmaceuticals, which allows quantitative analysis of the size and reversibility of the defect.

The prognostic value of myocardial perfusion scanning in patients with suspected CAD and angiographically proven CAD has been comprehensively reviewed, and numerous studies have established the value of planar thallium myocardial perfusion scanning in predicting prognosis in CAD.[49,50] High-risk findings include multiple reversible defects, large reversible defects, increased uptake in the lungs, or transient LV dilatation post-exercise. However, some studies have identified the presence of a fixed perfusion defect as the single scintigraphic variable most predictive of cardiovascular events.

Thallium SPECT scanning provides additive prognostic information to clinical and exercise variables in the evaluation of stable angina.[51] Dipyridamole and exercise sestamibi tomography have also been demonstrated to be independently predictive of outcome in stable CAD.[52,53] The absolute risk of events varies considerably between studies, according to stressor, the population examined, eg, chest pain patients with no prior history of MI or patients with proven CAD, and the events chosen as outcome measures, as some studies include revascularization as an outcome measure.

In an analysis of 3594 patients in 16 studies of patients with known CAD,[49] a negative thallium scan predicted an annual combined MI or death rate of <1%, and, in a large prospective study of over 5000 patients, negative SPECT was associated with <0.5% annual rate of death or MI, with increasing rates of coronary events in other groups according to the extent of the size of the defect.[51] The excellent negative predictive value of myocardial perfusion scanning makes this technique an ideal candidate to hold a gatekeeper function to further, more invasive, testing or revascularization.

Myocardial perfusion scanning compares favorably with exercise ECG in discriminating high-risk from low-risk individuals, particularly in patients known to have CAD. In the Economics of Noninvasive Diagnosis (END) study of over 8000 patients with confirmed CAD,[18] clinical, exercise, and perfusion data were predictive of death and MI in an incremental fashion, and from these data a scoring system was developed using all of the modalities for predicting the risk of MI and death over 1 and 2 years. Perfusion data added independent prognostic information even when the coronary anatomy and exercise data were included. The results of perfusion scanning add to the prognostic capabilities of clinical and exercise ECG data in an incremental fashion and are particularly useful in those patients with known CAD who have a negative or nondiagnostic exercise ECG, or in patients who have previously had coronary artery bypass grafting (CABG).[54]

The performance of myocardial perfusion or stress echocardiography as alternative methods of functional imaging of the myocardium may depend to some extent on local expertise and availability of services. In terms of prognostic accuracy, although stress echocardiography adds incrementally to clinical and exercise data in risk allocation, myocardial perfusion scanning has superior sensitivity in detecting ischemia in known CAD. When compared, the event rate in those with negative stress echocardiography is higher than those with negative myocardial perfusion scanning, which may limit its usefulness to act as a gatekeeper for additional invasive and interventional procedures.[55]

Detection of coronary calcification

The detection of coronary calcification, particularly a high calcium score, is useful in the diagnosis of CAD in symptomatic and asymptomatic populations; however, its role in the determining prognosis, particularly in stable CAD, is less well established. Electron beam (EBCT) or ultrafast CT has superseded cardiac fluoroscopy as an efficient, sensitive, and specific means to quantify the degree of coronary artery calcification. ECG-triggered high-resolution scanning is performed at

a very rapid rate and a complete scan of the heart may be completed in one or two breath holds. A calcium score is determined by multiplying the area of calcification by a factor based on maximal calcium density. A positive correlation exists between the calculated calcium score and the severity of CAD, and the absence of coronary calcification has a negative predictive value of 85% to 95% for the exclusion of coronary stenotic lesions >50%. The sensitivity of EBCT in detecting any CAD is high >90%, but the specificity is low to moderate, ranging from 35% to 38% for any narrowing to 66% for significant disease. Noninvasive identification of angiographic disease or left main CAD is feasible using an algorithm that includes clinical risk factors (sex and diabetes) and coronary calcium scores for individual arteries. However, the additional prognostic value of EBCT in patients with angiographically proven disease is questionable. In one study of 501 symptomatic patients who underwent coronary angiography and EBCT, a calcium score threshold of 100 was highly predictive in separating patients with cardiac events from those without, and in multivariate analysis with age, gender, and coronary angiographic findings, only log calcium score predicted events.[55] However, reports of the prognostic importance of coronary calcification have not been consistently so encouraging. There is insufficient evidence as yet to suggest that EBCT adds independent prognostic information to that afforded by standard investigative techniques, and EBCT has not been recommended as a routine method of risk stratification in patients with confirmed CAD in the recent American Heart Association (AHA) guidelines on the subject.[56] EBCT has been suggested as a method of noninvasively monitoring disease progression/regression, but the test variability over time may hinder the use of EBCT in this context.

Other imaging techniques

Alternative means of imaging the coronary anatomy, characterizing the vessels and assessing the effect of CAD on the myocardium, both structurally and functionally, such as intravascular ultrasound (IVUS), CT angiography, and magnetic resonance imaging, contribute to our understanding of the pathophysiological processes at work, and some may be employed to assess prognosis in the future.

IVUS involves the intraluminal introduction of a transducer with rotating reflectors on the tip of a coronary catheter,[57] which allows imaging of the coronary artery in cross-section during cardiac catheterization. The soft lipid core and the presence and the extent of calcification may be identified, in addition to improved perception of luminal narrowing. However, IVUS is an invasive and expensive technique, and its use is currently limited to relatively large-caliber proximal vessels. Although this technique allows characterization of coronary plaque, including some potential "vulnerability" features, and has been used to assess angioplasty success and stent deployment, these considerations have prevented the investigation of its potential as a routine prognostic test.

CT angiography using intravenous contrast has seen development as a noninvasive imaging technique as recent advances in software and hardware available to acquire and process images have made it possible to achieve improved resolution with shorter scan times. Problems still exist, however, with movement artifact and poor visualization of distal vasculature. Reported sensitivity and specificity of 78% and 91%, respectively, in diagnosis of CAD are not sufficiently impressive to see CT angiography replace conventional x-ray angiography in the near future.[58]

Magnetic resonance angiography (MRA) has the advantage not only of being noninvasive, but also of not exposing the patient to radiation. However, there are some fundamental problems with this technique, which although they have been addressed, have not been corrected completely, for example, cardiac and respiratory motion, signal-to-noise ratio, and contrast-to-noise ratio. Although portions of the coronary system may be visualized with excellent resolution, evaluation of the coronary tree remains mostly limited to the proximal and mid-coronary segments. MRA-specific contrast agents have shown promise in enhancing definition between coronary blood and myocardium. In a recent study of 50 patients using this method of contrast-enhancement MRA, the sensitivity and specificity of MRA in correctly identifying patients with and without significant coronary stenosis as determined by x-ray angiography was 94.4% and 57.1%, respectively.[59] MRA has been used to noninvasively identify stenosis in coronary artery bypass grafts and within stents with some success.[60]

While the prospect of routine MRA as an alternative to conventional x-ray angiography remains indistinct, there are exciting developments in the field of plaque characterization. MRA may be used to determine plaque composition, as it is able to identify all components of complex atherosclerotic plaque, including lipid-rich, fibrous, calcified, and hemorrhagic components.[61] It is increasingly recognized that the majority of coronary

events occur in vulnerable plaques with a large necrotic lipid core and a thin fibrous cap, which when disrupted exposes the thrombogenic lipid core, promoting thrombus formation. As the technology is refined, it is conceivable that with the feasibility of MRA, identification of vulnerable and ruptured plaque in an accurate and reproducible manner could add significantly to prognostic information from conventional angiography, which only provides a 2-dimensional image of luminal stenosis and minimal information on the composition and character of lesions.

Cardiac magnetic resonance imaging (MRI) can provide detailed and accurate information about the structure and shows considerable promise as a useful tool in functional assessment of the heart.[62] Gadolinium- and necrosis-avid magnetic resonance contrast agents allow detection of reversible perfusion defects and accurate definition of irreversibly damaged myocardium post-MI.[63] Such techniques may be used to discriminate between viable and nonviable myocardium, which has important consequences when considering revascularization.[64]

Vulnerable plaque may also be identified by detection of thermal heterogeneity with intracoronary probes.[65] Novel imaging methods such as these, based on our increasing understanding of the complex processes in operation in the coronary arteries that determine susceptibility to plaque rupture and acute events, remain as yet too inaccurate and cumbersome for widespread clinical application, but may spawn a new generation of technology, which will advance current risk prediction capabilities.

Inflammatory and hemostatic markers

Our knowledge of the pathogenesis of atherosclerosis and of the incidence of acute coronary syndrome has advanced considerably in recent decades. Injury to the vessel wall in CAD is both chronic, as repeated insults lead to the development of atherosclerotic plaque, and acute, when physical forces such as shear stress or iatrogenic injury damage the delicate endothelium. Molecular events, such as metalloproteinase degradation of the protective fibrous cap, may lead to rupture of vulnerable plaques characterized by increased inflammatory cell activity and a large lipid core. Exposure of this lipid core promotes thrombus formation, which is in part determined by the thrombogenic potential in the blood. Surrogate measures of the degree or extent of arterial "injury," plaque vulnerability, and mea-

sures of thrombogenicity might therefore have the potential to predict the occurrence of acute events and mortality.[66,67]

Acute and chronic inflammation are increasingly recognized as key processes in atherosclerotic disease and in particular in acute coronary events.[67] Vulnerable plaques are characterized by an inflammatory infiltrate, and unstable coronary syndromes are associated with lymphocyte disturbances and increased systemic markers of inflammation. It is pathophysiologically attractive as a concept that a measure of arterial inflammation could predict the likelihood of coronary events, but a specific measure of inflammatory activity in the coronary arteries is not available. Systemic markers of inflammation are nonspecific, but despite this, the potential of ultrasensitive C-reactive protein (CRP), serum amyloid A, phospholipase A_2, interleukins 1 and 6, cellular adhesion, and other molecules has been investigated as prognostic indicators in stable CAD. Of the inflammatory markers, ultrasensitive CRP has been most extensively investigated, but serum amyloid A, phospholipase A_2 cellular adhesion molecules, and macrophage colony-stimulating factor (MCSF), which are other rather nonspecific markers of systemic inflammation, have also been associated with adverse outcome, death, nonfatal MI, and unstable angina in patients with CAD.[68-71] In one study of 142 patients with angiographically proven disease, levels of phospholipase A_2,[71] were the strongest predictor of coronary events, even when CRP, angiographic findings, and ejection fraction were included in multivariate analysis. However, this was a small study and included revascularization in the combined end point. Studies that have demonstrated the prognostic value of CRP in stable CAD are listed in *Table IV*.[14,68,72]

CRP levels have been found to be associated with smoking, obesity, diabetes, hypertension, extent of CAD, and LV dysfunction, but remain predictive of mortality and cardiovascular events in multivariate analysis even when these factors are included. Elevated CRP interacts in an interesting fashion with serum cholesterol, increasing the already elevated risk of events associated with high cholesterol, and the coexistence of high CRP, high fibrinogen, and high cholesterol confers even higher secondary risk in a population with CAD.[66] Furthermore, CRP levels are reduced by aspirin and statins.[71,73] In the Cholesterol And Recurrent Events (CARE) study, the risk reduction attributable to pravastatin was substantially greater (54%) in patients with high baseline CRP than among those without evidence of inflammation (25%),[74] introducing the concepts of

Study	Population	Follow-up (years)	Level of CRP	Risk of cardiac death or MI (adjusted for other risks)
CARE[72]	Nested case-control study Post-MI n=782	5 y	Highest quintile vs first four quintiles	RR (death/MI) = 1.77
ECAT[68]	Prospective study of angina patients n=2121 in total	2 y	Highest quintile	RR (death/MI) = 2.25
	Stable angina subgroup n=743	2 y	Per 1 SD increase in CRP	RR (death/MI) = 1.5 (vs 1.45 per 1 SD↑ in all patients)
Anderson et al[14]	Prospective study of patients with angiographic CAD n=1412	2 y	Per tertile increase in CRP	RR of death = 1.42

Table IV. *Risk of cardiac death or nonfatal myocardial infarction associated with CRP levels in patients with stable CAD or angina.*

Abbreviations: CAD, coronary artery disease; CARE, Cholesterol And Recurrent Events; CRP, C-reactive protein; ECAT, European Concerted Action on Thrombosis; MI, myocardial infarction; RR, relative risk; SD, standard deviation.

inflammation as a potentially modifiable risk factor and also statins as pleiotropic drugs with anti-inflammatory in addition to other effects.

Support for the hypothesis that measures of impaired fibrinolysis and other hypercoagulable states can be used to predict risk of future acute coronary events is strong in population-based epidemiological studies. There is also evidence that tissue plasminogen activator (tPA) antigen, plasminogen activator inhibitor (PAI) antigen, and fibrinogen may be useful in predicting death and MI in a population with established CAD. In the European Concerted Action on Thrombosis (ECAT) study of patients with angina, each standard deviation increase in tissue tPA antigen, PAI antigen, and PAI activity was associated with an RR of death or MI of 1.5, 1.41, and 1.29, respectively.[73,75] Of the three, tPA was the most robust marker of subsequent events and remained significant when adjusted for factors related to inflammation, endothelial cell damage, and insulin resistance, but not when adjusted for all of these factors together.[75] tPA was the only variable independently predictive of mortality in Jansson et al's study of the fibrinolytic system in angina with an RR of death of 3.85 in the highest quartile compared with the lowest.[76]

Fibrinogen was also identified as a potent predictor of outcome in the ECAT study, with an RR of coronary events of 1.31 per standard deviation increase in fibrinogen when adjusted for confounding factors,[73] and has been found to increase the risk of events substantially in hypertensive subjects. A meta-analysis of stud-ies of fibrinogen in cardiovascular disease identified a strong graded relationship between fibrinogen and cardiovascular risk, with a greater than 2-fold increase in risk of coronary events in patients in the highest tertile of fibrinogen distribution compared with the lowest.[77] The risk associated with elevated fibrinogen is substantially increased by coexistence of hypercholesterolemia and hypertension. Treatment of hyperlipidemia with fluvastatin in the Fluvastatin Alone and in Combination Treatment (FACT) study was accompanied by a reduction in fibrinogen levels, in addition to reduced cardiovascular risk,[78] and fibrates also reduce fibrinogen.

Markers of inflammation and hemostatic factors have clearly been shown to assist prediction of acute cardiac events and mortality, but how this information combines with established risk assessment modalities, such as coronary angiography or myocardial perfusion imaging, which for the most part quantify the extent of CAD and jeopardized myocardium, awaits definition. Furthermore, although aspirin, statins, and fibrates have shown some promise in this field as alluded to previously, how the individuals identified as at increased risk by these means will benefit from treatment targeting the parameter of interest requires further investigation.

TREATMENT OPTIONS

The treatment of angina must be guided by two objectives, improving prognosis and abolishing or at least controlling symptoms. The physician, armed with a

thorough understanding of the factors that influence prognosis in stable angina, must plan a strategy of management for the individual patient that will achieve both. Conventionally, treatment of angina is categorized into medical, surgical, or percutaneous interventional modalities. However, medical therapy is more than merely a means to achieve symptomatic relief, but also provides an adjunct to surgical or percutaneous intervention aimed at reducing the progression of disease and the rate of acute events. Lipid-lowering measures, antihypertensive drugs, and glycemic control in diabetics may be expected to slow the rate of disease progression and, particularly in the case of lipid lowering, have been shown to reduce the rate of acute events and mortality. The prognostic benefit of antithrombotic therapy in CAD has been established, and there is ongoing research into the potential of angiotensin-converting enzyme (ACE) inhibitors to reduce mortality in the CAD population in addition to their proven benefit in those at high risk of atherosclerotic complications. An awareness of the impact of specific antianginal drug therapy, surgery, and angioplasty on prognosis in the population with angina as a whole and on specific groups is essential in formulating an individual patient management plan tailored to improve event-free and overall survival.

Risk-factor modification

In addressing medical treatment and risk factor modification, although pharmacological intervention is not a universal requisite, mention of smoking cessation cannot be omitted. A linear relation exists between cardiovascular risk and cigarettes consumed, with RRs approaching 5.5 for fatal cardiovascular events among heavy smokers compared with nonsmokers. An average smoker dies 3 years earlier than a nonsmoker, and a person known to be at high risk for CAD dies 10 to 15 years sooner if he or she smokes. Smokers who continue to smoke after MI have an increased risk of death ranging from 22% to 47%, and continuation of smoking after CABG is associated with a doubling of the RR of death. Smoking cessation reduces the risk of cardiovascular events, and should be strongly advocated in any patient with CAD.[79]

The benefits of cholesterol lowering, particularly low-density lipoprotein (LDL) cholesterol reduction, are well established. Prior to β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors—or statins—reduction of cholesterol by dietary, pharmacological, or more extreme interventions such as partial ileal bypass, had been shown to reduce the incidence

of cardiovascular events and, in some studies, was associated with angiographic disease regression, albeit minor. With the advent of the statins, the magnitude of cholesterol reduction achievable has increased and the benefit in terms of reduction in cardiovascular events and mortality has become more dramatic. In a meta-analysis of the randomized controlled trials of statins, active treatment conferred a ≈30% reduction in risk of CAD mortality in the secondary prevention trials (including the Scandinavian Simvastatin Survival Study [4S], the Cholesterol And Recurrent Events [CARE] study, and the Long-term Intervention with Pravastatin in Ischemic Disease [LIPID] trial). The benefits of statin therapy are evident not just in patients with elevated cholesterol levels, but across a broad range of cholesterol values.[80] This and the time course of the clinical benefit obtained with statin treatment, before plaque regression could occur, have lead to considerable interest in alternative beneficial actions of the statins, including anti-inflammatory, plaque-stabilizing, and antithrombotic effects, in addition to improvement in endothelial function and reduction of ischemia on perfusion scanning.

Treatment of hypertension has been shown to substantially reduce cardiovascular morbidity and mortality, but the majority of this benefit is from reductions in the incidence of stroke and development of heart failure, which, it must be recognized, are more impressive than the nevertheless statistically significant reduction in coronary mortality.[81] There are surprisingly few data on the effect of blood pressure reduction specifically in the stable angina population, but, on the basis of known benefits in reducing overall cardiovascular mortality, close attention to blood pressure control in this "at-risk" population is advised. Similarly, in the diabetic population, intensive glycemic control has been shown to reduce microvascular complications in diabetics. However, the benefits of glycemic control in reducing coronary mortality, in comparison, are somewhat disappointing.[82] With alternative antidiabetic drugs, such as the glitazones, which have a favorable effect on cardiovascular risk parameters, it may be possible to improve prognosis to a greater extent in the future. Furthermore, the target of treatment may have to change from glycemic control to a measure of vascular damage or endothelial dysfunction, and treatment redirected appropriately.

Antiplatelet and antianginal medication

The prognostic benefit of aspirin in angina is undisputed. In the Swedish Angina Pectoris Aspirin Trial

(SAPAT),[83] there was a 34% reduction in the primary end point of MI and sudden death in patients on sotalol who also received aspirin, and an average 33% reduction in risk of adverse cardiovascular events in over 3000 patients with stable angina treated with aspirin in a meta-analysis of other studies.[84]

The cornerstone drugs used in control of anginal symptoms are the β-blockers, calcium antagonists, and nitrates, although potassium channel openers such as nicorandil and metabolic agents such as trimetazidine are also employed. Despite the routine use of these medications in CAD, there have been surprisingly few large studies published that address their effect on mortality in stable angina patients, and even less conclusive proof of improved survival with individual drugs or drug classes. In the TIBET[3] trial of atenolol and nifedipine, there was a nonsignificant trend toward a lower rate of death, MI, and unstable angina in the group on combination therapy, while, in APSIS,[85] there was no difference between metoprolol and verapamil treatment with respect to the combined cardiovascular end point (death or MI) or quality of life. The Atenolol Silent Ischemia Trial (ASIST)[86] randomized patients with mild angina to atenolol or placebo, and demonstrated a reduction in the combined end point of death, MI ventricular arrhythmia, hospitalization, aggravation of symptoms, or revascularization in the atenolol treated group. The Impact Of Nicorandil in Angina (IONA)[87] trial is the first large trial to convincingly demonstrate an improved outcome with medication—in this case the addition of nicorandil to existing antianginal therapy. Although nitrates are routinely used in the management of anginal symptoms, an improvement in prognosis has not been established. Antianginal medication is effective in reducing symptoms (symptoms are controlled in 40% to 50% of patients on treatment), and, in the post-infarction population, β-blockade confers definite prognostic benefit. Further prognostic benefit of treatment in the stable angina population is difficult to prove because of the ethical considerations of a placebo-controlled study and the numbers required to show statistical benefit in a population with an overall annual mortality of less than 2%.

ACE inhibitors

The role of the ACE inhibitors in hypertension, heart failure, and post-MI has been established, with evidence of successful blood-pressure lowering in the first and mortality benefit in the latter two conditions. Of particular note, ACE inhibitor therapy reduced the rate of recurrent MI and unstable angina in the post-MI

population. From the results of the Heart Outcomes Prevention Evaluation (HOPE) trial, it has become apparent that ACE inhibition reduces cardiovascular mortality in a population at high risk for major cardiovascular events.[88] These data, combined with experimental data indicating that ACE inhibition may have beneficial effects on the myocardium and coronary circulation in addition to antiatherosclerotic and plaque-stabilizing effects, suggest a further role for ACE inhibitors in CAD with normal LV function. The EURopean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)[89] and the Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE)[90] trial are two large-scale randomized controlled trials of 11 000 and 14 000 patients, respectively, designed to explore the potential benefit of ACE inhibitors in patients with CAD and normal LV function. The results, if they demonstrate as expected a survival advantage in the ACE-inhibited patients, will set the stage for a new era in prognosis directed anti-ischemic therapy.

Surgery

The role of CABG surgery in management of patients with CAD has been largely defined by moderately scaled (by today's standards) randomized trials of surgery versus medical therapy conducted in the 1970s. These studies, VACS,[27] ECSS,[28] and CASS[91] established surgery as an effective means of controlling symptoms and also provided evidence of improved prognosis with revascularization in selected groups of patients, particularly those with left main stem stenosis and three-vessel disease with reduced LV function. In a meta-analysis of the long-term follow-up of seven randomized trials of the effect of CABG on survival, initial surgery was associated with lower mortality than initial medical therapy in medium- and high-risk patients.[92] Maximum benefit was associated with surgery in patients with three-vessel or left main stem disease, poor LV function, or an abnormal exercise test. In patients in the middle or highest tertile of risk determined by a stepwise risk score, CABG was associated with a close to 45% reduction in mortality at 5 years, compared with initial medical management. There was a nonsignificant trend toward increased mortality with initial CABG in the low-risk group of patients (lowest tertile of risk) *(Table V, next page)*.

Over a 10-year period, extension of survival was greatest for patients with left main CAD, ie, a mean increase of 19 months, and intermediate for patients with three-vessel disease or with abnormal exercise tests, with

STEPWISE RISK SCORE

(0.015 × age) + (0.56 × class III/IV angina) +
(0.35 × history of MI) + (0.62 × abnormal EF) +
(0.53 × proximal LAD lesion) + (0.29 × RCA lesion) +
(0.43 × presence of diabetes) + (0.37 × history of
hypertension)

Table V. *Stepwise risk score used in Yusuf et al's[92] 1994 meta-analysis of the effect of coronary artery bypass grafting (CABG) on survival.*

Abbreviations: EF, ejection fraction; LAD, left anterior descending coronary artery; MI, myocardial infarction; RCA, right coronary artery.

mean increases in survival of 5.7 and 5.1 months, respectively. These trials were carried out before the importance of aspirin in preventing graft attrition or prevention of coronary events was recognized (only 3.2% of the population studied were on aspirin) and before the routine use of internal mammary or other arterial grafts. It is conceivable that the now widespread use of prognostically beneficial treatment modalities such as aspirin and cholesterol-lowering agents and the use of arterial grafts may alter the implications of these trials for the stable angina population of today.

Angioplasty

Since the pioneering work of Gruntzig in the late 1970s, catheter-based intervention has expanded dramatically. Percutaneous transluminal coronary angioplasty (PTCA) has been adopted as routine alternative to antianginal medication or surgery, and the data concerning the outcome associated with percutaneous intervention deserve careful scrutiny. There have been relatively few large-scale randomized trials comparing the outcomes of PTCA and medical therapy in the stable angina population. Of 429 trials of PTCA identified by Bucher et al,[93] 423 were excluded from their meta-analysis because of lack of a control group, evaluation of cotreatments and different techniques, comparison with surgery rather than medical therapy, performance of PTCA in acute coronary syndromes, and failure to randomize treatment, leaving only 6 trials remaining that were suitable for inclusion in the meta-analysis.

Of these studies, three included patients with single-vessel disease only, the Angioplasty Compared to MEdicine (ACME) study,[94] the Medicine, Angioplasty, or Surgery Study (MASS),[95] and the study of Sievers et al.[96] Initial success rates varied from 82% to 100%, but the outcome of the trials was in other respects consistent. In the ACME trial, patients who underwent PTCA were more likely to be free of angina at 6 months' fol-

low-up than those on medical therapy (64% vs 46%), and had a greater improvement in exercise duration, but showed no benefit in terms of mortality or rates of MI. In MASS, medical therapy, PTCA, and internal mammary grafting were compared. While both forms of revascularization produced significantly better relief of symptoms and reduction in inducible ischemia on exercise testing, there was no difference in mortality or rates of MI between the three groups. Similarly, Sievers et al showed no difference in mortality or MI in a group of 88 asymptomatic patients after 2-years' follow-up, and there was no difference in exercise tolerance or development of symptoms in favor of PTCA. Data from the Duke database suggests that patients with single-vessel disease involving the proximal left anterior descending (LAD) have a better 5-year survival with PTCA than with medical therapy, but a randomized controlled trial is necessary to confirm this suggestion before clinical practice may be so guided.[29] For the present, evidence exists to support the use of PTCA for symptomatic relief in patients with single-vessel disease, but there is no definite evidence of prognostic benefit.

The Second Randomised Intervention Treatment of Angina (RITA-2) study,[97] Folland et al, on behalf of the ACME investigators,[98] and the Atorvastatin vs Revascularization Treatment (AVERT) trial[99] have investigated the outcome of PTCA versus medical therapy in patients with multivessel disease, including patients with prior MI. As might be expected, initial success rates were lower (69% to 99%) than in the trials of single-vessel disease. In the RITA-2 trial of over 1000 patients, the primary combined end point of death or MI occurred in 6.3% of the PTCA group and 3.3% of the medically treated group during the median 2.7 years' follow-up period (P=0.02). PTCA-treated patients had greater freedom from angina at 6 months and superior exercise tolerance. In the AVERT study, angioplasty was compared with medical therapy including aggressive lipid-lowering with 80 mg of atorvastatin, and similar benefit in reducing symptoms was demonstrated in favor of angioplasty (54% in the PTCA group compared with 41% in the medically treated group). The combined end point in this study included death, nonfatal MI, resuscitation after cardiac arrest, cerebrovascular accident, repeat revascularization, and hospitalization with unstable or progressive angina, and occurred less frequently in the medically treated compared with the angioplasty group (P=0.045). It must be noted that the difference in combined end points was contributed to largely by repeat revascularization; nevertheless, overall, a strategy of PTCA did not confer a survival advantage.

In fact, in the meta-analysis of Bucher et al,[93] although pooled results demonstrated a statistically significant improvement in angina control in the PTCA group compared with the medically treated group, there was a trend towards increased death, MI, and repeat PTCA in the PTCA-treated group compared with the medically treated group, and a statistically significant increase in the rate of CABG. While advances in antithrombotic medication and the widespread use of intracoronary stenting, which have improved both the initial success rate and the restenosis rate of percutaneous procedures, have come about since the performance of the majority of these trials, randomized controlled trials are necessary to determine if these advances will translate into additional survival or survival free of MI. The Stent or Surgery (SoS) study reported at the scientific sessions of the American College of Cardiology in 2001 does not include death or MI or angina as a primary end point, but reports significantly less revascularization procedures in the stented group.

At least 8 randomized trials have compared the outcome of angioplasty with surgery. These trials were conducted in highly selected patient populations. Of over 91 000 patients screened, only 5.2% were randomized, which raises the issue of the broad clinical applicability of the results. The results of trials of PTCA versus CABG in multivessel disease, excluding the Bypass Angioplasty Revascularization Investigation (BARI) trial, have been submitted to meta-analysis.[100,101] No difference exists in the combined end point of death or nonfatal MI between the groups, but patients undergoing PTCA were significantly and substantially more likely to undergo repeat revascularization within the first year (33.7% vs 3.3%), and were less likely to be free of angina at 1 year than the surgically revascularized group. BARI was a large study of angioplasty versus surgery in patients with multivessel disease,[16] of whom, it must be noted, 64% had unstable symptoms. The results were consistent with the findings of previous studies, suggesting that PTCA is a safe alternative to CABG in patients with angina, but is associated with increased rates of subsequent revascularization procedures. The identification of a survival advantage with

surgical revascularization in the diabetic patients in BARI was an important finding, supported by other studies,[17] and should influence the management of diabetic patients with multivessel disease considered for revascularization.

CONCLUSIONS

The management of stable angina must encompass symptom control and treatment of the progressive atherosclerotic disease process underlying the symptoms. This requires an in-depth understanding of the pathogenesis of CAD in general and acute coronary syndromes in particular, a comprehensive knowledge of the clinical and serological features and investigative procedures that identify patients at high risk of subsequent events, and an evidence-based approach to treatment focused on the individual's risk.

With regard to symptoms, antianginal medication achieves symptom control in almost half of patients, and CABG or PTCA provide an effective solution for those whose symptoms cannot be controlled medically or who are intolerant of medication. In a significant number of patients, particularly those with left main stem stenosis, three-vessel disease, poor LV function, or evidence of a large area of inducible ischemia, surgical revascularization is of definite prognostic benefit. Angioplasty has not been shown definitively to improve prognosis, but provides a useful and safe alternative to surgery in low-risk patients, with the caveats that subsequent revascularization procedures are more frequent and that diabetics with multivessel disease fare better with surgery. Aspirin and lipid-lowering medication are of proven benefit in improving survival in patients with CAD, irrespective of their revascularization status, and should be prescribed almost universally in the absence of contraindications, although the cutoff point below which cholesterol should not be treated in this population remains controversial. The emergence of ACE inhibitors and other drugs aimed at reducing ischemia and halting or reversing the advance of atherosclerosis offer hope for the future, but much remains to be done to improve the management of stable angina.

THREE KEY QUESTIONS

Some readers, glancing at the cover of this issue of *Dialogues* devoted to angina, may be tempted to shrug off the topic as "déjà vu." And yet, isn't angina the very bread and butter of cardiology, and isn't it embarrassing for us specialists to have to come down from the lofty heights of sophisticated research and the latest procedures and pharmaceuticals to face the ordinary, run-of-the-mill patient complaining of pain in the chest recurring despite treatment? To bring this point further home, the experts called in by the author of the Lead Article were asked to focus their attention on three fundamental aspects of angina that continue to pose vexing problems to the cardiologist. Filippo Crea, reflecting on the still unelucidated relationships between anginal pain and myocardial ischemia, asks: **"How can we optimize the clinical information contained in the symptom angina pectoris?"** Mario Marzilli, acknowledging the fact that angina treatment has hitherto failed to provide consistent control of anginal symptoms and effective protection from major coronary events, asks: **"What more can be provided for the medical management of angina?"** This topic is taken one step further by Michael R. Chester, who looks at the plight of the angina patient refractory to medication and conventional revascularization. Reminiscing about the days when the "it's ischemia, stupid" doctrine reigned supreme, he asks: **"How should we manage patients with angina after revascularization?"** and champions what he describes as a novel holistic patient-centered treatment paradigm. This three-pronged investigation of the challenges that continue to confront the cardiologist shows that some of the answers—in terms of both basic science and treatment options—are either already there or well on their way, while promising new avenues are being investigated. Yet, all these approaches, which herald a better future for the anginal patient, still have to pass the muster of evidence-based assessment before decisions are reached that are bound to have a long-lasting impact on health care costs.

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How can we optimize the clinical information contained in the symptom angina pectoris?

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The angina/myocardial ischemia relationship is a complex one. Angina can occur with normal coronary arteries while being absent in one third of acute myocardial infarctions, thus pointing to the primacy of central modulation in the perception of cardiac ischemic pain. Furthermore, the features of angina do not identify the causes of ischemia, and the site of angina is a generally unreliable guide to the site of ischemia. However, certain patterns of angina have reliable clinical correlates: a stable pattern suggests stable angina or syndrome X; an unstable pattern suggests unstable or vasospastic angina; and preinfarction angina predicts improved postinfarct outcome, possibly due to ischemic preconditioning.

The majority of patients with ischemic heart disease consult doctors because of angina. However, transient myocardial ischemia and even necrosis can occur without pain, while severe angina can occur in the absence of obstructive atherosclerosis (as is the case in variant angina) or even in the absence of obstructive atherosclerosis and detectable myocardial ischemia (as it is the case in cardiac syndrome X). Thus, the presence of pain can serve the useful purpose of eliciting a protective reaction, but it can also become a major component of the disease when it is disproportionate to the severity of the injury and of the prognosis.

MECHANISMS OF ANGINA

At the turn of this century, Colbeck proposed that ischemic cardiac pain might be related to distention of the ventricular wall ("mechanical hypothesis"). Three decades later, Lewis hypothesized that ischemic pain might be elicited by the intramyocardial release of pain-producing substances induced by ischemia ("chemical hypothesis"). Studies carried out in the past 10 years have given strong support to the chemical hypothesis as they have consistently shown that adenosine is a mediator of angina *(Figure 1, page 96).*[1] It is worth noting, however, that stretching of epicardial coronary arteries can cause pain; this can be a mechanism of angina in the absence of ischemia following coronary successful stent implantation.[2] The nervous activity generated by the stimulation of cardiac receptors is modulated in intrinsic cardiac, mediastinal, and thoracic ganglia, and is further modulated in the central nervous system. Finally, it projects bilaterally to the cortex, as demonstrated in man using positron emission tomography, where it is decoded as a painful sensation *(Figure 2, page 96).*[3]

RELATIONSHIPS BETWEEN ANGINA AND MYOCARDIAL ISCHEMIA

Myocardial ischemia can be: (i) painful; (ii) painless, but symptomatic because of dyspnea or fatigue (due to transient left ventricular failure), palpitation, syncope (due to transient arrhythmias); or (iii) totally silent without any clinical manifestation *(Figure 3, page 97).* Painful ischemia is more easily recognized clinically when the pain has all the typical features initially described by Heberden, than when it has only some of those features (ie, location only in the epigastrium, jaw, wrist, or elbow). Painless, but symptomatic, myocardial ischemia has to be confirmed by the documentation of objective signs of ischemia on the electrocardiogram, as its clinical signs (indicative of severe heart failure or severe rhythm disturbances) can also be due to nonischemic

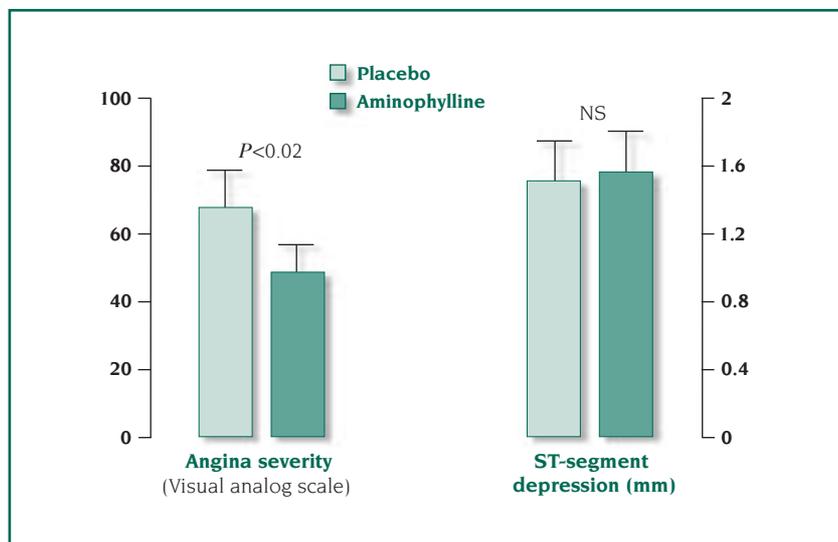*The angina pectoris—myocardial ischemia relationship - Crea*

Figure 1. *The graph shows the severity of angina during exercise stress test in patients randomized to placebo or aminophylline, a nonspecific antagonist of adenosine receptors. For a similar degree of exercise-induced myocardial ischemia, the severity of pain (assessed using a visual analog scale) was lower in patients randomized to aminophylline. The demonstration that adenosine antagonists reduce the severity of angina for a similar degree of myocardial ischemia and the demonstration, in several other studies, that intracoronary adenosine administration causes angina in the absence of myocardial ischemia, have convincingly proved that the increased myocardial concentration of adenosine during ischemia stimulates cardiac receptors, thus causing angina.*

Modified from reference 1: Crea F, Pupita G, Galassi AR, et al. Role of adenosine in pathogenesis of anginal pain. Circulation. 1990;81:164-172. Copyright © 2002, American Heart Association.

causes. Silent ischemia, by definition, can only be recognized by techniques capable of detecting ischemia.

Relationships between angina and severity, duration, and causes of ischemia

The results obtained in patients with angina at rest during continuous electrocardiographic and hemodynamic monitoring have led to the following conclusions: (i) transient ischemic episodes lasting less than 3 minutes and causing an increase in left ventricular pressure smaller than 7 mm Hg are typically silent; (ii) longer and/or more severe episodes can be either painful or silent even in the same patient; and (iii) milder transient ischemic episodes are more likely to be silent than severe ones, although episodes so severe as to cause massive deficit of regional myocardial perfusion

Figure 2. *Schematic representation of the neural pathways activated by stimuli triggering angina.*

and even myocardial infarction can remain completely silent. Therefore, a critical duration and severity of myocardial ischemia is needed for the development of angina.[4]

The failure of myocardial ischemia of sufficient duration and severity to provoke angina may result from various causes. The lack of pain might result from variable local concentrations of adenosine or of other (still unknown) pain mediators, transient failure of transmission of afferent cardiac impulses, or transient failure of the perception of pain *(Figure 4).*

The causes of ischemia do not influence the features of angina. For instance, patients with chronic stable angina (caused by increased demand) usually have the same type of pain when they develop unstable angina or infarction (caused by thrombosis). Some patients with spasm superimposed on a fixed coronary stenosis experience the same type of angina during attacks of variant angina at rest with ST-segment elevation (indicative of coronary spasm) and during effort-induced angina with ST-segment depression in the same leads.

Spatial relationships between angina and myocardial ischemia

Location of cardiac pain in somatic regions is determined by the convergence of visceral and somatic afferents on the same neurons in the central nervous system. A number of studies have shown that afferent sympathetic fibers are responsible for the transmission of cardiac pain.[5] Other studies have shown that afferent vagal fibers could also be involved in the transmission of cardiac pain.[6] As the intramyocardial portion of afferent fibers runs parallel to the coronary artery branch-
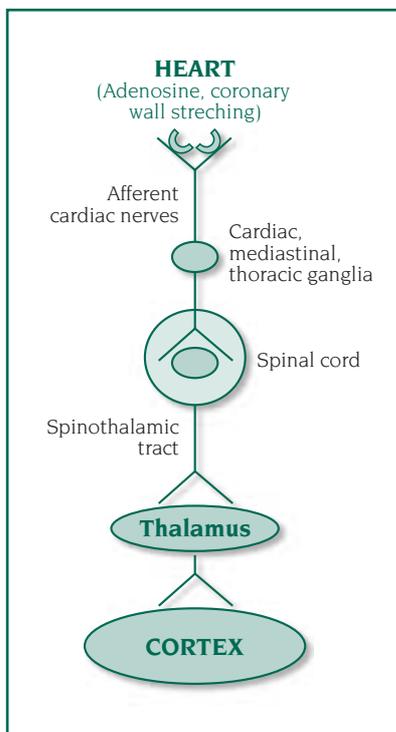
es,[5,6] ischemia caused by occlusion of a coronary branch has the potential of stimulating specific sympathetic fibers, resulting in specific locations of the angina. Yet, Eriksson et al[7] and Pasceri et al[8] found that patients with anterior or inferior myocardial infarction have a remarkably similar distribution of cardiac pain. Furthermore, the prevalence of symptoms caused by vagal activation, such as nausea or vomiting, in patients with either anterior or inferior infarction is similar, thus suggesting that, in man, vagal and sympathetic nerves are evenly distributed on both anterior and inferior wall.[8] It is worth noting, however, that sequential adenosine infusion into the right or left coronary artery in the same patient results in a similar distribution of pain in about 75% of patients, while pain distribution is different in the remaining patients.[9] Furthermore, about 70% of patients with a history of both anterior and inferior myocardial infarction experience cardiac ischemic pain in different body regions.[8]

Taken together, these findings indicate that the location of cardiac ischemic pain does not allow the site of myocardial ischemia to be predicted; yet, in the same patient, different locations of cardiac ischemic pain are likely to be caused by ischemia in different myocardial regions.

Temporal relationships between angina and myocardial ischemia

In patients with obstructive atherosclerosis who develop severe transient ischemia, angina typically follows the onset of metabolic, contractile, and electric alterations by several minutes.[10] This is not the case, however, in patients with angina and normal coronary arteries (cardiac syndrome X) who typically

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CLINICAL CONSEQUENCES OF MYOCARDIAL ISCHEMIA

- Angina
- Symptoms of acute heart failure
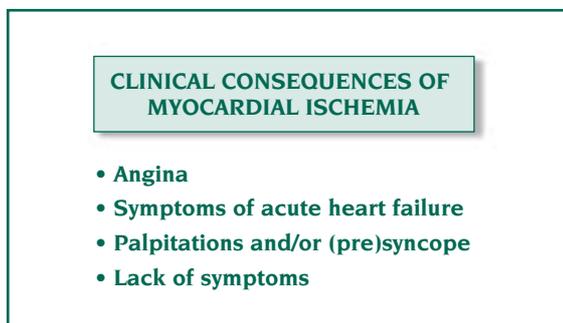- Palpitations and/or (pre)syncope
- Lack of symptoms

Figure 3. Clinical manifestations of myocardial ischemia. Angina is the most frequent and typical symptom. Myocardial ischemia, however, can be painless, but revealed by symptoms caused by acute cardiac failure or severe arrhythmias, or can be totally asymptomatic.
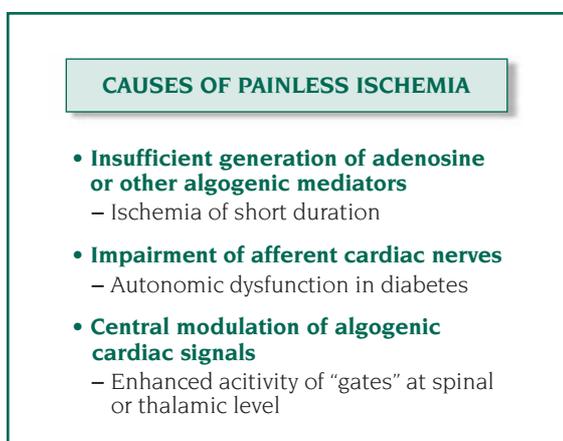

CAUSES OF PAINLESS ISCHEMIA

- **Insufficient generation of adenosine or other algogenic mediators**
  – Ischemia of short duration
- **Impairment of afferent cardiac nerves**
  – Autonomic dysfunction in diabetes
- **Central modulation of algogenic cardiac signals**
  – Enhanced acitivity of "gates" at spinal or thalamic level

Figure 4. The multiple causes of painless ischemia. Dynamic changes in "gates" located at various levels in the central nervous system play an important role in determining the variability of angina perception during myocardial ischemia.

ISCHEMIC CASCADE IN DIFFERENT CORONARY SYNDROMES

Stable or unstable angina	Cardiac syndrome X
• Metabolic markers	• Angina
• Diastolic dysfunction	• ECG changes
• Systolic dysfunction	• Highly sensitive metabolic markers
• ECG changes	
• Angina or angina equivalents or no symptoms	
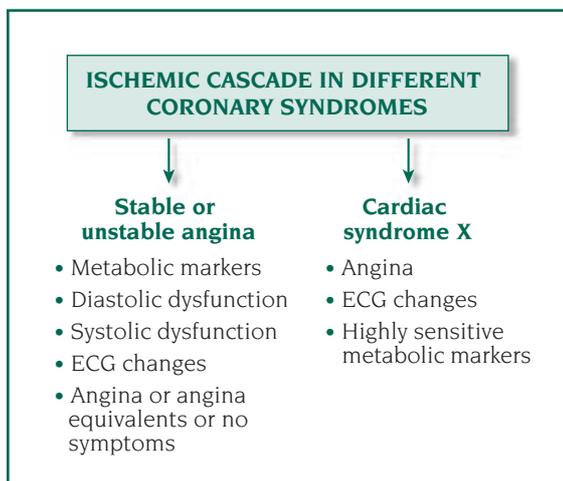
Figure 5. Sequence of events during myocardial ischemia: stable or unstable angina vs cardiac syndrome X.

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present chest pain before or even in the absence of ischemic-like electrocardiographic changes *(Figure 5).*[11] These different sequences of events may be in relation to different mechanisms of ischemia in addition to a different individual sensitivity to painful cardiac stimuli. Indeed, during massive transmural ischemia related to the presence of obstruc-

tive atherosclerosis in large epicardial arteries, accumulation of anaerobic metabolites in the central core of the ischemic region contributes to the very rapid deterioration of myocardial function. Thus, the first marker of ischemia is an alteration in regional function. In contrast, in syndrome X, where hypoperfusion is likely to occur in multiple tiny re-

gions scattered within the myocardium, the impairment of regional ventricular function can be very limited because of both compensatory hypercontractility of adjacent myocytes and more rapid washout of anaerobic metabolites that impair ventricular function when they accumulate in large ischemic regions.[12] Hence, it may be difficult to detect regional wall motion abnormalities by monitoring myocardial function with currently available techniques. Instead, the compensatory sustained release of adenosine may be sufficient to stimulate afferent fibers, thus causing pain.

CLINICAL SIGNIFICANCE OF ANGINA IN DIFFERENT CORONARY SYNDROMES

For an intuitive understanding of the clinical significance of angina, the analogy with the ringing of a doorbell and its various pitches and variable intensity is enlightening. According to this analogy, angina is characterized by the fact that it is a rather inefficient doorbell. Indeed, a pain indistinguishable from cardiac ischemic pain may also be elicited by nonischemic cardiac causes or by noncardiac causes, ie, the doorbell rings when it should not do so. Furthermore, cardiac ischemic pain is often not elicited at all by ischemia, ie, the doorbell does not always ring when it should do so. Finally, the features of cardiac ischemic pain are unrelated to the causes of myocardial ischemia and often not even to the severity of myocardial ischemia, ie, the pitch of the ring does not reveal who is ringing. However, despite all these limitations, the pattern of the doorbell rings, ie, their duration and frequency, if appropriately interpreted, can provide some information on who is ringing the doorbell. Thus, a stable pattern of occurrence of ischemic episodes with or without pain sug-

gests a stable cause of ischemia. Conversely, recent onset of ischemic episodes and/or rapid worsening of their severity and duration or the presence of ischemia at rest, whether associated with pain or not, suggest an unstable cause. More detailed analysis of the pattern of the ischemic episodes within stable and unstable subsets of patients may often provide further useful clues to their causes.

Chronic stable angina

Although, by definition, this form of angina is characterized by a stable pattern of symptoms over months and years, a detailed history of the circumstances in which anginal attacks develop can provide valuable information about the actual cause of ischemia. Attacks occurring predictably only when a certain level of physical activity is exceeded suggest a fixed impairment of coronary flow reserve. Attacks that occur unpredictably during levels of effort that are usually well tolerated suggest a variable impairment of coronary flow reserve caused by "dynamic" coronary stenoses or transient vasoconstriction of distal coronary vessels.[13,14] The range of this modulation can be appreciated by assessing the variability of heart rate at the onset of painless or painful ischemic episodes during Holter monitoring. However, the constancy of the number, duration, and severity of both painful or painless transient ischemic episodes over long periods of time suggest a stable cause of myocardial ischemia.

Syndrome X

A careful history can also provide clues on the puzzling syndrome combining angina, normal coronary arteries, and exercise-induced ischemic-like electrocardiographic changes, ie, cardiac syndrome X.[15]

Such patients predominantly exhibit typical effort or emotion-related angina similar to that of patients with stable angina due to obstructive coronary atherosclerosis. Yet, there are some distinctive features that help identify patients with syndrome X: (i) the duration of chest pain is occasionally, or even frequently, longer than 30 minutes; (ii) angina frequently occurs in the absence of electrocardiographic changes[11]; and (iii) stress-induced chest pain and ST-segment depression typically develop in the absence of detectable signs of regional wall-motion abnormalities.[16] These features are in sharp contrast to the impairment of left ventricular function in the absence of pain and ST-segment changes that can be observed in patients in whom ischemia is due to abnormalities of large epicardial vessels.[10] Furthermore, patients with syndrome X have a generalized lower threshold and tolerance to pain when challenged with painful stimuli like forearm ischemia, cold pressor test, skin electrical stimulation, or adenosine infusion, and exhibit an abnormal cardiac sensitivity to catheter manipulation and injection of contrast media.[17-19] It would appear, therefore, that compared with patients with unstable, variant, or chronic stable angina who predominantly exhibit painless myocardial ischemia in spite of obvious impairment of left ventricular perfusion and function, patients with syndrome X are at the other extreme of the spectrum of the sensory manifestations of ischemic heart disease, where even myocardial ischemia not impairing ventricular function may be perceived as painful.

Unstable angina

The sudden onset and rapid worsening of angina with more severe and longer-lasting attacks and at-

tacks occurring at rest is a marker of an unstable cause of ischemia, most frequently caused by transient thrombosis,[20] modulated by proximal and distal coronary vasoconstriction,[21,22] and, therefore, demands prompt medical attention and aggressive management. It should be pointed out, however, that the diagnosis of instability is only straightforward when symptoms are rapidly worsening, while it cannot be made based only on the mere presence of angina occurring at rest or for variable efforts.

Indeed, a variable anginal threshold, and even occasional episodes of angina at rest, occur in patients with chronic stable, predominantly effort-related, angina because of transient vasoconstriction at the site of coronary stenoses or in the coronary microcirculation, as noted above.[13,14] In this case, however, the pattern of recurrence of the anginal episodes at rest and during efforts that are usually well-tolerated is stable over months and years.

Variant angina

An unstable pattern of anginal attacks may also be caused by coronary spasm. Although this pattern is substantially similar to that of unstable angina caused by transient thrombosis, it exhibits some distinctive features. Thus, attacks of variant angina caused by coronary spasm are typically nocturnal, frequently come in clusters, and are, sometimes, associated with palpitations due to arrhythmias. More importantly, effort tolerance is usually preserved.[23]

Acute myocardial infarction

In a systematic analysis of the time course of cardiac ischemic pain during acute myocardial infarction, the pain was found to be discontinuous in about 40% of patients; furthermore, 50% of patients had preinfarction angina.[8] Accordingly, previous studies have shown that, in a sizable proportion of patients, during the early phases of myocardial infarction, coronary occlusion is stuttering because of frequent spontaneous recanalizations.[24] It would appear, therefore, that the time course of pain probably reflects this early dynamic modulation of coronary occlusion. Interestingly, the prevalence of preinfarction angina is significantly higher in patients with discontinuous pain than in those with continuous pain, thus suggesting that both preinfarction angina and a discontinuous infarction pain reflect the initial ability of endogenous fibrinolysis to transiently overcome local coronary thrombotic stimuli. The improved outcome of patients with preinfarction angina may be due to ischemic preconditioning, collateral recruitment, or a quicker recanalization of the infarct-related artery.[25,26]

Despite the extreme severity of ischemia that characterizes myocardial infarction, in the Framingham study, about one third of acute myocardial infarctions were not associated with pain that could be recognized by the patient,[27] thus emphasizing how the central modulation of algogenic messages plays a pivotal role in determining the perception of cardiac ischemic pain.

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What more can be provided for the medical management of angina?

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The current treatment of ischemic heart disease does not provide consistent control of anginal symptoms and does not assure effective protection from main adverse coronary events (MACE), including cardiac death and myocardial infarction. Most prescribed drugs, including β-blockers, calcium channel blockers, and nitrates, are directed toward restoration of the coronary supply-to-demand ratio, which is regarded as the main pathogenetic mechanism of myocardial ischemia. Innovative approaches, focused on the protection of coronary microcirculation from ischemia-reperfusion damage in acute coronary syndromes and on shifting cardiac energy metabolism from fatty acid to glucose, have been shown to improve symptoms and preserve left ventricular function. Given their different mechanism of action, these new strategies offer the opportunity of combination with conventional agents, with greater benefit and improved patient tolerance.

HEMODYNAMIC APPROACH TO THE MANAGEMENT OF ANGINA

The medical treatment of stable angina pectoris aims to improve prognosis by reducing the risk of death and myocardial infarction, and to relieve symptoms. Given that chest pain, the main characteristic angina symptom, is attributed to an imbalance between myocardial oxygen supply and demand, drugs active on cardiac work and coronary vascular tone are generally regarded as the mainstay of the medical treatment of chronic angina.[1,2] Little evidence, however —if any—is available on the impact of these hemodynamic agents, including β-blockers, calcium channel blockers, and nitrates, on long-term morbidity and mortality. Combination therapy is often prescribed for more effective relief of anginal symptoms, despite limited scientific support for this approach.[3-7]

More recently, nonpharmacological methods (changes in lifestyle, cessation of smoking, physical exercise, etc), treatment of concomitant diseases (high blood pressure, diabetes, anemia, etc), and pharmacological agents for primary prevention (aspirin, lipid-lowering agents, if needed) have been recommended in addition to conventional antianginal agents. Nevertheless, failure of this "hemodynamic" approach does occur and many patients are eventu-

ally referred for revascularization procedures because of the persistence of chest pain despite "optimal" medical treatment. The impact of revascularization procedures on the symptoms and natural history of the disease is discussed in the following chapter of this issue of *Dialogues.*

Regarding the efficacy of current medical therapy in alleviating angina and protecting patients from main adverse coronary events (MACE), it was stated several years ago that:

> "From a cohort of patients with chronic stable angina, 70% had more than 1 associated illness and 64% took more than 1 cardiovascular drug. Despite that, effort angina was present in 90% of patients."[8]

A recent paper comparing the clinical outcomes of patients treated medically with those of patients who underwent revascularization suggests that little progress has been made since then.[9] In fact, at follow-up, 60% of the patients that had been maintained on medical therapy for any reason, complained of persistent angina, and, within 2.5 years, 16% of them had suffered a main adverse coronary event, including death and nonfatal MI *(Figure 1, page 102).*

These figures demonstrate that current medical treatment of chronic angina does not assure consistent symptomatic improvement and has limited impact on

What more can be provided for the medical management of angina? - *Marzilli*
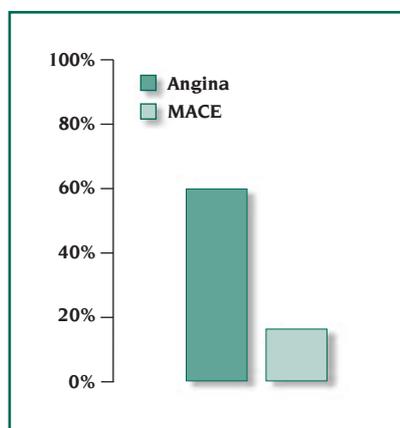

Figure 1. *Prevalence of angina and main adverse coronary events (MACE) in ischemic heart disease patients receiving conventional medical therapy.*

Modified from reference 9: Hemingway H, Crook AM, Feder G, et al. Underuse of revascularization procedures in patients considered appropriate candidates for revascularization. N Engl J Med. *2001;344: 645-654. Copyright © 2001, Massachusetts Medical Society.*

prognosis. Conversely, an unbiased appraisal of these data makes it clear that there is a need for innovative approaches to the medical therapy of ischemic heart disease.

METABOLIC APPROACHES TO THE MANAGEMENT OF ANGINA

Encouraging results have been recently reported in acute and chronic ischemic syndromes with treatment strategies focused on myocardial metabolism and/or on the coronary microcirculation.

Glucose-insulin-potassium

A purely metabolic approach, the infusion of a glucose-insulin-potassium (GIK) solution, as proposed many years ago by Sodi-Pallares, has been reevaluated in two multicenter, randomized trials, and proven to be effective in reducing mortality in acute myocardial infarction. The benefit from this intervention appears to be of special value in diabetic patients.[10]

Adenosine

To remain in the setting of acute myocardial infarction, use of adenosine in association with primary percutaneous transluminal coronary angioplasty (PTCA) in the early phase has been shown to protect the coronary microcirculation from reperfusion damage. This intervention effectively prevented the "no-reflow" phenomenon, and lowered in-hospital mortality as well as left ventricular remodeling.[11] Echocardiographic assessment of left ventricular function at the time of discharge demonstrated a marked recovery of regional contractile performance and better global left ventricular function in patients receiving adenosine at the time of primary PTCA *(Figure 2).*

Trimetazidine

In chronic angina, several metabolically active agents have been shown to oppose the deleterious consequences of ischemia. Four agents—carnitine, ranolazine, etomoxir, and trimetazidine—share a similar action of shifting energy production from fatty acids to glucose under ischemic conditions. All have been shown to protect the isolated heart from various forms of ischemic in-

sults under a variety of experimental conditions. Clinically, the largest experience, by far, has been gained with trimetazidine. Trimetazidine has been approved as an antianginal throughout Europe as well as in many Asian, African, and South-American countries.[12] It has recently been demonstrated that, by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, trimetazidine alters energy metabolism via inhibition of fatty acid oxidation and stimulation of glucose oxidation.[13] On the basis of this recent observation, trimetazidine is regarded as the prototype of a new class of antianginal agents: the 3-ketoacyl coenzyme A thiolase inhibitors.

The benefits of increased glycolytic substrate utilization are attributed to a number of mechanisms. The number of moles of adenosine triphosphate (ATP) produced per mole of carbon oxidized is approximately 29% higher for free fatty acids relative to glucose, but the number of moles of ATP produced per mole of oxygen consumed is 12% higher for glucose than for free fatty acid oxidation. Thus, under normal conditions, it is more efficient for the myocardium to utilize free fatty acids, but, during ischemia, glucose is a

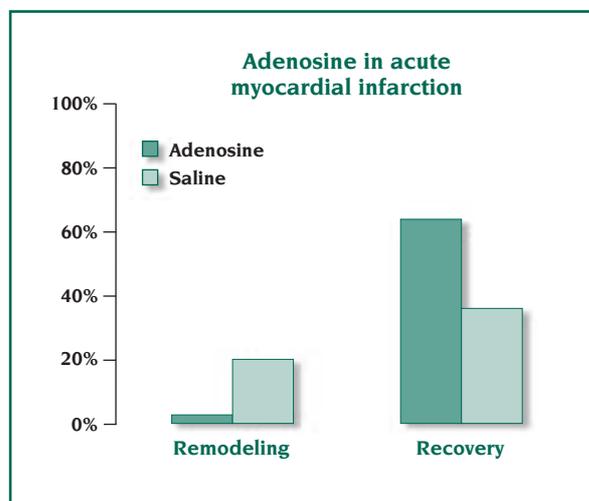**Figure 2.** *Adenosine as an adjunct to primary percutaneous transluminal coronary angioplasty (PTCA) prevents left ventricular remodeling and increases contractile recovery.*

Modified from reference 11: Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty. Circulation. *2000; 101:2154-2159. Copyright © 2000, American Heart Association.*

better substrate.[14] By decreasing fatty acid oxidation and stimulating glucose utilization, trimetazidine restores coupling between glycolysis and carbohydrate oxidation and leads to ATP production with less oxygen consumption. Moreover, trimetazidine redirects fatty acids toward phospholipids, leading to stimulation of membrane phospholipid turnover during ischemia and reperfusion.[15,16]

The efficacy of trimetazidine as an antianginal drug has been assessed in randomized, placebo-controlled studies, both as monotherapy and in combination with β-blockers and calcium channel blockers. In patients with chronic angina, trimetazidine increases work capacity and delays the appearance of symptoms and ECG changes during exercise.[17,18] The benefits observed after acute administration are maintained during chronic treatment with trimetazidine, which is well tolerated by patients.[19] Comparative studies have shown that the efficacy of trimetazidine in chronic angina is similar to that of nifedipine and propranolol, but that it has a lower incidence of adverse effects, since it is free of any hemodynamic effect.[20-23]

In patients already on nifedipine or propranolol, addition of trimetazidine significantly improved clinical status and reduced the number of ischemic episodes per week. These clinical effects were associated with prolongation of exercise duration and a delay in the appearance of ischemic symptoms and diagnostic ST-segment changes. Side effects were significantly less frequent in patients receiving trimetazidine than in patients receiving nifedipine or propranolol.[20-23]

Evidence in support of the hypothesis that the benefit from the metabolic approach may be additive to

that of hemodynamic agents was gained from a multicenter, randomized, double-blind study in which the addition of trimetazidine to propranolol was compared with addition of nitrates to propranolol.[24] The study, conducted in patients with chronic effort angina and documented coronary artery disease, concluded that the combination of trimetazidine with propranolol was more effective and better tolerated than the combination of nitrates with propranolol.

Consistent results were obtained in studies performed in patients with angina uncontrolled by diltiazem.[25,26]

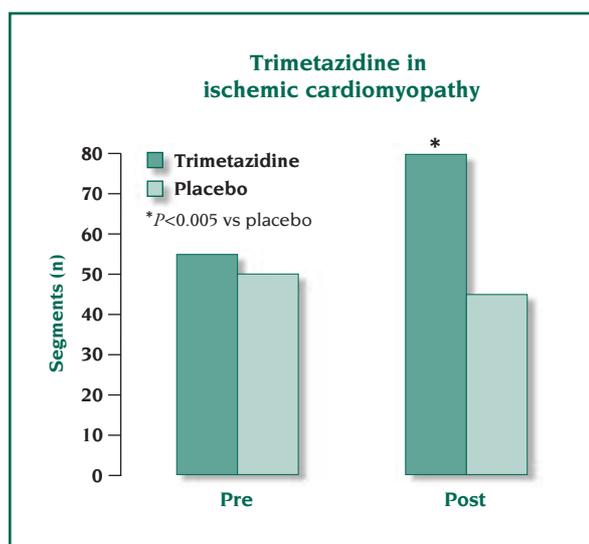**Trimetazidine in ischemic cardiomyopathy**

Figure 3. Increase in the number of segments responding to dobutamine infusion with trimetazidine.

Modified from reference 29: Belardinelli R, Purcaro A. Effects of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischemic cardiomyopathy. Eur Heart J. 2001;22: 2164-2170. Copyright © 2001, European Society of Cardiology.

Again, the addition of trimetazidine significantly reduced the number of ischemic attacks, prolonged exercise duration and time to onset of angina, and increased maximum work at peak exercise.

All of these clinical benefits have been recently confirmed in a randomized, double-blind, placebo-controlled, multicenter study conducted in Poland,[27] which proved the efficacy and acceptability of trimetazidine in patients with angina resistant to monotherapy with metropolol.

Thus, a large body of evidence conclusively demonstrates that an agent that exerts no effect whatsoever on cardiac work and coronary blood flow can effectively treat myocardial ischemia with sustained symptomatic benefit. However, symptomatic improvement and prevention of major adverse events do not exhaust the objectives of therapy in ischemic heart disease. With the growing emphasis on quality of life, reversing myocardial dysfunction is becoming a prominent target for therapy. The effects of myocardial revascularization on the recovery of function, as well as the benefits of pharmacologic modulation of

neurohumoral responses to ventricular dysfunction, have been extensively explored.

Metabolic manipulation of ventricular function is emerging as a promising alternative strategy to preserve cardiac performance in the long term. Trimetazidine has been shown to exert a cardioprotective effect in patients with severe ischemic cardiomyopathy and improve the contractile response of chronically dysfunctional myocardium without interfering with the oxygen supply-to-demand ratio *(Figure 3).*[28,29]

It has been postulated that trimetazidine acts on chronically hibernating myocardium by diminishing the effects of ischemia, thus improving function in a way similar to revascularization.

CONCLUSION

Long-term management of ischemic heart disease remains a difficult challenge for the clinical cardiologist. Macrovascular and microvascular disease limit the efficacy of revascularization procedures and increase early and late complications in patients managed medically. Progressive worsening of ventricular function jeopardizes quality of life and requires specific treatment. Conventional hemodynamic agents do not provide consistent protection and are often poorly tolerated. Prevention of microvascular damage at the time of acute events and manipulation of cardiac metabolism in chronic ventricular dysfunction hold promise as an innovative and effective approach to the medical management of ischemic heart disease.

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How should we manage patients with angina after revascularization?

A novel holistic patient-centered treatment paradigm

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Chronic angina that is refractory to medication and conventional revascularization is a growing clinical problem. Several approaches are in use in treating these "heart sink" patients and range from doing nothing through extremely low-cost and low-risk treatments to high-cost and high-risk procedures. The UK National Refractory Angina Consensus Guideline sets out a logical order in which these therapies should be tried based on the available evidence. There is no doubt that these complex patients and their families are best managed within a patient-centered multidisciplinary framework, and perhaps it is time to consider a new subspecialty that embraces the best of cardiology, pain management, and psychology.

Recurrent angina following revascularization is already a major clinical problem in health care systems with high rates of coronary revascularization. *Table I*[1-7] summarizes the relevant data from key angioplasty versus coronary artery surgery studies.

It is important to appreciate that the figures quoted represent the percentage of patients with recurrent angina at the time of follow-up. These underestimate the true recurrence rates because the figures do not include those patients with recurrent angina who had already been satisfactorily treated with repeat revascularization. For example, in the Bypass Angioplasty Revascularization Investigation (BARI) study, half the percutaneous transluminal coronary angioplasty (PTCA) patients who were angina-free at follow-up had already undergone repeat revascularization.[5] Importantly,

the practical management of recurrent angina in the trials is closely matched by the registry data. Thus, repeat revascularization rates at 7 years for angioplasty and surgery were 60% and 12%, respectively, and were the same in the BARI trial and registry patients.[6] The commonest reasons for repeat revascularization is recurrent angina, which occurs at some time or another in at least 60% of PTCA patients and 25% of surgical patients within 5 years. Overall, these data fit in with clinical experience and tell us that, in the long run, recurrent angina is the norm following PTCA and is common following coronary artery bypass grafting (CABG). It is clear from the data that most cardiologists are comfortable with managing recurrent angina as long as angioplasty or surgery is an option. The problems arise in those patients who continue to have pain despite repeat revascularization and (presumably)

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SELECTED ABBREVIATIONS AND ACRONYMS	
BARI	Bypass Angioplasty Revascularization Investigation
CABG	coronary artery bypass grafting
CABRI	Coronary Angioplasty vs Bypass Revascularization Investigation
EAST	Emory Angioplasty vs Surgery Trial
PTCA	percutaneous transluminal coronary angioplasty
RITA	Randomized Intervention Treatment of Angina

	PTCA	Need for repeat revascularization	CABG	Need for repeat revascularization	Study
1 year	29	48	12	–	BARI[1]
1 year	25	34	15	7	CABRI[2]
2 years	32	38	22	4	RITA[3]
3 years	20	63	12	14	EAST[4]
5 years	21	52	15	124	BARI[5,6]
5 years	49	53	34	12	RITA[7]

Table I. *Percentage of patients with recurrent angina in percutaneous transluminal coronary angioplasty (PTCA) versus coronary artery bypass grafting (CABG) studies. For full names of studies, see Abbreviations and Acronyms box.*

optimal medication (see below). Therefore, the question is not "how should we manage patients with angina after revascularization?" but "how should we manage patients with angina after revascularization when further revascularization is unfeasible or the risks cannot be justified?"

CHRONIC REFRACTORY ANGINA

For the purpose of this article, I will avoid dwelling on the vexed question of what is meant by "unjustifiable risks" except to ask "when is a high-risk, irreversible palliative procedure justified when low-risk, reversible options are available?" I will concentrate instead on those patients with recurrent angina in whom revascularization is deemed technically unfeasible. The UK National Refractory Angina Guideline Group recently recommended that the term chronic refractory angina should be used to describe all patients with stable angina that was not controllable with optimal medication and in whom revascularization is unfeasible or the risks cannot be justified.[8] This definition includes the small number of patients who present de novo with inoperable disease, but excludes syndrome X. Except in clear-cut cases, the diagnosis should be made after joint consultation between an interventional cardiologist and a cardiac surgeon.

PREVALENCE OF CHRONIC REFRACTORY ANGINA

The prevalence of chronic refractory angina is not known, but it is certainly related to both the size of the main at-risk population, ie, previously revascularized patients and the time after revascularization. The majority of patients survive beyond 10 years[9-11] and so, with the exception of those health care systems with a stable postrevascularization population, the rest of us can expect to see an inexorable rise in chronic refractory angina in the foreseeable future.[12]

In the remainder of this article, I will set out a practical "patient-centered" stepwise approach to care that can be highly effective in alleviating symptoms in these inoperable patients. By and large, the nonrevascularization strategies useful in recurrent postrevascularization angina were developed by pain specialists and, therefore, are counterintuitive, if not frankly heretical, to the practicing cardiologist brought up on the "it's ischemia, stupid" doctrine. Nevertheless, it has been my experience that for a cardiologist to provide the highest standard of care to patients with chronic refractory angina a fundamental change in treatment approach is necessary. In my own case, this was made easier by the realization that the heart is one

of the viscera and that chronic refractory angina is a chronic (ischemia-related) visceral pain problem.

CHRONIC REFRACTORY ANGINA VIEWED AS A PAIN PROBLEM

The term angina pectoris coined by Heberden[13] was an attempt to define a constellation of symptoms that he and others had elicited from an apparently new group of patients in the early-to-middle 18th century. The association between coronary obstruction and angina was quickly recognized,[14] and, immediately after that, the notion that angina was a warning signal was proposed by Lister, the pioneer of vaccination. Lister confided his idea to Heberden and a small circle of friends, but, fearful of the effect, deliberately did not tell his friend and surgical colleague John Hunter who was suffering from angina at the time. Hunter was an archetypal type A personality who eventually famously died of a ruptured syphilitic aneurysm at St George's, London, after a row with hospital administrators. Medical technology may have moved on, but the bureaucrats haven't, it seems. As a footnote to the story, one of Lister's original confidants later published Lister's idea as his own.[15]

For almost a century after the term entered common use, a debate developed centered on the question

of whether angina was a symptom or a disease. By the beginning of the 20th century, standard English-language medical textbooks had nearly all abandoned any reference to the debate, and the concept of angina as a mere symptom became accepted dogma without any scientific validation. Whether angina is a symptom or a disease may seem to be a minor point, but it is not. It fundamentally influences the treatment approach. As a mere symptom of a disease it is easy to justify treatments directed at the disease itself and see the resolution of symptoms as a natural consequence of successful disease treatment. On the other hand, if symptoms have deleterious consequences and the disease is untreatable, then treatments directed at the effects of the disease are necessary. This is the fundamental starting point of the development of pain management. On the other hand, there is a clear reluctance to interfere with the angina pain pathway in chronic stable angina. This is the largely the result of the dogma going back over 200 years that angina is an important mechanism protecting against the effects of ischemic injury. The reasons for this lie in the misconceptions that most cardiologists have about pain and its meaning. It was Sherrington who, in 1906, introduced the notion of pain as the psychic adjunct to protective mechanisms, and this has undoubtedly had a major influence on the way we think about the meaning of pain. However, it is important to understand that Sherrington was referring to somatic pain that has evolved highly specialized nociceptors and pain-signaling pathways that generally accurately detect injury and convey that to consciousness for a more or less appropriate response. It should never have been applied to pain originating from visceral structures such as the heart, for which evolutionary pressures

have been quite different and did not include a biological pressure to develop a specific ischemia pain pathway. The idea that the usual rules of evolution by mutation/adaptation should have made an exception several million years ago and produced an ischemia pathway so that cardiologists could be alerted to the need for thrombolysis or angioplasty to an acutely thrombosed coronary artery is preposterous. I suggest that had life-threatening myocardial ischemia been present in our biologically active ancestors (which it almost certainly was not), any mutation that enabled them to be conscious of it through pain would have conferred a lower biological survival advantage. After all, if the somatic "warning" model of pain is properly applied the organism rests and avoids further provocation. In other words don't run, don't fight, and don't have sex. Hardly the hallmark of a selfish gene.

The fact is that the cardiac pain pathway is not a pain pathway at all. To be sure, patients describe pain, so it is certain that they feel something. It is also clear that the signals originate from the heart and are promoted by ischemia. However, the heart has no specific angina or ischemia receptors, but relies heavily on the sympathetic nervous system (and possibly to a lesser extent on the vagus) to convey afferent signals to the spinal cord.[16] After a complex process of neuronal cross-talk through intraspinal neurons, spino-thalamic cells are activated. The brain locates the pain according to the topographic location of the originating spinothalamic cells. The cardiac-spinothalamic tract connections are more or less random over a small region, mostly to the left of the upper thoracic and lower cervical spine, and this explains inter-individual variations in angina distribution. Whichever spinothalamic

cells are activated, the usual suspects in the brain (thalamus, limbic system anterior cingulate gyrus, etc) light up on positron emission tomography.[17] The meaning allocated to the incoming stream of impulses determines the intensity of the response. Thus, angina accompanied by severe anxiety results in a greater fight-or-flight response than does the same angina without anxiety. Ironically, the primary efferent pathway is the same sympathetic pathway that carried the information in the first place. We are all familiar with the deleterious effects of angina and its consequences in acute coronary syndromes. The use of β-blockers to limit the consequences of excess catecholamine drive reduces myocardial damage in myocardial infarction.[18] In addition, experimental models of myocardial infarction have shown that the price paid for an intact angina pain pathway is a significant increase in infarct size.[19] Despite this, cardiologists and patients alike are concerned about interfering with the angina warning signal. To my mind, that is a little like worrying about disconnecting with a faulty smoke alarm that happens to spray petrol onto the fire when it is activated, but it is understandable nevertheless. Apart from destructive sympathectomy, none of the nonrevascularization strategies are capable of completely removing the sensation of angina—they merely modify the amount of pain, its character, and its effects. Moreover, patients must be made aware that while gentle regular exercise is good for them, overexertion is not.

PATIENT-CENTERED MODEL OF REFRACTORY ANGINA MANAGEMENT

The whole management program is underpinned by a continuous diagnostic process in which the objective is that the clinician and the

patient should understand how the disease or its consequences diminish the patient's quality of life. Once that process is complete, it is essential that all parties agree to a set of desirable objectives. Anything less than 100% congruence between the medical team and the patient is suboptimal. Extra clinic time must be set aside to facilitate a clearer understanding of what it is the patient really wants, and in every case reach an agreement about what is realistic and achievable.

Our holistic patient-centered approach to defining treatment strategies is based on the biopsychosocial model in which angina is seen as the "enemy," capable of forming alliances and changing tactics to extort the patients and their carers' quality of life. It is important to understand that these alliances are one-sided and one of the most powerful is the one between angina and the unenlightened cardiologist. For example, who do you think gains most from the phrase "I am very sorry to have to tell you that you are inoperable"?—the patient, the clinician, or the angina? Contrast that with an alternative truth "You will be pleased to hear that you will not have to go through another operation." Avoidance behavior is an excellent example of shifting tactics. Consider a patient who believes that angina is wearing out his heart (a common enough misunderstanding), in which case avoidance behavior makes obvious sense. Exercise causes angina, therefore exercise is dangerous, therefore don't do exercise. The logic is clear and there is no need for the patient's wife to nag him to rest, he does it himself. While it is true that heavy physical exertion can provoke a myocardial

Table II. Best management stepwise algorithm for patients suffering from chronic refractory angina. Copyright © 2000, www.angina.org

1a. **Diagnosis** requires a cardiological and cardiothoracic surgical opinion that the patient has angina of ischemic origin and that revascularization is unfeasible or the risks unjustifiable. Regular angiographic review is recommended to exclude the development of "new" revascularizable disease.

1b. **Outpatient assessment to include:**
- Review of pain history, drug history, and physical exam.
- Evaluation of additional/complicating noncardiac causes of pain (common).
- Assessment of the what and why of functional impairment.
- Consideration of depression as component to their total pain experience.
- Realistic and achievable "treatment targets" should be agreed at this and each subsequent stage.

1c. **Outpatient therapy to include:**
- (Re)education.
- Standard risk factor modification.
- Explanation of management plan.
- Optimize medication.

2. **Rehabilitation.** Based on recommended guidelines involving a combination of education, stress management, and a graded exercise program.[29]

3. **Transcutaneous electrical nerve stimulation.**[30]

4. **Temporary sympathectomy, stellate ganglion block,[31,32] T3/4 paravertebral block,[33] or high thoracic epidural.**[34]

5. **Spinal cord stimulation (SCS).**[35-37] Implant data and outcome should be recorded in a registry.
Note: although SCS is licensed for use in "pain" it does not yet have approval for use in "angina" in the US. Conversely, SCS has grade A Safety and Efficacy Register of New Interventional Procedures (SERNIP) classification for use in angina in the UK and is in widespread use across the EU.

6. **Opioids.** There is limited evidence of the effectiveness of opioids in refractory angina. In clinical practice, oral and transdermal opioids that can be effective are often limited by side effects. Trial of epidural followed by intrathecal opioids might be beneficial if side effects are intolerable.[38]

7. **Destructive sympathectomy.**[39]

8. **External enhanced counterpulsation (EECP)**[40] undoubtedly has a role in refractory angina management and is currently under review.

Section 2. While all therapies require further evaluation in clinical trials, the therapies in section 2 were considered too high-risk to justify their use in routine clinical practice while we await the outcome of ongoing trials. We recommend that these therapies should only be undertaken as part of a formal clinical trial except in experienced centers in exceptional circumstances.
- Myocardial (percutaneous or transmyocardial) laser.[41-45]
- Gene therapy and cardiac transplantation have no place in routine management.

infarction,[20] regular low-level exercise is protective.[21] In this example, it might take several hours for the clinical team to convince the patient that, contrary to his beliefs, a gentle exercise program would be good for him, but all the angina has to do is to persuade the patient's wife that if she lets him exercise he will die. She stops him exercising (vicarious avoidance behavior), the strategy is undermined, angina wins, and the patient, his wife, and the clinical team lose.

THE ROLE OF REEDUCATION

Almost all patients have mistaken beliefs, often with emotional distress that impairs their ability to cope with angina. These ideas have evolved over many years and are deeply entrenched and cannot be dealt with in a short time. Moreover, there is good evidence that one of the main reasons for failure to respond to revascularization is that it was addressing the wrong organ. A series of studies have shown that psychological factors play a major role in the failure of CABG.[22-24] In addition, very high proportions of patients who go on to develop recurrent angina post-PTCA have modifiable psychological problems that are identifiable on the day of the procedure.[25] An old-fashioned good bedside manner and time can resolve a lot of these damaging beliefs, but, if these resources are in short supply, rehabilitation services based on cognitive behavioral therapy are highly effective.[26,27] For patients who fixate on unachievable objectives, the services of a cognitive psychologist are invaluable.

There are a number of nonrevascularization treatment options available for the management of refractory angina and these vary enormously in terms of cost, safety, efficacy, and evidence. The lack of a coherent treatment strategy and consequent gross variation in clinical practice prior to 1998 prompted the inauguration of the UK National Chronic Refractory Angina Guideline Group. The Guideline Group, jointly commissioned by the UK Pain Society and the British Cardiac Society, has formal representation from the Royal College of General Practitioners and the British Cardiac Patients Association, and meets annually to review the guideline in the light of new evidence. In the absence of comparative trials, therapies are ordered pragmatically according to relative risk, reversibility, and simplicity of application. Relative cost is used when therapies are otherwise equally ranked. The first consultation guideline document was produced in November 1998 and was endorsed by the British Cardiovascular Interventional Society (BCIS) and formed the basis for the European Society of Cardiology Refractory Angina Study Group Document.[28] The guideline was first published in the *British Journal of Cardiology*[8] and is available on www.angina.org.

Table II (page 109) presents a brief description of the treatment stages. Patients advance through successive stages until they have achieved their objectives or are unwilling to proceed.

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Trails of Discovery

Calcium antagonists and the importance of pharmacological specifity of action

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Therapeutic research on calcium antagonists began in German pharmaceutical companies over 40 years ago and continues in many companies today. The first generation of calcium antagonists were prenylamine (Segontin, Hoechst 1960),[1] verapamil (Isoptin, Knoll 1962),[2] and nifedipine (Adalat, Bayer 1967).[3] The therapeutic target for these compounds was an improved treatment for angina pectoris, which had to meet certain stringent performance criteria. These included[4]:

• A dose-dependent increase in coronary flow with no increase in other vascular beds.
• An increase in the oxygen content of the coronary sinus blood.
• No increase in stroke volume, blood pressure, heart rate, heart work, and myocardial oxygen consumption.
• It should have a wide therapeutic margin and good general tolerability.

This is the therapeutic target profile, which was defined in the Haas and Hartfelder paper describing the initial pharmacological studies on verapamil in 1962.[2] The hemodynamic profile of verapamil (0.15 mg/kg) in the anesthetized dog showed an 86% increase

in coronary flow, an 88% increase in coronary sinus oxygen saturation, but a 20-beat reduction in heart rate and a reduction in blood pressure of 28/33 mm Hg. Thus, several of the theoretical criteria were not met. The authors suggested that the reduction in blood pressure and the negative inotropic effects were seen only at higher doses and concluded that verapamil (D365) would be an improved treatment for coronary artery disease.

The hypothesis that selective dilatation of coronary blood vessels was the best way to treat stable angina pectoris was universally held by the majority of clinical cardiologists at that time. This is in contrast to Black's hypothesis that reducing cardiac work by the blockade of endogenous catecholamine–mediated stimulation of β-receptors was more likely to be successful because calcified coronary vessels would not be able to dilate satisfactorily.[5] Thus, the scientific stage was set for prolonged debate concerning the emerging Anglo-Saxon approach of reducing excessive cardiac work and the central European view that selective dilatation of coronary vessels was the preferred approach for treating angina pectoris.

The predecessor of verapamil was prenylamine (Segontin), which also possessed a marked coronary vasodilator action at doses that caused little change in heart rate and blood pressure. In anesthetized dogs, it increased coronary flow by 100% and coronary

sinus oxygen saturation by 20%. However, when administered chronically in higher doses, prenylamine also depleted the content of norepinephrine in cardiac and brain tissue. This observation indicated that prenylamine had multiple pharmacological actions.[6] In other words, it had some nonspecific actions. In pharmacology, specificity of action is a pivotal characteristic, and, in the case of calcium antagonists, the question of specificity of action became an important and, for a time, a highly controversial scientific issue.

CALCIUM ANTAGONISTS AND SPECIFICITY OF ACTION

It must be emphasized that when prenylamine and verapamil were evaluated clinically, their mode of action in relaxing vascular smooth muscle was unknown. At that time, the target was selective relaxation of coronary vessel smooth muscle based on the original assumptions that this is how amyl nitrite and glyceryl trinitrate (GTN) exerted their beneficial effects in angina. In 1964, the mode of action at the cellular levels of either trinitrin or verapamil was unknown.

In 1963, scientists from Knoll, and subsequently Hoechst, approached Professor Albrecht Fleckenstein, Director of the Institute of Physiology, at the University of Freiburg, in Germany *(Figure 1, next page),* seeking his help in explaining why these potent coronary vasodilator compounds also

Figure 1. *Albrecht Fleckenstein.*

Photograph courtesy of
Prof Dr med Gisa Fleckenstein-Grün.

compounds were evaluated in his laboratory including, β-blocking drugs, antiarrhythmic agents, barbiturates, and selected local anesthetics. Many of these agents caused a dose-dependent depression of cardiac contractility.[9,10] Given the broad chemical structural diversity, the key issue of pharmacological specificity became of great practical importance. Fleckenstein's studies showed that verapamil could completely suppress the contractile function of the isolated myocardium without a major alteration of the transmembrane action potential, the upstroke of which depends on activation

of the fast channels of sodium. Thus, compounds such as lidocaine or quinidine predominantly inhibit the fast sodium channel and reduce myocardial excitability with secondary effect on cardiac contractility. The fact that the β-blockers pronethalol and propranolol also depressed cardiac function in Fleckenstein's preparation, suggested to him initially that they worked by nonspecific depression of cardiac function. Such a view plunged the Black hypothesis into uncertainty and confusion by implying that specific antagonism at β-receptors was not their predominant mode of action.

had cardiac depressant actions, which were regarded as undesirable. Fleckenstein's research had been focused on excitation-contraction coupling mechanisms and their relationship to myocardial energy utilization.[7] His laboratory had excellent skills in studying the transmembrane action potential in myocardial tissue, contractile force in isolated muscle, as well as tissue creatine phosphate and inorganic phosphate concentrations. In examining the role of calcium in excitation-contraction coupling, his group had shown that the bivalent cobalt and nickel ions could compete with calcium ions in such a way that excitation-contraction coupling was abolished.[8] It was also shown that the absence of calcium in the perfusion fluid prevented the breakdown of adenosine triphosphate (ATP), and this could be restored by replacing the calcium.

Within a year of receiving the compounds, Fleckenstein had shown that prenylamine and verapamil reduced contraction of the guinea pig papillary muscle in a manner similar to the withdrawal of calcium from the perfusion medium, and that adding excess calcium to verapamil-treated muscle restored contractile function *(Figure 2)*. Thereafter, more than 30 different

Figure 2. *Selective inhibition of cardiac contractility by verapamil, and the reversal of this effect by isoproterenol. Experiments on electrically-driven (2 shocks/s) isolated papillary muscles of guinea pigs.*

Reproduced from reference 20: *Varter W, Kroneberg G, Hoffmeister F, et al. Zur Pharmakologie von 4-(2'-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarbonsauredimethylester (nifedipine), BayA1040 [On the pharmacology of 4-(2'-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethylester (nifedipine), BayA1040].* Arzneimittelforschung. *1972;22:1-14.*
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β-BLOCKERS AND SPECIFICITY OF ACTION

The question of the specificity of action of β-blockers had already been raised by the Oxford pharmacologist Myles Vaughan Williams. His group showed that pronethalol and propranolol shared with quinidine the ability to raise the electrical threshold of isolated rabbit atria and to reduce their contractions, the cardiac conduction velocity, and the rate of rise of the intracellular action potential (fast sodium channel).[11] Subsequent studies showed that both β-receptor antagonists had local anesthetic activity similar to lidocaine and twice as potent as procaine. Furthermore, his group showed that propranolol (3×10^{-6} gm/mL) depressed the rate of rise and overshoot of the transmembrane action potential in a manner similar to quinidine.

CLINICAL IMPLICATIONS

In undertaking applied pharmacology for improved therapy, it is important to identify, if possible, the mode of action of novel compounds, in order to understand both their benefits and their potential drawbacks. In the case of angina pectoris, it was important to understand whether the novel therapy was causing nonspecific myocardial depression, either in the case of calcium antagonists or β-blockers.

This became an issue of practical medical importance when verapamil was marketed in the United Kingdom in 1968. It was recommended for angina pectoris on the basis of its *β-blocking effects* not its calcium antagonist properties. It might be argued that such pharmacological niceties of distinction were unimportant to clinicians, but this is not so in this particular instance. For example, the coadministration of verapamil with a β-blocker can lead to proarrhythmia and/or marked reduction in cardiac function.[12] Conversely, if propranolol was effective in angina

pectoris due to its nonspecific properties rather than its β-blocking properties, then it should be safe to use it in patients with obstructive airways disease, which is clearly untrue.

The evidence that verapamil had β-blocking properties was the subject of extensive debate in the correspondence columns of the *Lancet* in September 1968. Experimental studies with verapamil in animals and man had failed to show a dose-dependent inhibition of either isoproterenol or exercise-induced tachycardia.[13,14] This argument was dismissed by F. J. Bateman (Medical Director of the UK licensees), who concluded his letter with the statement:

> The β-blocking effect of verapamil, admittedly mild, is associated with a potent plain muscle–relaxing effect, which annuls the bronchoconstriction and coronary vasoconstriction induced by β-blockade, so that the advantage of this type of treatment can now, for the first time, be offered to the large number of patients with coronary artery disease complicated by bronchospasm, and the hazard of coronary vasoconstriction, surely undesirable angina, is removed. Finally, verapamil can safely be given to some patients in whom propranolol would be contraindicated by cardiac insufficiency, and this fact alone does not agree with it being merely a nonspecific myocardial depressant.[15]

A subsequent letter pointed out that the verapamil literature contained inconsistent statements in that the advertisements claimed, "Has not been shown clinically to cause or to worsen existing heart failure." Yet, the package leaflet, under *Precautions,* stated:

> Cordilox reduces cardiac output and, like other β-receptor blocking agents, may precipitate cardiac failure if this is threatening or aggravated it if it exists.[16]

Subsequently the view that verapamil, in clinical doses, was a β-blocker was quietly withdrawn, perhaps due to the opinion expressed in the *Prescribers Journal* that:

The mode of action of verapamil (Cordilox), which was claimed to be a mild *β*-adrenergic blocker, has not been clearly established and, at present, there would appear to be few clinical situations in which its use could be recommended.[17]

SOURCES OF THE CONTROVERSY

There were three elements causing the early confusion about the pharmacological properties of calcium antagonists.

Firstly, Fleckenstein's first major paper described propranolol as a compound causing reversible blockade of excitation-contraction coupling in a manner analogous to verapamil.[10] However, at the end of his paper he was careful to distinguish two possible modes of action—a distinction that was not understood by many workers in the field:

> Activity can be reduced: (a) by blocking the movements of calcium from the excited fiber membrane to the contractile system or by competing with calcium for the active sites where ATP is split; (b) by blocking β-adrenergic receptors since sympathetic transmitter substances are calcium synergists in activating myofibrillar ATPase in a "co-catalytic" way. The negative inotropic effects of Segontin and Isoptin (verapamil) seem to be primarily due to the first mechanism (a)… On the other hand, the negative inotropic action of specific β-receptor antagonists is always accompanied by complete adrenergic blockade.[10]

The second element was the data provided by Haas and Busch on the pharmacology of verapamil. In a paper published 5 years after the initial publication, these authors described verapamil as a "coronary dilator and β-receptor affinity substance" based on inhibition of isoproterenol and cardiac sympathetic nerve stimulation.[18] These effects, unlike those of propranolol, were not dose-dependent or competitive.

The third element causing the confusion was the presence of membrane-stabilizing properties (local anesthetic or quinidine-like actions) of propranolol when administered in concentrations several hundred times greater than those causing complete blockade of endogenous catecholamines (50-100 μg/kg/IV).

The reason why verapamil modulates the response of myocardial and smooth muscle tissue to β-receptor stimulation became clear once it was shown that the β-stimulants epinephrine and isoproterenol increased transmembrane calcium influx through *receptor-operated channels.* This mechanism is quite separate from *potential-dependent calcium channel opening.* Calcium entry brought about through receptor-operated channel activation is due to phosphorylation of the calcium ion channel secondary to the catechol-amine-mediated rise in intracellular cyclic adenosine monophosphate (cAMP).[19] In the presence of a specific calcium antagonist, the primary cate-cholamine effect will be reduced—but not in a competitive receptor antagonist mode.

SUBSEQUENT EVENTS

The term "calcium antagonist" was coined by Fleckenstein between 1964 and 1967. In a later review, Fleckenstein defends the original designation of "calcium antagonist," preferring it to the alternative terms such as: "slow channel blocker," "calcium channel blocker," "calcium entry blocker," or "calcium blocker," because "from a medical point-of-view they are misleading since real 'blockade' of transmembrane calcium entry in a strict sense is incompatible with life."[20] The initial observations triggered a significant increase in drug research in this field. Paradoxically, the initial discovery of both nifedipine (a dihydropyridine) and diltiazem (a benzothiazepine) was based on the search for selective coro-nary vasodilatation and their calcium antagonist properties were defined serendipitously. These compounds differed markedly in chemical structure compared with verapamil. Nifedipine in low doses inhibited calcium channels in vascular smooth muscle more effectively than in myocardial muscle and, therefore, caused less reduction in cardiac contractility in doses that caused optimal coronary vasodilatation. In the initial publication on nife-dipine,[20] the Bayer pharmacologists concluded that "Bay A1040 (nifedipine) is a potent, nonspecific and myotropic spasmolytic," despite the fact that they also refer in the discussion section of their paper to Fleckenstein's observations that it had calcium antagonist actions. Similarly, the initial publication on diltiazem (CRP-401, a D-*cis* isomer) emphasized its potent, coro-nary vasodilator effects and concluded that "CRP-401 has a property acting directly on the coronary vascular bed." Thus, even in 1971-72, several years after Fleckenstein's description of cal-cium antagonism in 1964, the mode of action of the newer coronary vasodila-tors was not initially attributed to this property. Diltiazem, while having potent vasodilator actions, also had addition-al electrophysiological actions delaying conduction through the atrioventricu-lar node.

The debate concerning the importance, or otherwise, of the membrane-stabi-lizing properties of the β-blockers was resolved in two ways. Firstly, agents with no membrane-stabilizing action, eg, sotalol, practolol, and atenolol, were shown to be effective antianginal and antiarrhythmic agents. Secondly, the non–β-blocking action of the dex-troisomer of propranolol was shown to have no benefit in anginal patients.

The field of calcium antagonist research expanded in many directions over the subsequent years and it is salutary to compare their status today with that of their early days.

The first striking feature is that, despite their potent vasodilating actions, there were no studies in experimental hyper-tensive animals prior to clinical trials. Furthermore, a few German investiga-tors only studied their role in essential hypertension, so that even in the late 1970s information on the hypotensive action of verapamil was sparse.[21] In contrast, their major commercial return today is as antihypertensive agents.

The second aspect is that despite a large body of experimental studies in experimental myocardial ischemia, calcium antagonists have not been shown to be "cardioprotective" in acute myocardial infarction.[22] In fact, nifedipine is contraindicated in unsta-ble angina unless the patient is already on β-blockers![23] Fleckenstein was firmly convinced calcium antagonists would be cardioprotective.[24] Ironically, despite the fact that β-blockers do not increase coronary flow, they do reduce cardiac mortality and morbidity in patients surviving acute myocardial infarction.[25] A further paradox is that despite the legitimate concerns about the myocardial depressant action of β-blockers, they are now considered to be of benefit in patients with con-gestive heart failure.

The field of calcium antagonist research has been characterized by recurring controversy. Firstly, in the 1960s, the mode of action of these drugs was con-sidered by the companies that discov-ered them to be a form of β-blockade. Secondly, in the 1980s, their utility as cardioprotective agents in acute myo-cardial infarction could not be con-firmed.[22] Finally, in the 1990s, there was controversy about their efficacy in reducing morbidity and mortality in essential hypertension.[26-28] Despite this, a large number of calcium antag-onists have been successfully market-ed. The most popular one, amlodipine, has achieved sales of over $2 billion annually and its popularity is perhaps associated with its excellent pharma-

cokinetic profile and channel-binding profile rather than with any unique pharmacological property.

The importance of the slow inward calcium channel in both sinus node and atrial ventricular node function was not appreciated when the first generation of calcium antagonists was discovered. It was not until the mid-1970s that the action of verapamil in slowing heart rate and atrioventricular nodal conduction was shown to be due to the inhibition of the slow inward current in these tissues.[29,30] Nifedipine does have a similar effect on the sinoatrial node, but only at concentrations 1000-fold greater than the maximum vasodilator concentration. Verapamil has developed into a notable agent in the treatment of atrial fibrillation, an application that had to await advances in electrophysiological techniques.

The story of the discovery and development of the calcium antagonists illustrates yet again the limitations of pharmacological targets based on a popular concept of a disease mechanism when trying to predict the final therapeutic utility of compounds with novel actions. This is perhaps also a cautionary tale for the current expectations of the potential of genomics and proteomics to enhance the certainty of predicting the utility of compounds with novel, speculative pharmacological properties.

Nevertheless, the availability of radio-labeled calcium antagonist ligands, combined with the cloning techniques of molecular biology, have revealed the structural complexity and heterogeneity of the calcium channels, which would now astonish those who pioneered this fascinating field.[31]

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Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing

M. H. Ellestad, M. K. Wan

Prior to the publication of this paper, controversy had surrounded the usefulness of exercise testing in reliably diagnosing coronary artery disease. Today, it is the most widely used investigation to risk-stratify patients presenting with symptoms of coronary artery disease (CAD). This study retrospectively assessed patients for whom follow-up was available 8 years after they had performed a treadmill exercise test to investigate CAD. The exercise test was terminated when the maximum predicted heart rate was reached or when chest pain or ECG changes of severe ischemia developed. Criteria for a positive exercise test were ≥1.5-mm ST-segment depression or 1-mm ST-segment elevation.

Patients with a positive test had a coronary event rate of some 10% per year, with 4- and 8-year event rates of 46% and 76%, respectively. In comparison, those with a negative test had 4- and 8-year event rates of only 7% and 25%. The authors identified a third group, with "equivocal" ECG changes of 0.5- to 1.4-mm ST-segment depression, in whom the event rate was 25%, between that predicted by positive and negative tests. The treadmill results were also independently predictive of myocardial infarction and death. The 4-year incidence of myocardial infarction was 15%, 5%, and 1% in those with positive, equivocal, and negative test results, respectively.

In those with a positive test, the earlier the ECG changes occurred, the greater the risk of coronary events, with the highest event rate in those who developed significant ST-segment depression by 3 minutes (4 metabolic equivalents [METS]). Beyond 2 mm of ST-segment depression, neither the magnitude of further ST-segment depression during the test, nor the time for ischemic ST-segments to return to baseline, were predictive of future events. In those with prior myocardial infarction, a positive test predicted a much poorer outlook. In fact, the 4-year event rates following a positive or a negative stress test were 70% and 40%, respectively, ie, twice the rates of those without infarction. In general, patients with a negative result could be reassured that the likelihood of a future coronary event was low, with the exception of patients in whom the test re-vealed chronotropic incompetence. The event rate in this group was similar to that of patients with a positive test result, unless the patient had been preconditioned by regular exercise.

Since this was a retrospective analysis, event rates are likely to have been overestimated as a result of selection bias in those in whom exercise testing was undertaken, and the likely exclusion of many who were event-free, due to lack of follow-up data. The predictive results are therefore probably not applicable to population screening.

This paper demonstrated the predictive value of the simple, noninvasive treadmill exercise test, at a time when diagnostic angiography was gaining momentum as the gold standard investigation of CAD. It showed that the rate of coronary events was sevenfold greater in those with a positive test and qualified the more serious prognostic significance of the exercise test result in the postinfarct patient, allowing for a more targeted use of angiography and intervention. Furthermore, it identified a high incidence of coronary events in those with an equivocal exercise result, leading to a revised definition of a positive test to a lower threshold of 1-mm ST-segment depression.

1975

Margaret Thatcher is elected the first woman
leader of the British Conservative Party;
Sir Julian Huxley, British scientist, author
and humanist, dies, aged 87;
and birth of US actress Drew Barrymore

Value of the history and physical in identifying patients at increased risk for coronary events

D. B. Pryor, L. Shaw, C.B. McCants, K. L. Lee, D. B. Mark, F. E. Harrell Jr, L. H. Muhlbaier, R. M. Califf

Much has been written about the predictive value of noninvasive testing in evaluating patients with cardiac symptoms for the likelihood of coronary artery disease (CAD), assessing prognosis, and guiding the need for further investigation. When deciding between such tests, in addition to sensitivity and specificity, the cost effectiveness of each technique is often used to argue in favor of a particular approach. As the plethora of diagnostic investigations available to the physician ever increases, it is of interest to weigh the usefulness of these techniques against the information obtained by the physician through simple history taking and baseline investigation. Traditionally, the referral for noninvasive tests has been justified on the grounds that clinical assessment is subjective and poorly reproducible. But just how predictive is the information from the initial assessment? And how does it compare with the oldest noninvasive test available, the treadmill exercise test?

The study by Pryor et al investigated the usefulness of a regression model, derived from data obtained at the initial consultation with the physician, in predicting the likelihood of CAD and long-term survival, in comparison with the treadmill test. Earlier, the investigators had developed regression models to estimate the severity of CAD at angiography and long-term survival. The predictive model was retrospectively derived from the initial assessment data of patients undergoing coronary angiography between 1969 and 1983. Equations were derived for estimating the probability of any significant CAD (≥75% stenosis in a major epicardial coronary artery), left main stem disease, and severe disease (3-vessel or left main stem disease) to predict 3-year survival.

This study prospectively validated the predictive models, using data obtained at the initial consultation in 1000 consecutive patients referred for investigation of suspected CAD, a proportion of whom subsequently underwent angiography. The characteristics of the history, examination, ECG, and chest x-ray were entered into the regression equations to derive a predictive index, which was correlated with angiographic findings and 3-year survival. The models closely predicted coronary anatomy at subsequent angiography and also performed well in predicting survival. Compared with the treadmill test, the predictive models were slightly better at differentiating patients with and without significant CAD, and were equal in the ability to discriminate between those with severe disease. There was a trend for greater discriminatory ability of the regression model compared with the treadmill in predicting survival.

In summary, the data obtained at the initial consultation, despite intuitively appearing subjective, can be meaningfully employed to help identify those who benefit most from further investigation and to improve the cost-effectiveness of subsequent tests by refining the referral population. The cheap and non–labor intensive method compares favorably with exercise testing. It is, however, important to remember that this study validated complex regression equations with input of data from the consultation, rather than assessing the predictive value of the raw data, and since the regression models are superior to the judgment of clinicians, the same predictive information cannot be inferred from the physician's clinical impression.

1993

William Jefferson Clinton is inaugurated
as the 42nd president of the USA;
death of Audrey Hepburn, film actress
(born, May 2nd, 1929);
and former East German communist leader
Erich Honecker is exiled to Chile

Survival of medically treated patients in the coronary artery surgery study (CASS) registry

M. B. Mock, I. Ringqvist, L. D. Fisher, K. B. Davis, B. R. Chaitman, N.T. Kouchoukos, G. C. Kaiser, E. Alderman, T. J. Ryan, R. O. Russel Jr, S. Mullin, D. Fray, T. Killip 3rd

Prior to the widespread use of coronary angiography to quantify atherosclerotic burden, studies had reported varying survival rates for patients with coronary artery disease (CAD), ranging from 15% to 75% at 5 years. Later, angiographic studies reported on the prognosis of CAD, but were too small for meaningful statistical analysis of the impact of vessel burden or left ventricular function on long-term outcome.

This study evaluated the relationship between the number of obstructed coronary arteries and left ventricular performance, and the subsequent survival of medically treated patients. Drawn from a multicenter registry of some 28 000 patients, the study cohort included some 20 000 medically treated patients who had been evaluated with angiography at enrollment and were followed up for 4 years. The cohort was predominantly male, and nearly half had a history of myocardial infarction. CAD was defined angiographically as ≥70% reduction in luminal diameter or ≥50% reduction in left main stem lumen. The left ventriculogram was classified by both ejection fraction and ventricular score, which analyzed wall motion in five segments of the ventriculogram.

The anatomic extent of disease was directly related to survival. 4-Year survival without significant disease was 97%, compared with 92%, 84%, and 68% for 1, 2, and 3-vessel disease, respectively. The presence of left main stem disease significantly reduced survival in patients with 3-vessel disease. Left ventricular function predicted survival, independently of the number of diseased vessels. In patients with good, moderate, or poor ventricular function, 4-year survival rates were 92%, 83%, and 58% respectively. In those with good ventricular function and 1, 2, or 3-vessel disease, survival rates were 94%, 91%, and 79%; in those with poor ventricular function, rates were 67%, 61%, and 42% respectively.

Extrapolating these data to current populations is difficult, due to advances in medical therapy since the 1970s, when treatment consisted of aspirin and β-blockade. Since the study included few women and very few diabetics, prognosis for these groups cannot be inferred from this registry.

Angiographic criteria were also very stringent, many patients with stenoses of <70% today would be regarded as having significant CAD.

This massive registry established survival rates for patients with CAD, and has served as the benchmark for subsequent evaluations of new therapeutic options. Since patients were not randomly allocated to surgery or medical treatment, the operative rate was much lower among those with poor ventricular function. This reflected the contemporaneous operative mortality of 2% for all coronary bypass, 5% in those with prior heart failure, and 8% in those with pulmonary edema.

This study established that survival was directly related to the number of diseased vessels and to left ventricular function, but left ventricular function was a more important predictor of survival, especially in patients with greater severity of CAD. It confirmed the excellent prognosis of patients with 1- or 2-vessel disease with good ventricular function, emphasizing that this group does well without intervention. Furthermore, in underscoring the prognostic importance of left ventricular function, it was instrumental in changing surgical practice towards surgery in those with an impaired ventricle despite the operative risk, since these patients gain most in survival benefit.

--- 1982 ---

Princess Grace of Monaco dies, aged 52, when her car plunges from a mountain road in Monte Carlo; the social democrats win a decisive victory under Olof Palme in the Swedish elections; and Jimmy Connors defeats Ivan Lendl, to win his fourth US Open tennis title

Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients

Antiplatelet Trialists' Collaboration

As far back as the fifth century BC, Hippocrates made therapeutic use of willow bark to ease aches and reduce fever. Willow bark, containing salicin, is the pharmacological ancestor of the world's most widely used drug: aspirin. Before the publication of this overview, trials had already established that antiplatelet therapy reduced death, nonfatal myocardial infarction (MI), and stroke in patients with unstable angina, MI, stroke or transient ischemic attacks (TIA). The aim of this study was to assess the benefit of antiplatelet therapy in a much wider range of patients and evaluate long-term safety. This was a landmark meta-analysis that incorporated 145 randomized trials of antiplatelet therapy versus placebo and 29 randomized comparisons between aspirin and other antiplatelet regimens.

The aspirin versus placebo trials included 70 000 patients at high risk of an occlusive vascular event and 30 000 low-risk patients. High-risk patients had a definite prior thrombotic event or important risk factors for thromboembolism. Aspirin was given for at least 1 month and the average duration of treatment was 2 years.

In each of four high-risk categories, antiplatelet therapy reduced vascular events by about 25%. In acute myocardial infarction, the incidence of a vascular event, namely, nonfatal MI, stroke, or vascular death, was reduced from 14% to 10%. Similar reduction in vascular events was also achieved in patients with prior MI, stroke/TIA, or unstable angina. In a broad group of high-risk patients including stable and unstable angina, atrial fibrillation, vascular surgery, angioplasty, valvular disease, and peripheral vascular disease without a prior vaso-occlusive episode, aspirin reduced the incidence of vascular events from 8% to 6%. The benefits were independent of age, sex, hypertension, or diabetes, and, compared with the benefit, the absolute risk of major or fatal bleeds was small. Although in the setting of primary prevention antiplatelet therapy reduced MI by one third, this was offset by a nonsignificant increase in stroke and, therefore, antiplatelet therapy could not be recommended for routine use in low-risk patients.

Direct comparison of aspirin with other antiplatelet regimens, mainly with aspirin plus dipyridamole, or with sulfinpyrazone or ticlopidine, included some 10 000 patients. There was no clear evidence of superiority with any these agents over aspirin. With regard to dosing, 75 to 160 mg aspirin per day was as efficacious as 160 to 325 mg per day. In addition to the more gastrotoxic profile, large doses of aspirin (1000 mg/d) were no more effective than medium doses.

Due to varying treatment periods in the trials, no definitive recommendations can be inferred regarding the optimal duration of therapy. Nevertheless, the observed increase in benefit with continued treatment beyond the end of year 1 would indicate that longer treatment is more protective.

Since its synthesis in 1853, aspirin has become the most widely used medicine to date. This meta-analysis established the role of antiplatelet therapy in reducing vascular events, not only in patients with MI, stroke, or TIA, but also among patients with important risk factors for thromboembolism. Antiplatelet therapy was to become recommended for all patients at high risk of vascular events, and aspirin was to become not only the most tested antiplatelet regimen available, but the single most cost-effective lifesaving therapy for patients at high risk of a vaso-occlusive event.

1994

The Japanese city of Kobe is struck by
a devastating earthquake;
death of Joe Slovo, leader of the South African
Communist party; and one million people
turn out to greet Pope John Paul II
in the Philippines at the start of his Asian tour

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)

For the best part of the last century, the observation that atherosclerotic plaque contains a lipid-rich core has fuelled the belief that the buildup of coronary atherosclerosis is a direct result of high serum cholesterol. In 1987, the US Food and Drug Administration (FDA) approved the first statin, a drug that blocked the cellular synthesis of cholesterol and increased hepatocyte low-density lipoprotein (LDL) receptor expression, facilitating cholesterol uptake from the blood. Several other statins soon followed, including simvastatin. Since the 1970s, several cholesterol-lowering interventions had been shown to reduce cardiac events, but up until this point, no trial of cholesterol lowering had been shown to prolong life. This, combined with the overview of trials suggesting that the observed reduction in coronary deaths was offset by an apparent increase in noncardiac deaths, including carcinoma and suicide, had resulted in a cautious approach to lipid lowering among most physicians, except in patients with extreme hyperlipidemia.

The 4S study was begun in 1989, to test the hypothesis that cholesterol lowering with simvastatin would improve survival, even in patients with only moderately raised cholesterol. In a prospective multicenter trial, 4444 patients with prior myocardial infarction or angina were randomized to simvastatin or placebo. Eligibility criteria included a total cholesterol of 5.5 to 8 mmol/L after lipid-lowering diet. After 1 year, 72% of the simvastatin group had achieved the target cholesterol level of 3.0 to 5.3 mmol/L. The mean changes in total, LDL, and high-density lipoprotein (HDL) cholesterol were -25%, -35%, and +8%, respectively. Patients with heart failure were specifically excluded to avoid an excess mortality due to cardiac failure or arrhythmias, which may have diluted the postulated effect of simvastatin on coronary atherosclerosis. Therefore, although 80% of patients had a history of infarction, the risk of death was much lower than that of all-comers with myocardial infarction.

Over a 5-year follow-up, simvastatin achieved a 30% relative risk reduction in all-cause mortality, predominantly due to a 42% reduction in coronary deaths. Additionally, there was a 44% reduction in major cardiac events, and the need for revascularization was reduced by 37%. The incidence of adverse events, cancer, or violent deaths was similar to placebo. The benefit of simvastatin began about 1 year after treatment and increased steadily thereafter. Earlier studies had shown that lipid lowering could slow the angiographic progression of coronary atheroma and that progression of coronary atherosclerosis clearly predicted subsequent coronary events. It was therefore hypothesized that the benefit observed with simvastatin reflected an ability to stabilize coronary lesions at risk of rupture, perhaps by reversing the lipid:smooth muscle cell ratio within the plaque.

This study changed clinical practice by establishing the undisputed role of cholesterol lowering on mortality in patients with heart disease, even when cholesterol levels were only moderately raised. It confirmed that long-term treatment was safe and well tolerated, and simvastatin became widely prescribed overnight. Subsequent studies with other statins have demonstrated similar findings in other patients groups. These studies essentially "closed the loop" by definitively showing a cause-and-effect relationship between elevated blood cholesterol levels and coronary artery disease in humans, which had been presumed, but not proven, by decades of basic, animal, and epidemiological studies.

--- 1994 ---

King Hussein of Jordan makes his first
official visit to Israel;
death of Grand Ayatollah Mohammed Ali Araki,
the spiritual leader of the Shia Muslims;
and George Forman, aged 45, defeats
Michael Moorer to win the world heavyweight
boxing championship

Circadian variation of total ischaemic burden and its alteration with anti-anginal agents

D. Mulcahy, J. Keegan, D. Cunningham, A. Quyyumi, P. Crean, A. Park, C. Wright, K. Fox

Lancet. 1988;2:755-759

How antianginal therapy impacts upon the circadian variation of ischemic episodes in patients with coronary artery disease is illustrated in this important paper. Anginal episodes peak in frequency and duration between 7 AM and 9 AM, coinciding with a rise in heart rate and plasma catecholamines. This pattern matches that occurring in sudden cardiac death and myocardial infarction. Since most episodes of myocardial ischemia in these patients are silent, the authors employed Cohn's concept of total ischemic burden on ambulatory ST-segment monitoring. The study was designed to examine this phenomenon and then focus on the independent effects of β-blockade and nifedipine therapy upon this circadian pattern of ischemic burden.

A total of 150 unselected patients were enrolled into the study; 6264 hours of monitoring were recorded, from which it was determined that 75% of the episodes were silent, ie, symptom-free. Two peaks in the prevalence of these episodes were identified, with the largest in the morning and the lesser in the evening. Thirty-three patients underwent a total of 1313 hours of ST-segment monitoring on nifedipine therapy and 41 patients monitored over 1581 hours received atenolol. These patients were investigated in a double-blind controlled study design. Nifedipine did not affect the pattern of ischemia. In contrast, atenolol not only abolished the morning peak of silent ischemia, but also reduced the total duration of ischemia. The evening peak of ischemic episodes was diminished.

The reasons for the enhanced efficacy of β-blockade in these patients are complex. The effects may be related to reductions in sympathetic tone influencing coronary vasomotor tone, although metoprolol does not affect tone and yet still reduces ischemic burden. Also, most episodes of silent ischemia occur without a significant increase in the hemodynamic determinants of myocardial oxygen consumption. A number of factors explaining the morning peak of ischemia are discussed, including the circadian variations in platelet activity and the fact that the time of peak ischemia is preceded by a trough in fibrinolytic activity. The effects of nifedipine are not restricted to coronary vasodilatation as it also reduces systemic vasomotor tone. This may result in an increased sympathetic drive and hence a reflex sympathetic tachycardia, leading to the observation that heart rate is increased by nifedipine treatment. This probably offsets any potential gains achieved by coronary vasodilatation.

This paper illustrates the importance of tailoring therapy to the circadian variations in ischemic burden in patients with angina. This may translate into reductions in mortality and morbidity in significant subgroups of patients.

1988

Canadian sprinter Ben Johnson is stripped of his
100 meters gold medal at the Seoul Olympics
after testing positive for steroid use;
the Colombian soccer team wins a match,
ending a 44-game, 5-year loosing streak;
and Naguib Mahfouz becomes the first Arab
writer to win the Nobel prize for literature

The pathogenesis of atherosclerosis: a perspective for the 1990s

R. Ross

I n this landmark review, the late Russell Ross has not only provided a perspective for the 1990s, but also insight into fundamental shifts in therapeutics extending into the first decade of the millennium. It elegantly synthesizes the response to injury hypothesis of atherosclerosis.

Atherogenesis occurs through an excessive inflammatory-fibroproliferative response to insults directed at the endothelium and smooth muscle cells in the arterial wall. Oxidized low-density lipoprotein (ox-LDL) induces endothelial damage that triggers an inflammatory response as monocytes and T lymphocytes adhere to endothelial cells. These migrate transendothelially and accumulate in the intima, scavenging lipid to form foam cells. The complex interaction between local smooth muscle, endothelial, and T cell elements drives a fibroproliferative process resulting in a plaque with a fibrous cap, lipid-rich core, and intimal smooth muscle overgrowth. This inflammatory disease may also include an autoimmune element, as antibodies to ox-LDL have been identified.

It is not possible to justifiably summarize the review in this short space. However, one can elucidate three aspects of Ross's work that are now having a major impact on modern cardiovascular therapies. The greatest impact of the hypothesis has been in the targeting of cholesterol accumulation as a promoter of the exaggerated inflammatory response. Ross recognized that these lesions could be impeded/reversed. It is supposed that statin therapy stabilizes plaque through reduction in the size of the lipid-rich core and the creation of a thick stable fibrous cap that is less likely to fissure and cause acute vessel occlusion. It is undisputed that reducing this important trigger to inflammatory injury translates into substantial reductions in myocardial infarction, stroke, and all-cause mortality. Indeed, it is now clear from intravascular ultrasound studies that these plaques may regress following statin treatment.

Restenosis rates post–percutaneous transluminal coronary angioplasty (PTCA) were as high as 50% in the era prior to stent deployment. This is due to injury induced by mechanical stretch and endothelial denudation, triggering a smooth muscle proliferative response akin to that seen in atherosclerotic plaque. The cytokine and cellular mechanisms inducing this process are described in detail in this review focusing upon the roles of platelets, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). Ross proposes the use of oligonucleotides and cytokine receptor antagonists to inhibit the intimal thickening process. This targeted approach was prophetic, since we are now entering an era where inhibition of the smooth muscle cell intimal proliferative response is becoming a reality by employing stents coated in cell growth cycle antagonists.

Ross also observed that during advanced stages of atherosclerosis the lesions develop large numbers of capillary and venule-like channels, most probably due to the local release of angiogenic cytokines. These channels compromise the stability of the fibrous cap. Furthermore, they pose a hazard to current angiogenic strategies attempting to promote coronary collateral growth, as the plaque capillaries may also be stimulated to grow, producing small unstable structures liable to hemorrhage and fissure the fibrous cap.

The fact that Ross's work has had such far-reaching implications with respect to both our understanding of atherosclerosis and the design of therapeutic strategies is a testimony to his genius.

1993

Monica Seles is stabbed
during a tennis match in Hamburg;
death of Alfred Butts, the US inventor
of the board game Scrabble;
and flames end the Waco siege in Texas
when the FBI storms the cult's compound

Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease

G. A. Diamond, J. S. Forrester

N Engl J Med. 1979;300:1350-1358

Diamond and Forrester provide an interesting insight into the planning of noninvasive tests to diagnose coronary artery disease (CAD). Their paper forms the basis of the rationale behind current cardiological practice. These issues were intensely debated during the late 1970s and have major cost-efficacy implications relating to all aspects of clinical screening programs.

The authors reviewed the literature to assess the pretest likelihood of CAD defined by age, sex, and symptoms. Four diagnostic tests were analyzed for sensitivity and specificity: exercise ECG, echocardiography, thallium scintigraphy, and cardiac fluoroscopy, to identify coronary calcification; each against coronary angiography as the gold standard investigation. Coronary calcification is now used by electron-beam computerized tomography to identify subjects with CAD.

This paper elegantly illustrates how the probability of CAD can be determined by using information already available in the basic clinical evaluation before any noninvasive test. It then describes a method of "serial-likelihood analysis," whereby the results of different noninvasive tests can be integrated into a quantitative statement of the post-test probability of CAD.

Importantly, the history of angina pain was identified as the best discriminating clinical factor. The prevalence in patients with typical angina was 90%, falling to 50% in those with atypical pain. At autopsy, prevalence of CAD rose from 1.9% in men aged 30 to 39 to 12.3% in those aged 60 to 69. It was 7.5% in women in this age-group. The approach integrates Baye's theorem of conditional probability. Although it is recognized that sensitivity and specificity define the quality of a test, the result cannot be satisfactorily interpreted without a detailed knowledge of disease prevalence in the population in question. This is illustrated by the example where a "positive" test that has a 70% sensitivity and 90% specificity occurs in a patient with a pretest probability of only 5%. The likelihood of CAD after testing remains low, at 27%.

The paper is novel in that it introduces a methodology to plan investigation of patients with intermediate posttest likelihood of CAD. The uncertainty of such a result can be reduced by using other tests. When a second test is used, the posttest likelihood determined from the first test becomes the pretest likelihood of the second test. In the patient whose exercise ECG gives a 27% probability of CAD, a second test with cardiac fluoroscopy showing calcification raises the probability of CAD to 80%. This strategy was termed serial-likelihood analysis. It also illustrates that once a posttest probability crosses a certain threshold, additional investigations do not significantly alter the subsequent posttest likelihood of disease.

The authors make the important point that the sensitivity and specificity of any test vary depending on how the results are interpreted. A nonjudgmental quantitative estimate is more relevant as a test result than simply binary assignment to "normal" or "ischemic." These tests can only provide a probability of disease likelihood in a given patient. The authors admit that the publications utilized in this analysis included selected patient groups, and that the use of autopsy to identify prevalence of CAD has several limitations. Nevertheless, this paper illustrates important concepts in the noninvasive assessment of patients with suspected CAD.

1979

Evelyn Ashford becomes the first woman
to break 11 seconds for the 100 meters;
US actor John Wayne dies of cancer, aged 72;
and President Carter and Soviet leader
Leonid Brezhnev sign the SALT II arms
control treaty

Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration

S. Yusuf, D. Zucker, P. Peduzzi, L. Fisher, T. Takaro, J. W. Kennedy, K. Davis, T. Killip, E. Passamani, R. Norris, et al

This paper complements Bucher's meta-analysis of percutaneous transluminal coronary angioplasty (PTCA) versus medical therapy. In this meta-analysis, a strategy of initial coronary artery bypass grafting (CABG) was compared with that of initial medical therapy.

Information from seven clinical trials over the period 1972 to 1984 was utilized. This involved 1324 patients assigned to CABG and 1325 to medical therapy in the first instance. The findings have had important clinical implications in both the risk stratification/prioritization of patients for surgery and the distinction between referral for medical therapy or PTCA. The proportion of medical patients who underwent CABG at 5 years was 25%, rising to 41% at 10 years. The CABG group had significantly lower mortality than the medical group at 5, 7, and 10 years. This ranged from a 10.2% mortality in the surgical arm at 5 years versus 15.8% in the medical arm, rising to 26.4% and 30.5 %, respectively, at 10 years.

Of interest, a risk stratification approach reliably identified the patient subgroups most likely to benefit from CABG. This was based upon a stepwise logistic regression analysis of 10-year mortality involving both clinical and angiographic variables. These included age, class III/IV angina, history of myocardial infarction, abnormal ejection fraction, proximal lesion of >50% in the left anterior descending or right coronary arteries, and diabetes. This approach is established in predicting operative risk and survival in the more contemporary EuroScore. Patients with left main stem disease benefited from a 68% reduction in mortality by CABG at 5 years and 33% at 10 years. Three-vessel disease mortality was reduced by 42% at 5 years and 24% at 10 years. CABG did not significantly lower mortality in patients with one- and two-vessel disease, a finding consistent with the Coronary Artery Surgery Study (CASS) registry. This may be due to the 30-day mortality of 3.2% post-surgery. Surprisingly, in contrast to the CASS registry, this meta-analysis did not identify any significant reduction in mortality by CABG in patients categorized according to LV dysfunction. On average, CABG prolonged survival by 4.26 months over medical therapy. The greatest prolongation in survival was achieved in those patients with left main coronary artery disease, and three-vessel coronary artery disease. Abnormal exercise stress tests and left ventricular dysfunction also identified patients likely to gain a survival benefit from CABG.

This study showed that an early surgical approach, ie, mean delay to surgery of 1.4 months, significantly reduced mortality during a period when left internal mammary grafts were employed in only 9.9% of cases. Furthermore, the benefits of surgery have probably been underestimated since there was a 37.4% crossover from medical to surgical therapy. This study identified patients in addition to those with left main contrary artery disease that were most likely to benefit from CABG. The benefit of surgery in terms of mortality reduction has probably been even further enhanced through the use of arterial grafts, high-dose statins, β-blockers, angiotensin-converting enzyme (ACE)-inhibitors, and newer antiplatelet agents.

1994

Zimbabwean golfer Nick Price wins the US PGA
(Professional Golfers' Association) championship;
two-time Nobel prize laureate
Linus Pauling dies, aged 93;
and Carlos the Jackal (Illich Ramirez Sanchez),
the worlds most wanted terrorist,
is captured in the Sudan

Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials

H. C. Bucher, P. Hengstler, C. Schindler, G. H. Guyatt

The efficacy of percutaneous transluminal coronary angioplasty (PTCA) versus medical therapy in the treatment of stable coronary disease has not been addressed with the same level of interest as the comparison of PTCA with coronary artery bypass surgery (CABG). Bucher et al attempt to readdress this imbalance through meta-analysis. The cost efficacy of interventional strategies is coming under increasing scrutiny, highlighting the importance of this issue. This study was conducted in an extremely rigorous fashion, avoiding many of the common problems associated with meta-analyses. Trials were selected on the basis of the following criteria: random allocation of patients to treatment, direct comparison of PTCA with medical therapy employed in data analysis, no evidence of recent acute coronary events. The end points examined included presence of angina, nonfatal myocardial infarction, death, and CABG or repeat PTCA on completion of the trial. Only 6 trials met these strict criteria. These included the Randomized Intervention Treatment of Angina–2 (RITA-2) trial and the Atorvastatin vs Revascularization Treatment (AVERT) trial. It was not possible to examine objective measures of treatment efficacy such as exercise ECG time to ischemia, since the data set was incomplete. Three of the trials included patients with multivessel disease and preexisting Q-wave myocardial infarction. The success rates of PTCA varied between 80% and 100%. Between 1.5% and 2.8% of patients required immediate CABG following PTCA, and the incidence of MI varied widely between 0.01% and 2.8%.

The most relevant statistically significant outcome was a 30% reduction in angina in the PTCA group versus medical therapy alone. However, this was associated with a significant increase in the need for CABG (risk ratio 1.59). There was a large variation in the degree of angina reduction with the 95% confidence interval including a risk reduction of only 2%. This may be explained by the complex interaction between criteria employed to determine if a given lesion is suitable for PTCA, patient comorbidity factors, and operator experience. It was not possible to determine any significant differences in myocardial infarction, death, or subsequent revascularization.

The main deficiencies in this meta-analysis reflect the rapid expansion in device technology and the evolution of adjuvant therapies since the early 1990s. Stent implantation reduces restenosis rates versus routine PTCA and hence angina recurrence; glycoprotein (GP) IIb/IIIa blockers lower the incidence of non–Q-wave myocardial infarction post-PTCA. Advances in stent technology, eg, rapamycin-coating, will reduce restenosis rates further. Statin therapy and ACE inhibitors are now proven to both lower coronary event rates and increase survival. In RITA-2, only 13% of patients were placed on a statin. These issues plague the majority of interventional trials that are usually out of date as soon as they appear. Therefore, although this meta-analysis indicates PTCA reduces angina at the expense of increased CABG rates, this only reflects the situation in the mid-1990s. The whole issue must be revisited in the context of current adjuvant pharmacotherapy and stent technology to ensure a safe and cost-effective approach is undertaken in the future.

2000

Mullah Mohammed Omar, leader of the
Taliban militia, declares a total ban on opium
production in Afghanistan;
America and Vietnam normalize trade barriers
for the first time since US troops pulled out
25 years previously;
and the French government offers
limited autonomy to Corsica in an attempt
to end 20 years of separatist violence

Angina: A Continued Challenge for the Cardiologist

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selected by **Kim Fox, MD, FRCP, FESC; Caroline Daly, MRCPI**

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