Angina pectoris is a symptom that is usually, in the developed world, caused by obstruction to the coronary arteries by the enlargement of atheromatous lesions; there are other causes. The symptom can limit lifestyle, but more importantly is a repetitive reminder to the patient of the presence of heart disease, causing continual anxiety because of the belief that angina is the portent of early death. That is not true; the annual mortality in the absence of severe disease and with reasonable left ventricular function ranges between 1 and 3% (see Figure 1). Angina pectoris has been a rather dull topic in cardiovascular medicine because of a lack of new ideas and a conventional approach to management. That is set to change. Angina pectoris was known many centuries ago, but the first clear and elegant description was by Heberden in the 18th century. The exact cause and pathophysiology was established by the work of many physicians such as Hunter, Black, Fothergil, Jenner, Parry, and Burns, showing the link of angina to the heart and to abnormalities of the coronary arteries. Osler wrote eloquently about angina, but it was Obratzow and Straschenko in 1910 and then Herrick who first described myocardial infarction in a patient.

Recent work has established the role of the unstable, fissured, or eroded atheromatous plaques in the coronary arteries, thrombosis in the coronary artery leading to myocardial infarction, and the effects of platelet activation and accumulation of atheromatous material in the vessel wall. Most of these acute abnormalities in the vessel wall lead to acute coronary syndromes or myocardial infarction and carry a poor early prognosis. Chronic (stable) angina pectoris, in contrast, is usually a consequence of a fixed obstruction within the coronary artery. The atheromatous plaque may expand outwards from the lumen of the artery and only late in the progression of atheroma does the lesion reduce the size of the lumen. The extent to which the lumen is occluded by a lesion in the absence of an acute coronary syndrome is a poor guide to the natural history. The differences in pathology between these different coronary syndromes almost certainly account for the differences in prognosis and the better prognosis of stable angina pectoris.

In developed countries, the prevalence of coronary artery disease in the whole population is about 6%, and of angina, 3%. The prevalence depends critically on age, gender, ethnicity, and economic and social factors, so that in persons over 85 years the prevalence is between 10 and 20%. The incidence in that age group is about 2% per annum.

The traditional medical treatment of angina has changed little in the last few decades. Nitrates were used to treat the condition by Brunton in 1867. Beta-blockers were introduced for treatment in the 1960s following the development of beta-antagonists by James Black. Propranolol was the first beta-blocker to be widely used. Subsequently, many beta-blockers with different pharmacological properties such as duration of action, lipid solubility, and cardiac specificity have become available. These have been shown in large trials to have clinical efficacy in the treatment not only of angina but also of hypertension, post-myocardial infarction, and heart failure. Calcium antagonists were introduced in the 1970s for angina and hypertension. They have their major impact by increasing coronary flow as a consequence of dilatation of the coronary vessels. Several recent trials have demonstrated the long-term safety of these drugs following the suggestion in the 1990s that they might increase mortality from myocardial infarction.

Thus, the conventional medical treatment of angina pectoris is nitrates, beta-blockers, and calcium antagonists for symptoms, and aspirin and statins for prevention. Recent trials have shown that calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and blood pressure lowering combinations of drugs improve long-term outcomes. Alternative forms of treatment or treatments for angina pectoris not responding to medical treatment include percutaneous angioplasty (PCI), coronary artery bypass surgery, spinal cord stimulation, and enhanced external counterpulsation. Unquestionably, these treatments relieve the symptoms of angina in selected patients. Coronary artery bypass graft (CABG) reduces mortality and morbidity in patients with the most severe forms of coronary disease, although the data are now rather old and medical treatment has improved so much that it is unknown whether the benefit still holds with modern medical treatment.

Currently, CABG is usually recommended only in patients with severe obstruction of the left main coronary artery or with extensive obstructive disease risk management.
Disease Risk Management

Table 1: Goals of Treatment in Angina Pectoris

1. Reduce mortality (prognosis)
2. Relieve symptoms (improve quality of life)
3. Prevent cardiovascular events
4. Need for invasive or interventional procedures (morbidity)

Table 2: Drugs in Angina and Secondary Prevention of Coronary Heart Disease

| For Chest Pain | For Prognosis/Morbidity |
|----------------|-------------------------|
| • Nitrates     | 1. Aspirin               |
| • Beta-blockers| 2. Statins               |
| • Calcium antagonists | 3. Beta-blockers (after MI) |
| • Ivabradine   | 4. Calcium antagonists   |
| • Ranolazine   | 5. ACE inhibitors        |

Figure 1: Mortality in Medically Treated Patients with Angina

New Therapeutic Approaches

The key goals in the treatment of angina pectoris are shown in Table 1. In medicine there are traditionally only two objectives: prognosis and quality of life. In the context of angina pectoris, further objectives are the prevention of cardiovascular events and the avoidance of unpleasant, costly, and risk-associated procedures such as PCI or CABG.

The key features of management are lifestyle modification, drugs that impact on risk factors (hypertension, hyperlipidemia, diabetes), drugs that prevent anginal attacks, and coronary revascularization. Two new classes of drug have become available in the last year (see Table 2). Ivabradine acts on the If channel to cause bradycardias and thus increase coronary blood flow. Ranolazine was in the past, thought to act by modifying substrate use in the heart, but is now proposed to inhibit the slow sodium channel and thus diminish calcium overload and myocardial stiffness in diastole.

Several treatments (see Table 2) such as statins and aspirin have been shown to be effective in the prevention of events in patients with coronary heart disease. The data with aspirin come largely from studies in patients with acute coronary syndromes. One study has reported on the effect of aspirin in a group of patients with chronic angina pectoris.

Outcomes of Medical Treatment of Angina Pectoris

The availability of new drugs increases the options available to the physician (see Table 2). Long-term trials will be needed to assess the precise role of PCI. PCI is used for patients with angina pectoris and atherosclerotic lesions localized to one or two vessels and in whom symptoms remain unacceptable despite best medical treatment; that is a rare situation. The probable reason is that fatal or non-fatal myocardial infarction are both the consequence of erosion or rupture of an atherosclerotic plaque that is not necessarily the lesion that on a simple angiogram appears to be the lesion most hindering blood flow at the time of a coronary angiogram. Coronary angiography does not detect unstable plaques or the lesions most likely to be the cause of subsequent cardiac events. Thus, intervention for most patients with angina is a treatment for symptoms and must compete with medical treatments aimed at the same clinical target in addition to possible reductions of mortality.

There have been few recent studies of the natural history of stable angina pectoris. Before the introduction of invasive intervention techniques, several studies showed that the outcome of patients with angina was dependent on the severity of coronary disease and left ventricular function (see Figure 1). The recently published A Coronary Disease Trial Investigating Outcome with Nifedipine (ACTION) study reported on 7,665 patients followed for a mean period of 4.9 years. The analysis of this database has allowed the creation of a system for risk analysis in patients with stable angina pectoris. A finding which to some may be a surprise was how many patients with angina were treated quite satisfactorily with medical treatment and did not have interventional procedures. About 50% of patients had undergone procedures before entering the trial, but only 21% had procedures during the trial. The relationships between the severity of angina, the number of diseased vessels, and the number of drugs used for treatment were as expected, but with more variability than commonly anticipated. Importantly, the coronary angiogram did not contribute greatly to the prediction of outcome.

Figure 2: Outcomes in Recent Large Trials

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lesions in all three main coronary arteries. Mortality and the occurrence of myocardial infarction in stable angina are not reduced by PCI. Two large studies have indicated that CABG may have a small advantage over PCI. PCI is used for patients with angina pectoris and atherosclerotic lesions localized to one or two vessels and in whom symptoms remain unacceptable despite best medical treatment; that is a rare situation. The probable reason is that fatal or non-fatal myocardial infarction are both the consequence of erosion or rupture of an atherosclerotic plaque that is not necessarily the lesion that on a simple angiogram appears to be the lesion most hindering blood flow at the time of a coronary angiogram. Coronary angiography does not detect unstable plaques or the lesions most likely to be the cause of subsequent cardiac events. Thus, intervention for most patients with angina is a treatment for symptoms and must compete with medical treatments aimed at the same clinical target in addition to possible reductions of mortality.

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such drugs in management. At present there is little evidence for beneficial long-term outcomes of drugs in angina pectoris; the focus has been on the relief of chest pain. Early trials were short and compared one drug with another without a placebo. The evidence for the use of beta-blockers comes from studies on patients with different medical conditions such as heart failure and post-myocardial infarction. The only large long-term study in angina pectoris against placebo is the ACTION study, which followed 7,765 patients for a period of almost five years. That study showed calcium antagonists did not impact on mortality or myocardial infarction, but did show a benefit in reducing stroke, interventional procedures including CABG, and new-onset heart failure. Other trials in hypertension have confirmed the safe long-term use of calcium antagonists.

Angiotsenin-converting Enzyme Inhibitors and Calcium Antagonists in Patients with Coronary Heart Disease

Several studies have assessed the use of calcium antagonists and ACE inhibitors in altering outcomes such as death or cardiovascular events in patients with known cardiovascular disease or expected to be at high risk. Only the ACTION trial focused on patients with stable angina pectoris. These studies do provide a basis for believing that in certain groups of patients, probably those at highest risk, ACE inhibitors may prevent adverse cardiovascular outcomes. The difficult question is whether benefit accrues to patients who do not have any of the current established indications for ACE inhibitors such as hypertension, diabetes, renal disease, or heart failure. There were important differences in the baseline characteristics of the patients admitted to these trials. In the Heart Outcomes Prevention Evaluation (HOPE), patients were older, beta-blockers were underused, few patients were on lipid-lowering drugs, and diabetes was common. HOPE showed an effect on mortality whereas the other four trials with ACE inhibitors did not. The European Trial on Reduction Of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA) showed no effect on mortality but a reduction of myocardial infarction—defined using biomarkers—and this effect dominates all end-points in that trial. The annual mortality does provide an indication of the type of patient included in these trials and the degree of risk. Where the annual mortality is low, the power to demonstrate any clinical benefit is small.

Comparison of the major recent trials on outcomes in patients with coronary heart disease is difficult because of different definitions of end-points, the manner in which information is provided in publications, and the use of various combinations of end-points. An attempt to make a comparison is shown in Figure 2. Overall, there seems little difference between calcium antagonists and ACE inhibitors. One criteria for the demonstration of an effect on mortality or other end-points seems to be the baseline risk; where the baseline risk is high, there is a greater possibility of showing benefit.

That opinion differs from the current guidelines of the European Society of Cardiology. The authors of HOPE, EUROPA, and Prevention of Events with Angiotsenin Converting Enzyme Inhibition (PEACE) published an article putting forward the argument that all patients with vascular disease should receive an ACE inhibitor. The accompanying editorial came to the opposite conclusion, suggesting that ACE inhibitors were indicated only in patients at high risk with presumably the established indications such as hypertension, renal disease, diabetes, and heart failure. The outcomes in trials in patients without these established indications are not available. The American guidelines say that ACE inhibitors can be considered in this group. The European guidelines are confused. The formal report states: "ACE-inhibitor therapy in all patients with angina and proven coronary disease." The pocket guideline, likely to be more widely read, states: "In angina patients without co-existing indications for ACE-inhibitor treatment, the anticipated benefit of treatment (possible absolute risk reduction) should be weighed against costs and risks for side effects." The latter is a more thoughtful view and one with which most physicians would agree.

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