New treatments and therapies has enabled patients with cardiovascular disorders to live longer. On the other hand, such benefits allow long-standing stress to act upon an already weakened heart with resulting congestive heart failure (CHF). With recent advances in cardiac pharmacotherapy and percutaneous coronary intervention, the outcome of patients suffering from coronary artery disorders has improved while the death rate caused by CHF rose 64% between 1970 and 1990.

Prevalence of CHF
- The disease is more common in men than in women and incidence rises with advancing age.
- According to the American Heart Association, about 4.8 million Americans are afflicted with CHF with 550,000 new cases diagnosed each year.
- The incidence of CHF approaches 10 per 1000 population after age 65.

Mortality Rates
- According to the American Heart Association, 50,824 deaths occurring in 1999 were attributable to CHF.
- Mortality rates related to CHF have grown over the last 3 decades, with a 145% increase per each decade.
- CHF patients are 6-9 times more likely than the general population to experience sudden cardiac death.
- Overall, approximately 20% of CHF patients will die within 1 year of diagnosis, and 50% will die within 5 years.

Principles in Management of CHF
The first guiding principle in CHF management is the concomitant, continuous, and aggressive pursuit and treatment of the underlying disease or diseases that led to the development of CHF. For example, hypertension requires vigorous and adequate therapy. When CHF is due to obstruction of the coronary arteries, a demonstration of reversible myocardial ischemia, even in the absence of angina, can lead to a coronary revascularization procedure that in turn can lead to an improvement in myocardial function.

The second guiding principle in managing patients with CHF is to define precisely the stage of the disease when therapy begins. The syndrome of CHF is a dynamic process and the therapeutic goals and end points vary as the process evolves. Symptoms, even as judged by exercise testing, do not correlate with the severity of ventricular dysfunction as judged by measurement of the ejection fraction. Thus, symptoms should not be used to guide therapy in the early stages of the disease. Minimal serial measurement of the ejection fraction remains the guide to advancement of the primary diseases, and symptoms and their relief may not predict survival.

The third guiding principle in managing patients with severe CHF is the recognition that a key determinants of successful therapy is the intensity of care; this requires frequent visits, in-home monitoring, and meticulous attention to management details such as diet, daily activity level, daily weight, and the doses of the medications being used, with an appreciation of their adverse effects.

Pharmacotherapy

Angiotensin-converting Enzyme Inhibitors
Knowing that the rennin-angiotensin-aldosterone system (RAAS) is responsible for maintaining the salt and water homeostasis of the body. Landmark trials in the early 1990s were designed to study the angiotensin-converting enzyme inhibitor (ACEI) as an antihypertensive therapy. Subsequently ACEI was found to have significant benefit in patients with CHF. At present, all patients with documented LV dilatation should be treated with ACE inhibitors. The only patients with LV dysfunction who should not be treated with ACE inhibitors are pregnant women, patients with documented angioedema or anuria during earlier exposure to ACE inhibitors, and patients with severe bilateral renal artery stenosis. The benefits of ACE inhibitors have not been looked for in patients with serum creatinine levels >2.5 mg/dl, since those patients have been excluded from clinical trials.

Angiotensin II Receptor Antagonists
Several angiotensin II receptor antagonists/blockers (ARBs) are approved by the FDA for the treatment of hypertension (losartan, valsartan, irbesartan, candesartan, telmisartan and eprosartan). Although trials
are in progress involving the use of ARBs alone or in combination with ACE inhibitors in heart failure, none have been approved for this purpose. The present use of ARBs for the treatment of CHF is limited to patients who experience intolerable cough or angioedema while receiving ACE inhibitors. Patients who cannot tolerate ACE inhibitors because of worsening renal function or hyperkalemia are likely to experience similar side effects with ARBs.

**Other Vasodilators**
Vasodilators agents may be used as adjunctive therapy in the management of heart failure. The combination of hydralazine and isosorbide dinitrate is an alternative therapy when ACE inhibitors are contraindicated or cannot be tolerated. Daily doses of hydralazine up to 300 mg in combination with isosorbide dinitrate 160 mg in the presence of cardiac glycosides and diuretics probably have some effect in reducing mortality in patients with chronic heart failure but not in reducing hospitalization for heart failure.

**Calcium Antagonists**
Calcium Antagonists are not recommended for the treatment of CHF because of their negative inotropic effects. However, second-generation dihydropyridine-type calcium antagonists such as amlodipine and felodipine may be considered for the treatment of concomitant arterial hypertension or angina.

**Beta-Adrenergic Blockers**
In a study in 1984, it was found that serum levels of the neurotransmitter norepinephrine were elevated in direct correlation to the severity of heart failure. Originally beta-blocker was thought to be contraindicated in CHF as it should further weaken the heart. But in the end of the 20th century, it was demonstrated that beta-blockers are protective. It is indicated in heart failure in the absence of contraindication such as reversible airways obstructive disease, advanced heart block, or episodic decompensation, and functional class IV CHF. Treatment should be initiated at the lowest possible dose under close monitor by specialist with gradual advancement in dosage.

**Diuretics**
Sodium accumulation tends to occur in the early stages of CHF, with peripheral edema accompanied by weight gain. Diuretics, along with salt restriction, remain the best therapeutic tool for treating the edematous state in heart failure. Despite the advent of new agents for treating symptomatic CHF, diuretics continue to be among the most commonly prescribed drugs in the world.

**Loop Diuretics**
The most potent diuretics are those whose action occurs in the medullary thick ascending limb of Henle because of the percentage of filtrate reabsorption that occurs at this segment of the nephron. Loop diuretics with salt restriction monitored by weight measurement by scale remain the basis for the treatment of edema. As CHF progresses, increasing oral doses of loop diuretics tend to be needed. In severe CHF with hospitalization, intravenous loop diuretics, commonly at higher doses, become essential. Other agents, such as metolazone, may be required as well to increase and sustain sodium loss. Limitations to diuretic use include hyponatremia and a progressive increase in serum creatinine, which may require careful dose reductions.

**Thiazides**
The thiazide diuretics may be a reasonable first-line natriuretic agents in early LV dysfunction when renal perfusion is not yet significantly compromised. In overt ventricular failure, however, thiazides are usually ineffective or inadequate.

**Potassium-Sparing Diuretics**
Aldosterone level is increased in heart failure. The use of spironolactone has been associated with reduced mortality in CHF, perhaps by helping to maintain potassium levels, thus reducing the risk of arrhythmic death in patients with heart failure, or by inhibiting other pathologic processes influenced by aldosterone. Spironolactone, when used in combination with a loop diuretic also has been associated with an improvement in diuretic response in patients with CHF previously resistant to loop diuretics.

**Inotropic Agents**

**Digoxin**
For chronic CHF, digoxin is of use over the long term when administration in association with loop diuretics and ACE inhibitors. Benefits are most evident in patients with NYHA class III or IV CHF. In this circumstance, the response of the circulation is characterized by a decrease in venous pressures and ventricular filling pressures and an increase in cardiac output.

**Catecholamines**
In chronic CHF, the patient commonly is maintained on vasodilators such as ACE inhibitors, loop diuretics, and digoxin. Nevertheless, episodes of acute decompensation may intervene, characterized by increased pulmonary congestion and edema and reduced renal function with increasing fluid...
accumulation. The in-hospital addition of dobutamine, with or without milrinone, using a Swan-Ganz catheter to monitor hemodynamics, provides for an increase in cardiac output with a decrease in filling pressures, which, with added diuretics, may help restore a steady state for a variable period. Dopamine, at a low dose, commonly is used concomitantly to augment renal blood. This generally requires a short hospitalization and temporary hemodynamic monitoring. In CHF, norepinephrine is used only for a limited time to treat severe hypotension and shock unresponsive to dopamine and dobutamine, and then the outcome is generally very poor.

**Phosphodiesterase Inhibitors**
Amrinone and milrinone are prototypes of cardiotonic agents that activate the adenylcyclase system through inhibition of the enzyme that breaks down cyclic AMP, phosphodiesterase (PDE) III. Other members of this class of drugs include enoximone and pimobendan. Only intravenous amrinone and milrinone have been approved by FDA for the treatment of acute heart failure.

**Drug Therapies Under Investigation**

**Natriuretic Peptides and Their Enhancers**
Conventional diuretics are associated with undesirable stimulation of the renin-angiotensin axis, sympathetic nervous system, and vasopressin. ANP and brain natriuretic peptide (BNP), by contrast, induce diuresis and natriuresis while concomitantly suppressing the rennin-angiotensin axis with dilation of peripheral vascular beds. When the BNP nesiritide is infused in patients with CHF, it reduces pulmonary capillary wedge pressure and systemic vascular resistance while increasing stroke volume and cardiac index.

It is believed that the attenuation of responsiveness to endogenous ANPs with endopeptidase inhibition is due to activation of the RAAS. This has prompted the development of agents that both augment the action of ANP and block the RAAS, the dual Neutral endopeptidase-ACE inhibitor drugs (e.g. omapatrilat, sampatrilat), which are now being examined in patients with systemic hypertension and CHF. In patients with

**Chronic Heart Failure – Choice of Pharmacologic Therapy**

<table>
<thead>
<tr>
<th>Condition</th>
<th>ACE Inhibitor</th>
<th>Diuretic</th>
<th>Potassium-Sparing Diuretic</th>
<th>Cardiac-glycosides</th>
<th>Vasodilator (Hydralazine/ISDN)</th>
<th>Beta Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic dysfunction Asymptomatic LV dysfunction</td>
<td>Indicated in some</td>
<td>Not indicated (unless ↑ BP)</td>
<td>Not indicated</td>
<td>Only with atrial fibrillation</td>
<td>Not indicated</td>
<td>After MI</td>
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<tr>
<td>Symptomatic HF (NYHA-II)</td>
<td>Indicated</td>
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<td>Fluid retention</td>
<td>Indicated</td>
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<td>+ Fluid retention</td>
<td>Indicated</td>
<td>Persisting hypokalemia</td>
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<tr>
<td>Worsening/severe HF (NYHA III-IV)</td>
<td>Indicated</td>
<td>Indicated, combinations of diuretics</td>
<td>Persisting hypokalemia; spironolactone for efficacy</td>
<td>Indicated</td>
<td>If ACE inhibitors are not tolerated or insufficient</td>
<td>Indicated (under specialist care)</td>
</tr>
<tr>
<td>End-stage HF (persisting NHYA IV)</td>
<td>Indicated</td>
<td>Indicated, combinations of diuretics</td>
<td>Persisting hypokalemia; spironolactone for efficacy</td>
<td>Indicated</td>
<td>If ACE inhibitors are not tolerated or insufficient</td>
<td>Indicated (under specialist care)</td>
</tr>
</tbody>
</table>

*Preliminary data from the DIG (Digitalis Investigation Group) trial suggest that digoxin also may be indicated in NYHA II heart failure and sinus rhythm.
Note: ACE, angiotensin-converting enzyme; BP, blood pressure; HF, heart failure; ISDN, isosorbide dinitrate; LV, left ventricular; MI myocardial infarction; NYHA, New York Heart Association.
heart failure, omapatrilat has been shown to be more effective in improving symptoms and reducing the combined risk of death and hospitalization than is the ACE inhibitor lisinopril (IMPRESS trial).

**Endothelin Inhibitors**
Endothelin-1 exhibits potent inotropic activity in isolated hearts, cardiac muscle strips, isolated cells, and instrumented intact animals. High-affinity receptors for endothelin have been demonstrated in both the atria and the ventricles. Intravenous endothelin-1 produces a delayed prolonged augmentation of LV performance in addition to its biphasic vasoactive effects of transient vasodilation followed by sustained vasoconstriction. There is early clinical evidence that treatment with endothelin-A receptor antagonists and endothelin-converting enzyme inhibitors can influence the course of human heart failure favourably. Some of these agents are being investigated in clinical heart failure trials (bosentan, BMS193884, LU135252). ACE inhibitors also may benefit patients with heart failure because of their antiendothelin actions.

**Vasopressin Antagonists**
Vasopressin, which usually is elevated in patients with heart failure, correlates with the severity of disease and the incidence of hyponatremia. In human beings, this aquaretic hormone is released in response to the level of plasma osmotic pressure or osmolality. In human studies vasopressin antagonists have been shown to reverse the impaired urinary diluting capacity seen in chronic heart failure, increase sodium free water excretion, correct dilutional hyponatremia, decrease urinary aquaporin-2 excretion, promote peripheral vasodilation, and improve cardiac output. Two orally active V2 receptor antagonists (WAY-VP985 and SR49-059) and a combined V1A/V2 receptor antagonist YM087 are being evaluated in clinical trials in patients with class III and IV heart failure who are currently on standard treatment that included continuous inotropic drug infusion.

**Oral Dopamine Receptor Agonists**
The unique, selective vasodilatory and inotropic actions of intravenous dopamine are limited by the lack of an oral formulation. This has led investigators to develop newer dopamine agonists that are orally effective. Unlike L-dopa, which has been used in heart failure, these new drugs do not cross the blood-brain barrier but maintain most of the pharmacologic activity of dopamine. Ibopamine, which is an orally active derivative of dopamine, has dopaminergic D1 and D2 activity with alpha- and beta-adrenergic actions. In therapeutic doses, it is a peripheral vasodilator and appears to have favourable cardiovascular and renovascular actions in patients with heart failure. The results of the Prospective Randomized Study of Ibopamine on Mortality and Efficacy in Heart Failure (PRIME-2), however, raised serious questions about the safety of ibopamine and agents of this class in patients with heart failure. Fenoldopam is a selective D1 agonist that has been used to treat patients with CHF and hypertension. Because of bioavailability problems with the oral formulation, only the intravenous form is used in patients with severe hypertension. Dopexamine is an intravenous D1 and beta-receptor agonist that is being studied in patients with CHF and low cardiac output states.

**Nonpharmacologic Aspects of Treatment**
Nonpharmacologic factors contribute to the overall efficacy of care. Weight reduction by dieting is generally advisable when obesity is present. Often, however, nutritional status is compromised and cachexia is present. Limitation of salt intake is important and may delay the time when diuretics may be necessary as well as reduce the amount required. In advanced heart failure, strict salt limitation is essential, although it is difficult to maintain. A diet containing less than 20 g/day of salt is desirable. Intake of fluids should be reduced to 1 to 1.5 L every 24 h in patients with advanced heart failure, with or without hyponatremia, except in warm climates. As will be stressed in relation to the use of diuretics, a readable weight scale is essential, and daily weights are of great value in judging therapy.

Smoking should be discouraged strongly in all patients, especially in the presence of obstructive vascular disease. Alcohol is a cardiac depressant in general and should be forbidden if an alcoholic cardiomyopathy is suspected. In all other cases, daily intake of alcohol probably should not exceed 40 g/day in men and 30 g/day in women, although there are insufficient data on the effects of alcohol in patients with mild heart failure to support these recommendations.

Low-level exercise, such as walking, should be encouraged, whereas strenuous isometric activities should be discouraged. Specific exercise training needs to be tailored to the appropriate level of the patient’s disease and always should be performed under medical guidance. Isometric exercise should be avoided. In patients with stable heart failure, there is evidence that appropriate physical exercise and exercise training can lead to improvements in both exercise capacity and the quality of life of the patient, although the effect of this intervention on the prognosis is unknown. Specific
recommendations include dynamic aerobic exercise (walking) three to five times a week for 20 to 30 min and cycling for 20 min at 70 to 80 percent of the peak heart rate five times a week. In patients with acute heart failure and in those with exacerbations of chronic heart failure, rest is advisable. Prolonged rest, however, should not be encouraged in patients with stable chronic heart failure.

**Surgical Treatment**

**Cardiac Resynchronization Therapy (CRT)**
- Intraventricular conduction disorders manifest as a widened QRS interval (>120 ms) on electrocardiogram are mechanically characterized by ventricular dysynchrony.
- Ventricular dysynchrony means that the 2 ventricles are not beating together as in a normal heart, a condition known to compromise hemodynamic performance and pumping efficiency in patients with heart disease.
- Wide QRS intervals, found in as many as 30%-50% of congestive heart failure (CHF) patients, have been identified as predictors of poor outcomes.
- While traditional pacemakers pace one or both right chambers, cardiac resynchronization therapy (CRT) was developed to coordinate both right and left ventricle contractility through atrial-synchronized biventricular pacing.

**Clinical Trials**

**Trial Design**
- MUSTIC: 3 months CRT
- Long-Term MUSTIC: 12 months CRT, improves ex-tolerance and quality of life (QOL)
- MIRACLE: 5 months CRT, improves in exercise tolerance, QOL, NYHA
- CONTAK CD: prospective, combination of CRT + ICD is feasible and safe, benefit in a broader patient population
- MIRACLE ICD: prospective, patients indicated for an ICD also benefit from the simultaneous use of CRT
- PATH-CHF II: evaluate the benefit of CRT +/- ICD, patients with the longest QRS intervals derive the greatest benefit

At present, CRT has been shown to improve functional New York Heart Association class status, alleviate symptoms mainly improve exercise tolerance and improve QOL. It has also been shown that the technique reverses ventricular remodeling.

**Indications for CRT**
Currently the FDA has approved the use of systems that exclusively provide CRT for patients with the following criteria:
- Symptomatic despite stable optimal drug therapy
- NYHA class III or IV moderate to severe heart failure
- Ventricular dyssynchrony demonstrated by a QRS duration >130 ms
- Severe LV systolic dysfunction evidenced by an EF <35%

**Characterization of Non-responders**
In the study of ‘Long-term clinical and hemodynamic assessment of biventricular pacing for heart failure’ in France and Netherlands:
- 82% of patients improved after BiV pacing
- Responders: more patients with dilated cardiomyopathy (33% vs 45%, P<0.03)
- Non-responders: more patients with prior myocardial infarction (33% vs 18%, P<0.01)
- Mitral regurgitation worsened in the non-responders but improved in the responders

**Implantable Cardioverter Defibrillators**
In patients with documented sustained ventricular tachycardia or ventricular fibrillation, an implantable cardioverter defibrillator (ICD) is highly effective in treating recurrences of these arrhythmias by antitachycardia pacing or cardioversion-defibrillation, reducing morbidity and the need for rehospitalization. There is some evidence that the efficacy of this device in terminating ventricular tachycardia or ventricular fibrillation may translate into improved survival in patients with heart failure. For patients with severe heart failure and documented sustained ventricular tachyarrhythmias, implantable cardioverter defibrillators at present should be considered a bridge to transplantation, but their effectiveness in this setting has not been proved.

**Indications for Combination Systems of CRT + ICD**
Systems are also available that integrate an ICD component to CRT to address the fact that patients with CHF are predisposed to sudden cardiac death (SCD):
- NYHA class III/IV
- EF <35%
- Wide QRS >120ms
- High risk of SCD due to ventricular arrhythmias
  - Survival of ≥1 episode of SCD due to a ventricular arrhythmia
  - Recurrent poorly tolerated sustained ventricular tachycardia (VT)
- Prior myocardial infarction (MI)
- Documented episode of nonsustained VT, with an inducible ventricular tachyarrhythmia

**Left Ventricular Assist Devices**
In a patient who cannot be sustained with medical therapy and for whom ultimate cardiac transplantation is anticipated, an LV mechanical support device (LVAD) has been successful in serving to maintain ventricular function as a bridge to transplantation. With two portable devices now approved by the FDA, the question remains whether they eventually can be used as long-term destination therapy for patients with end-stage heart disease.

**Heart Transplantation**
Heart transplantation is now an accepted mode of treatment for end-stage CHF. Transplantation significantly increases survival, exercise capacity, return to work, and quality of life compared with conventional treatment provided that proper selection criteria are applied. Recent results in patients on triple immunosuppressive therapy have shown a 5-year survival of approximately 70 to 80 percent and a return to full- or part-time work or seeking employment after 1 year in about two-thirds of the patients in the best series. Patients who should be considered for transplantation are those with severe CHF with no alternative form of treatment. Predictors of poor survival are taken into account. The patient must be willing and able to undergo intensive medical treatment and be emotionally stable to withstand the many uncertainties that are likely to occur both before and after transplantation.

Besides a shortage of donor hearts, the main problem in heart transplantation is rejection of the allograft, which is responsible for a considerable percentage of deaths in the first postoperative year. The long-term outcome is limited predominantly by the consequences of immunosuppression (infection, hypertension, renal failure, malignancy, accelerated progression of atherosclerotic vascular disease) and by transplant coronary artery disease. Experimental work is under way looking at xenotransplantation of myocardial cells and entire organs (pig hearts) as potential heart failure treatment. The humoral immune response of the recipient against the graft remains a preeminent hurdle. There is also limited information regarding the physiology of the pig heart as a replacement for the human heart.

**Coronary Revascularization Surgery**
A major and important surgical approach to ischemic cardiomyopathies is reperfusion of ischemic tissue by coronary bypass surgery. This is based on the concept that transiently ischemic myocardium (stunning) and myocardium with reduced flow (hibernating) have reduced contractility, which may return to normal with restoration of adequate coronary blood flow. Moreover, revascularization of ischemic regions of the ventricle may prevent recurrent infarction in this area and thus help prevent further deterioration of ventricular function. In such patients, it is necessary to establish that significant amounts of viable tissue remain in an akinetic or hypokinetic zone; this can be accomplished with nuclear techniques such as 24-h thallium perfusion study and positron emission tomographic scanning. In this era, every patient with ischemic cardiomyopathy should be evaluated for possible revascularization and assumed to be a candidate until proved otherwise.

**Other Procedures**
Other surgical approaches to the dilated heart have included the recent concept of removing a segment of the left ventricular wall, the “Battista operation”, to reduce LV volume and thus wall stress. The surgical risk is immense, and specific benefits have not been established.

Enhanced external counterpulsation is a noninvasive therapy consisting of gated diastolic sequential leg compression, producing hemodynamic effects similar to those from an intraaortic balloon pump. The procedure has been shown to improve exercise capacity and LV failure in patients with heart failure who already are receiving medical therapy.

In summary, therapy for heart failure seeks the reversal for attenuation of the processes that initiated the syndrome while treating the patient to relieve symptoms and prolong life. The latter end is best achieved early in the disease process through prevention of further loss of myocardium (e.g. reperfusion) or reduction of loading (e.g. appropriate valve surgery or treatment of hypertension). In very late stages of the disease, relief of symptoms can now be accomplished with modest gains in life expectancy.
Randomised Trial of Cholesterol-Lowering Therapy and of Antioxidant Vitamins in 20,536 People at Increased Risk of Coronary Heart Disease Death

Dr. Louise Bowman, on behalf of the MRC/BHF Heart Protection Study Collaborative Group. Coordinating Centre: Clinical Trial Service Unit, Oxford University, Oxford, UK

The Heart Protection Study assessed the effects of cholesterol-lowering therapy and of antioxidant vitamin supplementation in various patient categories for which there had been uncertainty about the value of such treatment. Patients aged 40-80 with a history of occlusive vascular disease or diabetes were eligible provided their own doctors did not consider statin therapy clearly indicated. Between July 1994 and May 1997, 20,536 patients were recruited in 69 UK hospitals. Previous myocardial infarction (MI) was reported by 8510 (most of whom were elderly, female or had “low” cholesterol levels) and some other coronary heart disease (CHD) by 4876. Among the 7150 with no history of CHD, 1820 reported a previous stroke or transient ischemic attack (TIA), 2701 some other peripheral artery disease, and 3982 diabetes (with overlap between these categories). There were 5082 women and 15,454 men, with 4893 aged 65-69 and 5804 aged 70-80. Total cholesterol was <5.0 mmol/l (194 mg/dl) in 4072, and LDL cholesterol was <3.0 mmol/l (116 mg/dl) in 4072, and 4072, and LDL cholesterol was <3.0 mmol/l (116 mg/dl) in 4072, and LDL cholesterol was <3.0 mmol/l (116 mg/dl) in 4072. Participants were randomly allocated simvastatin 40 mg daily or matching placebo for 5½ years. On average during the study, about one-sixth of participants allocated simvastatin stopped taking statin therapy and about one-sixth of those allocated placebo started taking it, yielding an average LDL cholesterol difference of 1.0 mmol/l (39 mg/dl). Using a factorial design, half of each treatment group was also randomly allocated antioxidant vitamins (600 mg E, 250 mg C, 20 mg beta-carotene daily) and half allocated placebo. Preliminary analyses involve confirmed and (as yet) unrefuted reports of non-fatal MI or CHD death (“total CHD” events) in 2148 participants, non-fatal or fatal stroke in 1069, “major vascular events” (total CHD, total stroke or any revascularisation) in 4648, cancer (excluding non-melanoma skin) in 1636, and 2831 deaths. The vitamins did not produce any beneficial or adverse effects on vascular or non-vascular morbidity or mortality in this population. Cholesterol-lowering therapy reduced total and vascular mortality, total CHD, stroke, and revascularization procedures, with no good evidence of any effect on non-vascular mortality or cancer. Myopathy was reported in <0.1% of participants. After making allowance for non-compliance (including non-study statin use), simvastatin 40 mg daily produced reductions in “major vascular events” of at least one-third in a very wide range of high-risk patients for whom there had previously been uncertainty about using cholesterol-lowering therapy (including women, people aged over 70, those with LDL below 3.0 mmol/l, and those with diabetes or non-coronary occlusive disease without pre-existing CHD).

Restenosis After Stenting and Angioplasty – New Developments

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Since the advent of angioplasty in 1977, restenosis has been the major accompanying problem. Attempts at controlling restenosis have run the gamut from antithrombotic therapies to anti-inflammatory approaches. The medical literature is littered with negative studies involving lipid lowering agents, prolonged anticoagulation, ACE inhibitors, anti-metabolic compounds, anti-inflammatories and the like. A few clinical trials have shown promise, particularly those utilizing the antioxidant, probucol, but because of non-availability of this drug in the U.S. and lack of interest in promoting a drug that is out of patent, this compound has not achieved clinical utility.
At the present time, there are promising approaches to controlling restenosis. All are aimed at inhibiting proliferation of smooth muscle and periadventitial fibroblasts by varying mechanisms. There are endovascular radiation or brachytherapy, an anti-rejection drug, rapamycin coated onto implanted stents, and systemic therapies including tranilast, which was evaluated in the PRESTO trial.

Endovascular radiation is clearly the most potent agent for controlling the healing response following angioplasty in coronary stenting. Although this approach has been used primarily in the area of in-stent restenosis (an indication for which it is now approved by the FDA), it has also been successful in controlling restenosis in the absence of stents. Gamma and beta radiation have both been equally successful. There are recently completed studies of in-stent restenosis using gamma radiation (the GAMMA 1 trial) and beta radiation (WRIST, LONG WRIST, START and the INHIBIT trials). Each of these have reduced repeat restenosis following in-stent restenosis from the range of 45-60% down to 15-25%. Anticipated problems of late recurrence have not been noted but the follow-up remains short in these trials. The smaller single-center trial at Scripps Clinic includes patients now followed for five years with very little late attrition noted. The principal concern has been the observation that late vascular thrombosis has occurred producing myocardial infarction. This occurred in approximately 10% of patients in the WRIST, LONG WRIST, and GAMMA 1 trials. The more recent trials using beta radiation, START and the INHIBIT trials, had a much lower incidence of this event. In fact in the START trial, there were no late thrombotic events observed to 8 months. Possible explanations for this difference include the limited use of new stents in the later trials and the expanded use of clopidogrel and aspirin therapy. Six to 12 months of clopidogrel and aspirin therapy are now suggested. Vascular brachytherapy is now widely available in North America and Europe for in-stent restenosis.

Drug eluting stents have captured the most attention in recent months. The antibiotic, Rapamycin, used to prevent transplant rejection, has been shown to be effective when incorporated onto a polymer coating of a stent. The initial animal investigation revealed approximately 50% reduction in neointimal proliferation using this system but the clinical feasibility study, the RAVEL trial in Europe and now the first results from the SIRIUS trial in the U.S., have shown quite fascinating results. RAVEL included patients with fairly large vessels treated with single stents. In that study, it was reported that there were no in-stent restenosis reoccurrences. The recent interim report of the SIRIUS trial showed a low restenosis rate within the stent itself but the overall lesion restenosis rate, including the ends of the stent, was above 9%. This was significantly lower than the control group at 30% but showed that as yet restenosis may not have been completely eliminated. Other stent trials using paclitaxel have also been positive, and the field of drug eluting stents is likely to become very crowded in the near future.

Among anti-restenotic systemic agents that have been tested recently, the evaluation of Tranilast stands out. PRESTO was a trial of 11,000 patients randomized to tranilast or placebo. Despite positive results in early trials in Japan, this largest of all restenosis trials was entirely negative. Another trial of cilastizol has also been stimulated by small randomized trials and is currently underway.

Many other approaches to restenosis are possible, including genetic engineering of cells, reimplantation of endothelial cells on the vessel wall, and improving debulking and stenting methodologies. After a long history of failure, controlled restenosis finally seems to be within the reach of clinical applications.

**Size of Plaque Doesn’t Matter – The Roles of Arterial Function, Inflammation and Collaterals in Determining Risk**

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University of Sydney, Australia

It is becoming clear that there is only a poor relationship between size of arterial plaque and the risk of clinical coronary events. It is now well known that many patients survive with even large plaques, either clinically asymptomatic or with stable angina pectoris, whereas many patients present for the first time with acute myocardial infarction or even sudden cardiac death in the presence of previously only small (even angiographically invisible) plaques, but which are prone to rupture and thrombosis.
Therefore there must be other determinants of plaque-related risk, in addition to and perhaps even more important than plaque size. Recent research has indicated the importance of vascular function, plaque inflammation and collateralisation in determining plaque-related clinical risk.

Much recent attention has focused on the role of arterial function in the presentation of coronary artery disease. The tendency to dilate or constrict in arteries is determined in large part by the function of the vascular endothelium, which (in addition to a variety of other functions) exquisitely controls tone by the secretion of vasodilators such as nitric oxide and EDHF, and vasoconstrictors such as endothelin 1. Endothelial dysfunction appears to be a key early event in atherogenesis, with the loss of nitric oxide not only predisposing to vasoconstriction but also monocyte adhesion, platelet aggregation and smooth muscle proliferation. A variety of mechanistic and now prognostic studies have highlighted the importance of endothelial dysfunction and abnormal vascular reactivity in the determination of coronary risk, and recent studies have identified possible mechanisms of reversing endothelial dysfunction with consequent patient benefit.

It is also now apparent that atherosclerosis develops as a chronic inflammatory/fibroproliferative disease of the vessel wall. Although inflammation plays important roles in the early processes of attachment of monocytes and growth of plaques, greatest recent interest has focused on the role of inflammation in plaque vulnerability. Those plaques which rupture have high concentrations of macrophages and T lymphocytes, all of which can actively secrete matrix degrading enzymes (matrix metalloproteinase) and also the prothrombotic tissue factor. In particular, macrophages accumulate in the shoulder regions of plaques, and areas of high shear stress, elaborate metalloproteinases causing softness of the plaques and predispose to rupture and acute thrombosis. Understanding the role of inflammation has already prompted important diagnostic and therapeutic advances. Plasma levels of C-reactive protein, for example, appear to provide important prognostic information in patients with or at risk atherosclerosis, and the anti-inflammatory effects of aspirin and statins may well be important contributions to their major clinical benefits.

The role of collaterals is less well studied, and factors which promote or inhibit collateral formation are as yet poorly understood. Nevertheless, recent advances in gene therapy have highlighted the possibility of inducing collateral formation in patients with established vascular disease, such as by administration of VEGF.

In summary, plaque-related determinants of risk rely as much on novel concepts of vascular function, inflammation and collateral formation as they do on plaque size. This “paradigm shift” in the understanding of the biology of atherosclerosis already has practical importance for the way we manage out patients with coronary artery disease.