Clinical review

Recent advances

Cardiology

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Important advances are being made in acute ischaemic syndromes, chronic coronary artery disease, congestive heart failure, and sudden cardiac death. This review highlights some of the advances in cardiology and the resultant changes in clinical practice that are taking place.

Recent advances

Inhibitors of the platelet surface glycoprotein IIb/IIIa complex are promising treatments for acute ischaemic syndromes in conjunction with coronary angioplasty

Lipid lowering treatment is now more practical and is increasingly used in primary as well as secondary prevention of coronary artery disease

β blockade and direct angiotensin II blockade are potentially useful treatments for congestive heart failure

Risk of sudden cardiac death may be reduced by amiodarone and implantable defibrillators

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Methods

For this review, I have used data from published literature and information on ongoing trials obtained from colleagues. Since doctors usually look to clinical trials to guide their practices, I discuss recent important clinical trials (for explanation of study acronyms see box on *BMJ* website at www.bmj.com). I also used data from, and systematic overviews of, randomised clinical trials where available.

Acute ischaemic syndromes

Acute myocardial infarction and unstable angina are the main reasons for hospitalisation. Pathophysiologically, treatment focuses on the intracoronary thrombosis. Thrombolysis has been clearly shown to be efficacious and is widely used in acute myocardial infarction but is unproved in treating unstable angina. Adjunctive treatment with new antiplatelet and antithrombin agents are being investigated.

Platelet glycoprotein IIb/IIIa inhibition

Interest in the role of platelets in forming the thrombus has led to identification of the platelet surface glycoprotein IIb/IIIa complex, which, when activated by exposure to ADP or thrombin, binds fibrinogen and links platelets into large aggregates.[1] Inhibitors of this complex, a member of the integrin family of adhesion receptors mediating the final common pathway in platelet aggregation, have been evaluated in the acute ischaemic syndromes and after coronary angioplasty. One such inhibitor is a mouse monoclonal antibody, known as 7E3 or abciximab. When given to patients with evolving acute myocardial infarction or unstable angina who are undergoing coronary angioplasty, this agent has produced remarkable reductions in acute myocardial infarction and need for urgent revascularisation in the 30 days after the procedure and beyond (table 1).[2–5]

The effects of other inhibitors are less conclusive. Intravenous treatment with lamifiban has been tried with uncertain results (PARADIGM trial[6]), but preliminary data on tirofiban from the PRISM trials are promising (P Theroux, data presented at the 1997 American College of Cardiology meeting). Other agents in this class are being evaluated, both orally and intravenously.

Hirudin

Thrombin plays a central role in coronary artery thrombosis, promoting platelet aggregation, a process enhanced by a positive feedback loop, and catalysing cross linkage of the fibrin clot.[7] Although heparin remains the mainstay of antithrombin treatment, several other agents have been tested in patients with acute myocardial infarction and unstable angina. Hirudin, a direct thrombin inhibitor derived from the saliva of the medicinal leech (*Hirudo medicinalis*), shows some promise if safe and effective doses can be devised. Early trials showed that hirudin, at doses that were subsequently regarded as being too high, led to excess spontaneous intracranial bleeding (GUSTO IIa)[8] or other serious haemorrhage (TIMI 9A).[9] The results of GUSTO IIb, a continuation of GUSTO IIa with a lower dose of hirudin, were mixed and did not suggest a benefit at 30 days.[10]

Whether hirudin truly has no advantage over heparin or the dose used in GUSTO IIb was too low or other variables are involved is being evaluated in the OASIS trial. In an OASIS pilot study, which compared

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Table 1 Clinical outcomes in trials of treatment of acute ischaemic syndromes with platelet glycoprotein IIb/IIIa inhibitor abciximab compared with control (heparin). All values are percentages

	EPIC[2 3]		CAPTURE[4]		EPILOG[5]	
Outcome at 30 days follow up	Abciximab (n=708)†	Control (n=696)	Abciximab (n=630)†	Control (n=635)	Abciximab (n=935)†	Control (n=939)
Primary end point‡	8.3	12.8**	11.3	15.9*	5.2	11.7**
Death	1.7	1.7	1.0	1.3	0.3	0.8
Myocardial infarction	5.2	8.6*	4.1	8.2**	3.7	8.7**
Urgent or emergency coronary angioplasty	0.8	4.5**	4.5	6.6	1.2	3.8**
Major bleeding	14	7**	3.8	1.9*	2.0	3.1

*P<0.05, **P<0.01. †Data presented for most effective treatment regimen. ‡Composite end point of death, myocardial infarction, and urgent intervention.

two doses of hirudin (both higher than that in GUSTO IIb) with heparin, the effects on cardiovascular death, new acute myocardial infarction, or refractory angina at seven days were encouraging.[11] However, when the study treatment was stopped the number of ischaemic events increased in the group receiving the lower dose of hirudin after about 24 hours and in the group receiving the higher dose after about five days. Examination of the clotting parameters suggested the presence of a rebound phenomenon, which could perhaps be avoided with continued anticoagulation treatment.[11] The OASIS trial therefore uses a slightly higher dose of hirudin than in GUSTO IIb (or standard heparin), and before this treatment is stopped patients are randomised to oral warfarin anticoagulation treatment.

If it is proved safe and efficacious, the continued suppression of the coagulation parameters, plus antiplatelet treatment with the glycoprotein IIb/IIIa inhibitors, may represent a clear advantage over the current treatment with aspirin, with or without heparin.

Primary coronary angioplasty

An increasingly common practice in some centres is to use primary coronary angioplasty in acute myocardial infarction. This is driven by the generally accepted concept of the "open artery hypothesis," which suggests that early opening of the artery responsible or related to the region of myocardial necrosis reduces the risks of mortality and morbidity. In primary coronary angioplasty, the patient is brought directly to the cardiac catheterisation laboratory for coronary angioplasty without benefit of thrombolysis.[12–14] Two moderately sized trials, both enrolling over 300 patients with acute myocardial infarction, have reported significant reductions in short term mortality.[13 14] A systematic overview, conducted on 8496 patients in seven small trials of primary coronary angioplasty and in 16 trials in which coronary angioplasty was administered after thrombolysis, concluded that primary coronary angioplasty may be more beneficial than thrombolysis in some, but not all, circumstances.[12] In practice, primary coronary angioplasty is of limited application since the procedure can be carried out only in centres where the necessary staff and equipment are available 24 hours a day.

Chronic coronary artery disease

New developments in the treatment of chronic coronary artery disease include platelet IIb/IIIa inhibition, intracoronary stenting, and lipid lowering therapy.

Platelet IIb/IIIa inhibition

This has been discussed above. One agent, abciximab, has been clearly shown to be beneficial in a randomised, double blind trial of 2099 patients undergoing coronary angioplasty or atherectomy for severe unstable angina, evolving acute myocardial infarction, or high risk coronary morphology.[2 3] Results from this and other trials are consistently encouraging (table 1) and suggest that platelet IIb/IIIa inhibition can prevent abrupt closure after coronary angioplasty and reduce the need for subsequent coronary vascularisation. The disadvantage is that there is a small excess risk of serious bleeding with this treatment, and there may be other adverse effects as yet unknown.

Intracoronary stenting

This procedure is a high technology innovation in which a balloon-expandable, stainless steel tube is implanted at the site of a coronary lesion. The stent was developed initially to treat acute or threatened vessel closure after coronary angioplasty. Several studies have shown that stenting is feasible in most cases, and this procedure has resulted in impressive reductions in serious complications with coronary angioplasty.[15 16] Primary stenting in conjunction with coronary angioplasty is now being increasingly used to prevent restenosis in patients who do not have acute or threatened vessel closure, and this has been boosted by encouraging results from two randomised trials (table 2).[17 18]

Antiplatelet therapy seems to offer greater efficacy and safety in preventing the major problems of stent thrombosis and occlusion than the alternative treatment with intensive anticoagulation.[19] Similar conclusions can be drawn from the EPIC trial.[2 3] The new, heparin bonded stent is being tested in the observational BENESTENT II study and the randomised TOSCA trial.

Despite the relative lack of information on short term efficacy and long term outcomes, stents are increasingly being used. Although this practice seems to reduce the need for bypass surgery, the long term consequences are not clear.

Lipid lowering treatment

With the introduction of a new class of highly effective and easily tolerated drugs, the hydroxymethyl glutaryl coenzyme A reductase inhibitors, lipid lowering treatment in secondary and, to some extent, primary prevention is becoming more practical. Although there is a clear recognition of the central role of elevated serum cholesterol concentrations in the development

of coronary atherosclerosis, until recently cholesterol lowering clinical trials that showed beneficial reductions in cardiovascular events and mortality had been exclusively carried out in high risk patients with raised cholesterol levels. Little information has been available on the effects of cholesterol lowering treatment in patients with normal or mildly elevated levels.

Three secondary prevention trials[20–22] and a primary prevention trial of high risk subjects[23] have addressed these issues recently (table 3). The secondary prevention 4S trial showed, for the first time, that cholesterol lowering treatment does reduce total, as well as cardiac, mortality.[20] The CARE[21] and Post-CABG trials[22] further showed the safety and efficacy of reducing total cholesterol and low density lipoprotein cholesterol concentrations to levels that had been regarded by some as potentially harmful because of the so called J curve phenomenon. Altogether, data from these trials conclusively confirm that long term cholesterol lowering is safe and beneficial, even in patients with normal cholesterol concentrations.

Other treatments

Equally intriguing, but not proved conclusively, is the anti-ischaemic role of angiotensin converting enzyme inhibitors. These drugs are known to have several potentially beneficial protective effects on cardiac and vascular function, but whether these will translate into clinically useful effects is only now being tested in several large randomised trials such as the HOPE trial. Another potentially useful approach, again studied in the HOPE trial, is anti-oxidant therapy (vitamin E), which is based on the pathophysiological concept of lipid oxidation and atherogenesis.

Congestive heart failure

Despite the progress made in managing congestive heart failure, particularly with angiotensin converting enzyme inhibitors, morbidity and mortality associated with congestive heart failure have not changed greatly in the past two decades. Recent advances include completion of clinical trials on digitalis, other positive inotropic drugs, and β blockers.

Digitalis

Although the clinical use of digitalis is long established, its safety and efficacy in reducing mortality were only recently addressed in a large (7788 patient) placebo controlled, randomised clinical trial by the Digitalis Investigation Group (DIG) Investigators.[24] Mortality did not differ between the groups given active treatment and placebo (34.8% *v* 35.1%). There was, however, a slightly decreased risk of death attributed to worsening heart failure in the digoxin treated group compared with the placebo group (11.6% *v* 13.2%, $P = 0.06$) and fewer hospitalisations due to heart failure in the digoxin group (26.8% *v* 34.7%, $P < 0.001$). An ancillary trial of patients with presumed diastolic dysfunction gave results consistent with those of the main trial for the primary combined endpoint of death or hospitalisation due to worsening heart failure.[24]

Table 2 Clinical outcomes in trials of treatment of coronary artery disease by intracoronary stenting plus coronary angioplasty compared with coronary angioplasty alone. Values are percentages unless stated otherwise

	BENESTENT[17]		STRESS[18]	
Outcome	Stenting plus angioplasty (n=259)	Angioplasty alone (n=257)	Stenting plus angioplasty (n=205)	Angioplasty alone (n=202)
Angiographic success	96.9	98.1	99.5	92.6**
Procedural success	92.7	91.1	96.1	89.6*
At follow up:				
Minimum lesion diameter (mm)	1.82	1.73	1.74	1.56**
Restenosis	22	32*	31.6	42.1*
Death	0.8	0.4	1.5	1.5

*P<0.05, **P<0.01.

While the DIG trial may be disappointing to some because of the lack of a clear difference, the findings are important. They confirm that there are no long term safety concerns when digitalis is used to improve exercise tolerance and quality of life. It also reduces hospitalisation due to worsening heart failure. Symptomatic patients with preserved left ventricular function derive benefits similar to those experienced by patients with poor systolic function.

Other positive inotropic agents

Several other positive inotropic drugs have been tested in clinical trials recently, but practically all of these had to be stopped prematurely because of excess mortality in the groups of patients receiving the active agents. Unlike digitalis, these drugs—including milrinone,[25] enoximone,[26] and ibopamine[27]—demonstrate positive inotropism through stimulation of adrenergic receptors or the post-receptor pathway, but they are associated with increased frequency of ventricular arrhythmias and excess mortality.

Neurohormonal blockade

The concept of neurohormonal blockade in congestive cardiac failure, associated with activation of the sympathetic and renin-angiotensin neurohormonal systems, is important both prognostically and therapeutically. Angiotensin converting enzyme inhibition, by blocking the effects of renin-angiotensin activation, has been found to be highly effective in reducing mortality in congestive heart failure and reducing disease progression.[28 29] Drugs that selectively block the effects of angio-

Table 3 Clinical outcomes in trials of lipid lowering treatment of patients at high risk of cardiovascular events. Values are reductions in relative risk (95% confidence interval)

Outcome	4S[20] (simvastatin *v* placebo) (n=4444)	WESCOP[23] (pravastatin *v* placebo) (n=6595)	CARE[21] (pravastatin *v* placebo) (n=4159)	Post-CABG[22] (lovastatin 40 mg/day *v* lovastatin 2.5 mg/day) (n=1351)
Non-fatal acute myocardial infarction	37 (27 to 46)***	31 (15 to 45)***	23 (4 to 39)*	–12 (–79 to 30)
Death from coronary heart disease	42 (27 to 54)***	28 (–10 to 52)	20 (–5 to 39)	—
Death from cardiovascular disease	35 (20 to 40)***	32 (3 to 53)*	15 (–11 to 35)	–10 (–104 to 41)
Death from non-cardiovascular disease	5 (–41 to 37)	11 (–28 to 38)	11 (–22 to 35)	34 (–48 to 71)
Death from all causes	30 (15 to 42)***	22 (0 to 40)	9 (–12 to 26)	9 (–49 to 44)

*P<0.05, ***P<0.001.

tensin II at the receptor levels (A-II receptor antagonists) have been developed, and some are being tested. Preliminary data on one such drug, losartan, suggest that it or this class of drugs can improve symptoms and perhaps reduce mortality in congestive heart failure, as suggested by the results of the ELITE study.[30] Other studies are ongoing.

β blockade

Blockade of the chronically activated sympathetic system in congestive heart failure is the basis for the use of β blockers, despite the traditional view that β blockers are contraindicated in this condition. Again, preliminary data are promising.[31 32] Although sympathetic activity is essential in acute heart failure in order to maintain adequate cardiac output and perfusion pressure of the vital organs, chronic sympathetic stimulation, as in congestive heart failure, produces deleterious effects. While small studies of β blockade in congestive heart failure have suggested beneficial results,[31 32] the development of a new β blocker with α_1 blocking effect, carvedilol, has led to a greater impetus in testing and using β blockers in congestive heart failure.[33] The US Carvedilol Heart Failure Group has reported the experience of 1094 patients with congestive heart failure who were enrolled in a double blind, placebo controlled, stratified study: the group treated with carvedilol showed reductions in mortality at 6 months compared with the placebo group (3.2% *v* 7.8%, $P<0.001$), in hospitalisation for cardiovascular causes ($P=0.036$), and in the combined endpoint of hospitalisation or death ($P<0.001$).[33]

Although promising, the number of deaths is small because of the moderate size and short follow up of the trial. Thus, there is still a degree of uncertainty that needs further study. Should further evidence confirm these findings, however, it will prompt acceptance of the concept of β blockade in congestive heart failure and encourage the use of β blockers. In practice, care is needed to start treatment with β blockers at low doses and gradually titrate the dose upwards in order to avoid sudden haemodynamic shifts and symptomatic deterioration caused by the abrupt β blocking effects on heart rate and blood pressure. This deterioration may occur even in those patients who will eventually benefit from this treatment.

Sudden cardiac death

Two recent developments in the prevention of sudden cardiac death are amiodarone and implantable defibrillators.

Amiodarone

Although amiodarone is generally accepted as highly effective in reducing risks of sudden cardiac death in patients at very high risk, routine use of this drug in subsets of patients at high risk after acute myocardial infarction or with congestive heart failure is being debated. Meta-analyses of data from small clinical trials of amiodarone in such patients suggested a beneficial effect,[34] but data from two recent trials of patients with congestive heart failure were conflicting (for details see table on *BMJ* website at www.bmj.com).[35 36] It was hoped that the Canadian (CAMIAT)[37] and European (EMIAT)[38] trials of amiodarone in patients at high risk after acute myocardial infarction could settle the uncertainty. While both studies showed that amiodarone significantly reduced arrhythmic deaths or non-fatal arrhythmic events, they provided no conclusive data on overall or cardiac mortality (for details see table on *BMJ* website at www.bmj.com).

Implantable cardioverter defibrillators

These devices deliver an electric shock to the heart when ventricular fibrillation or tachycardia occurs. They are increasingly being touted as efficacious and cost effective initial treatment for preventing sudden death in patients with malignant ventricular tachyarrhythmias.[39] Although much of the evidence for this benefit comes from uncontrolled observational studies, some trial data are now available. Preliminary data from the small randomised CASH and NCES trials are promising.[39 40] The MADIT study also showed that patients treated with implantable cardioverter defibrillators had better survival rates than those treated conventionally with drugs.[41] While the preliminary data are promising, we must await results from the recently terminated AVID trial and the ongoing CIDS, MUSTT, and other trials for further answers.

Implications

It is generally assumed that results of clinical trials are automatically translated into improved patient care and outcomes. An important area of research is investigating how much these trial results have affected practice. Data from North America and Europe suggest that proved treatments such as β blockers, aspirin, thrombolytic drugs, angiotensin converting enzyme inhibitors, and lipid lowering drugs are being used much less frequently than expected, and reasons for such low rates remain unclear. Improved use of these proved treatments would probably improve patient outcomes to a degree rivalling those expected from the latest technological breakthroughs.

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Lesson of the week

Haemochromatosis as an endocrine cause of subfertility

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Haemochromatosis is well established as a cause of infertility in both men and women, usually because iron deposition in the pituitary or the gonads leads to hypogonadism. As haemochromatosis is a fairly common disorder it should be considered when subfertility from an endocrine disorder is being investigated. We report on two related patients being investigated for subfertility in whom haemochromatosis was diagnosed only when one of them became diabetic.

Case reports

Case 1

A 32 year old man was referred to a tertiary referral centre for subfertility. He complained of failure of ejaculation and limited facial hair growth. Examination revealed female type and scanty axillary and pubic hair, soft testes (volume 8 ml), full visual fields, and a reduction in his sense of smell. Investigation confirmed a male karyotype. Testosterone, follicle stimulating hormone, and luteinising hormone concentrations were undetectable even after gonadotrophin releasing hormone had been given intravenously. Thyroid stimulating hormone and prolactin concentrations and a computed tomogram of the head were normal. Initially he was treated with testosterone esters and then chorionic gonadotrophin and menotrophin. Subsequently his partner had two successful pregnancies.

Four years later he became diabetic and was referred to our hospital clinic. He was noted to be pigmented. Haemochromatosis was confirmed by an iron saturation of 93.4%, a ferritin concentration of 1036 µg/l, and typical pre-cirrhotic changes in a liver biopsy specimen.

Haemochromatosis should be considered and iron studies performed when investigating endocrine causes of infertility

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Case 2

The family of the patient in case 1 was screened for haemochromatosis. His 34 year old sister had an iron saturation of 99.9% and a ferritin concentration of 2130 µg/l. A liver biopsy confirmed haemochromatosis and established nodular cirrhosis.

At 24 years of age she had presented with amenorrhoea after stopping taking the contraceptive pill. Her gonadal function at that time was normal. Five years later she was still amenorrhoeic. Luteinising hormone and follicle stimulating hormone concentrations were undetectable. Prolactin and thyroid stimulating hormone concentrations were normal. Dye testing and examination under anaesthesia showed a small uterus and patent tubes. She was referred to a tertiary referral centre, but despite further investigation and treatment she did not become pregnant.

Discussion

Haemochromatosis is arguably the most common genetic disorder in Europeans.[1] The homozygote frequency is 0.3-0.5% and the carrier frequency 6.7-10%.[2] In prospective epidemiological studies of the general population the frequency of haemochromatosis was 0.37%, with a gene frequency of 6.1% and a heterozygote frequency of 11.5%.[3] Hypogonadism caused by haemochromatosis may be due to hypothalamic,[4] pituitary,[5] or gonadal dysfunction or to a combination of these.[6–8] Iron deposition at these sites has been seen at biopsy and on magnetic resonance imaging.[9 10]

An early diagnosis of haemochromatosis is important as aggressive venesection can restore hypothalamic-pituitary-gonadal[4 11] and reproductive[12] function. In older patients with more established disease venesection does not restore hypothalamic-pituitary-gonadal function.[13] Testosterone may, however, restore potency and libido in men,[14] and gonadotrophin treatment may restore fertility in women.[15]

Young patients presenting with endocrine abnormalities have a poor prognosis, but early diagnosis and prompt iron depletion may improve the prognosis with regard to other organ damage.[16] Survival analysis has shown that in the absence of cirrhosis or diabetes venesection leads to a normal life expectancy.[3]

Despite its frequency and effect on the endocrine system, haemochromatosis has attracted surprisingly little attention in endocrinology[17 18] and fertility textbooks,[19] although it is mentioned in the larger general medical textbooks.[20 21] A normal ferritin concentration is needed to confirm a diagnosis of adult onset idiopathic hypogonadotrophic hypogonadism.[22] Haemochromatosis should be considered when subfertility from an endocrine disorder is being investigated.

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A shaggy dog story

Caffeine and canine

I felt tired and hassled; there was still a long list of patients ahead of me. I was being interrupted for the third time. This distraction on a Friday afternoon was not welcome. The golden retriever nudged me once again. I realised that the only way to complete the consultation was to move my attention from the patient to her guide dog. I asked for the dog's name. He was called Charlie. I patted him on his head, hoping then to be able to concentrate on my patient again. Again I was being nudged, this time far more impatiently.

"What is it that he wants?" I eventually gave in.

"He usually gets a bowl of tea in this clinic," was the reply.

I went to ask the nurse for some tea. She already knew that the dog took his in a bowl with milk, no sugar. The thought of tea cheered me up and I seized on the opportunity to ask for an additional two cups for the patient and myself.

Content for the next few minutes we all had our tea before we continued where we had left off. Thank you, Charlie.

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from a patient or a relative if an identifiable patient is referred to.