Recent advances in percutaneous coronary intervention

Following development of the Seldinger technique of femoral cannulation in 1953 and selective coronary angiography in 1958, invasive cardiology has seen many changes. In 1977, Gruentzig introduced balloon dilatation of the coronary artery, which revolutionized this field. Since then advances have included use of an intracoronary stent, introduction of glycoprotein IIb/IIIa inhibitors, use of platelet adenosine diphosphate receptor antagonists in combination with aspirin, intracoronary brachytherapy and drug-eluting stents. In the near future cardiovascular gene therapy and myocardial cell transplantation could prove major advances.

This editorial will discuss the new technologies and the evidence which surrounds them.

MYOCARDIAL REVASCULARIZATION

Coronary stenting

The Achilles heel of percutaneous coronary intervention (PCI) has been abrupt vessel closure during the procedure (now solved with the use of intracoronary stents) and clinical or angiographic restenosis. Over 80% of PCI procedures involve stents and randomized trials have shown the benefit of stents in reducing the incidence of emergency surgery and restenosis in circumscribed lesions. The BENESTENT trial showed the superiority of stenting over balloon angioplasty with higher procedural success and lower restenosis rates in stented patients.

Adjuvant pharmacology

The EPILOG (1997) trial has shown that abciximab combined with weight-adjusted heparin reduces the risk of acute ischaemic complications in patients undergoing balloon angioplasty. There was no increased bleeding risk and risk reduction was sustained at 1 year.

The EPISTENT (1998) trial showed that use of abciximab either with a stent or balloon angioplasty reduced the incidence of 1 month composite of myocardial infarction (MI), death and revascularization rate from 10.8% to 5.3%. The most profound benefit was seen in the diabetes subgroup.

Multivessel disease

Trials like BARI (1996) and EAST (King et al, 2000) have established that (perhaps in the absence of diabetes) death and recurrent MI are similar in patients undergoing multivessel revascularization using PCI or coronary artery bypass graft surgery. However, the PCI arms generally have an increased need for repeat intervention. This is decreasing as PCI technology improves and is reported as 21% at 1 year in the ARTS trial, secondary to stents, use of abciximab and aggressive risk factor management.

The ARTS II trial will investigate the use of drug-eluting stents in multivessel disease and the CARDIA trial is investigating the effect of abciximab, bare and drug-eluting stents in diabetics with multivessel disease.

Treatment of in-stent restenosis

Restenosis rates following coronary stenting vary from 10 to 58% depending on the lesion characteristics and patient subset. In-stent restenosis (ISR) remains a challenge for interventional cardiologists. Vascular brachytherapy is the only clinically proven treatment for ISR, as shown by the SCRIPPS trial. At 3-year angiographic follow-up significant differences in restenosis rate persisted.

The START trial was a multicentre randomized beta radiation trial in ISR which showed a reduction in 8-month target vessel revascularization from 24 to 16%. Similar conclusions were drawn from other beta radiation trials.

Clinical efficacy of gamma radiation is sustained at long-term follow up of 5 years with 48% reduction in target lesion revascularization (TLR). Late stent thrombosis occurred in around 6% of patients in gamma trials, attributed to use of new stents and short duration of clopidogrel treatment. Current practice is to use clopidogrel for 1 year after brachytherapy. Recent trials found an equal incidence of late stent thrombosis in radiation and placebo arms.

Drug-eluting stents

Combining a stent with local delivery of drugs like rapamycin and paclitaxel to prevent restenosis in de-novo lesions has been substantiated by landmark trials like RAVEL (Regar et al, 2002).

The RAVEL trial compared the rapamycin-coated Cordis Velocity stent with a bare Velocity stent. The results were remarkable with a 0% restenosis and 3.4% clinical TLR rate in the rapamycin-coated stent compared to 26% and 13.6% in the bare metal stent.

The ELUTES trial evaluated the safety and efficacy of four doses of Taxol-coated stent against an uncoated Cook V-Flex™ Plus stent (Angiotech Pharmaceuticals, Vancouver, Canada). At 6-month follow up, quantitative angiography showed a clear dose relationship, with per cent diameter stenosis ranging from 34% for the bare stent, to 14–33% for descending dose densities of the paclitaxel-coated stents.

TAXUS II trial results were reported at a TransCatheter Therapy meeting in Washington. This looked at the effect of slow and moderate release (SR and MR) Translute™ polymer-based Taxol-eluting stents (NIR™ Conformer stents, Boston Scientific Corp, La Garenne Colombes, France). A total of 526 patients were treated with a 15 mm stent. The significant outcome of this trial was decrease in in-stent net volume obstruction by more than 60% in both SR and MR stents.

Advances in PCI in ACS

There is increasing use of early PCI in high-risk ACS. In the TACTICS-TIMI

18 trial combined use of tirofiban and early PCI resulted in extremely low incidence of death and MI at 30 days.

The CURE (Yusuf et al, 2001) trial showed the benefit of clopidogrel within 24 hours of presentation with an ACS. At 12-month follow up the composite of cardiovascular death, MI and stroke occurred in 11.5% of patients assigned to placebo and 9.3% of those assigned to clopidogrel. However, there was no significant difference in incidence of non Q-wave MI. The major benefits were observed at 30 days with small additional benefits over the next average 8 months.

Cardiovascular gene therapy

Gene therapy is being assessed for therapeutic angiogenesis in stable angina patients and to a lesser extent in restenosis following coronary intervention. Phase I–III clinical trials are looking into gene transfer product as a therapeutic agent, using vascular endothelial growth factor, fibroblast growth factor (FGF) and hypoxia inducible factor 1. In the AGENT trial 60 patients with mild to moderately severe stable angina suitable for revascularization randomly received five intracoronary doses of Ad5-FGF4. This trial was found to be safe, with a 20–30% improvement in exercise tolerance. Larger multicentre trials are ongoing.

This field is still in its infancy and issues such as safety, ethical consideration, availability of regulatable gene therapy vectors, pharmacokinetics and pharmacodynamics of gene products and delivery modalities need further clarification and research.

IMPROVING CARDIAC FUNCTION

Myocardial cell transplantation

Cardiac failure is a major medical problem. Angiotensin-converting enzyme inhibitors, β-blockers, cardiac resynchronization therapy and heart transplant are established modes of management, but a sizable number of patients remain symptomatic on these therapies. Cell transplantation as a therapeutic strategy is the focus of active research. Skeletal myoblast, fetal cardiomyocyte, embryonic stem cell, autologous bone stromal cell and endothelial progenitor cell using different delivery methods are being investigated. Controversy exists as to the best cell type, delivery method, immunogenicity, ethical consideration, efficacy and safety concerns. Phase I clinical trials have started and it will be some years before the results are known.

CONCLUSION

Advances in development of potent newer antiplatelet agents and stents have made PCI a safer, more predictable and durable treatment. The re-intervention rate following PCI is steadily falling, making this an attractive option for most patients with obstructive coronary disease. Novel techniques may well become available in the next few years to treat patients percutaneously who are not amenable to PCI. HM

KEY POINTS

- Advances in percutaneous treatment of occlusive coronary artery disease includes better stents with improved design, brachytherapy and drug-eluting stents.
- Drug-eluting stents reduce the incidence of restenosis significantly and treat complex and multivessel lesions.
- Brachytherapy remains the only proven effective treatment for in-stent restenosis.
- Cardiovascular gene therapy may be available in the near future for therapeutic angiogenesis and treatment for in-stent restenosis.
- Phase I clinical trials have started for myocardial cell transplantation with skeletal myoblast and bone marrow-derived pluripotent stem cells. This may be used to treat ischaemic and various other cardiac muscle diseases.

Trial acronyms

AGENT = Angiogenic gene therapy trial in patients with stable angina
ARTS = Arterial Revascularization Therapies Study
BARI = Bypass Angioplasty Revascularization Investigations
BENESTENT = BElgium Netherlands STENT
CARDia = Comparing balloon angioplasty with bypass surgery in patients with diabetes
CURE = Clopidogrel in Unstable angina to Prevent Recurrent ischemic Events
EAST = Emory Angioplasty versus Surgery Trial
ELUTES = EvaLUation of pacliTaxel-Eluting Stent
EPILOG = Evaluation in PTCA to Improve Long-term Outcome with abciximab GPIIb/IIIa blockade
EPISTENT = Evaluation of Platelet IIb/IIIa Inhibitor for STENTing
RAVEL = Randomised study with the sirolimus coated BX Velocity™ balloon expandable stent in the treatment of patients with de novo native coronary artery Lesions
SCRIPPS = Scripps Coronary Radiation to Inhibit Proliferation Post Stenting
START = Stents and Radiation Therapy
TACTICS = Treat angina with Aggrastat and determine cost of therapy with invasive or conservative strategy
TAXUS = Taxol coated stents trials

Arun Patil/Martyn Thomas

Honorary Specialist Registrar in Cardiology and Interventional Fellow/Consultant Cardiologist

Department of Cardiology

Kings College Hospital

London SE5 9RS

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