

Recent Advances and Future Trends in Cardiology

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Abstract: The field of cardiac sciences has seen a lot of new developments in the last few years. We have better drugs to treat life threatening diseases. There have been significant changes in cardiology practice because of exciting new developments in the last few years. We have more potent drugs, development of new diagnostic techniques, evolution of stent technology with more complex coronary anatomy being treated percutaneously. New valve therapies for high risk patients have emerged and likely to evolve further. Advances in technology have changed the way cardiology is practiced. This article dwells upon these recent advances and what we can expect in future.

INTRODUCTION

The field of cardiac sciences has seen a lot of new developments in the last few years. We have better drugs to treat life threatening diseases. Non invasive cardiology has benefitted from ever improving technology. Invasive cardiology has not lagged behind with the most exciting developments occurring in the field of percutaneous valve therapies which continue to evolve. Gene and stem cell therapy have also shown progress. These trends give us a glimpse into the future which appears very promising.

RECENT ADVANCES

1. Clinical Cardiology

Clinical cardiology is never static. Lot of effort is put on development of better drugs. The most recent has been the approval and availability of newer thienopyridine prasugrel which is used in treatment of acute coronary syndromes for those proceeding to percutaneous interventions. There is a significant reduction in cardiovascular deaths, myocardial infarctions, stroke, stent thrombosis and urgent target vessel revascularization, but with increased risk of major life threatening bleeds¹. For management of angina we have newer drugs ivabridine and ranolazine as add on therapy. Dabigatran an oral anticoagulant is a very exciting addition in stroke and embolism prevention in patients with atrial fibrillation². The fact that it does not require INR monitoring as compared to warfarin makes it a more attractive alternative besides being superior to warfarin in reducing stroke or peripheral embolic events³. Less risk of hemorrhage is an added attraction. Newer antiarrhythmics have become available which includes drugs like dronedarone which is indicated in prevention of recurrence of atrial fibrillation. Compared to amiodarone the incidence of pulmonary, hepatic and thyroid related side effects is almost negligible⁴. Among statins post Jupiter trial rosuvastatin has been approved for prevention of coronary events in a new subset of patients who were not initially considered candidates for statin therapy by using hsCRP as a stratification tool⁵.

2. Interventional Cardiology

There have been exciting developments in the field of interventional cardiology too. On catheterization table assessment of lesion severity using FFR has gained prominence lately. In a recent analysis from FAME trial⁶ the authors concluded that coronary angiography is an inappropriate tool to identify ischemia producing stenosis as detected by FFR and this discrepancy is present not only from 50%-70% range but also in 70%-90% range. FFR represents the maximum achievable blood flow after challenge with adenosine to myocardium supplied by stenotic artery as a fraction of normal maximum value. A value of less than 0.75 identifies stenosis with inducible ischemia. The measurement is done by pressure wire⁶. Fig 1 shows FFR assessment of stenosis severity. This has made multi vessel disease angioplasty much more

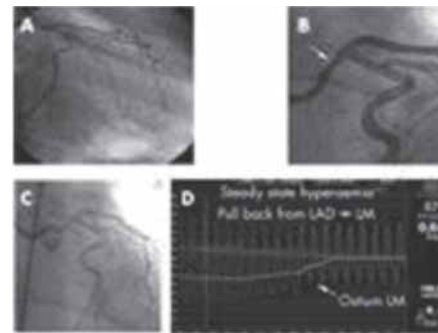


Fig 1: FFR Assessment

evidence based and unnecessary stenting in physiologically normal lesions is avoided.

The most important of recent trials have shown that coronary angiography and revascularisation within few hours after thrombolysis is safe and confers mortality benefit⁷. Hence treatment paradigms may change in future with patients being thrombolysed at a non PCI centre and then immediately shifted to a competent centre for immediate coronary angiography and revascularisation versus ischemia guided therapy⁸.

Recently lot of interest has been generated by concept of thrombus aspiration in primary percutaneous intervention. In a Bayesian meta-analysis, adjunctive thrombectomy improves early markers of reperfusion but does not substantially effect 30-day post-MI mortality, reinfarction, and stroke. The use of aspiration thrombectomy devices is not associated with a reduction in post-MI clinical outcomes. Thrombectomy is one of the rare effective preventive measures against no-reflow⁹. Fig 2 shows results of thrombectomy in acute MI.

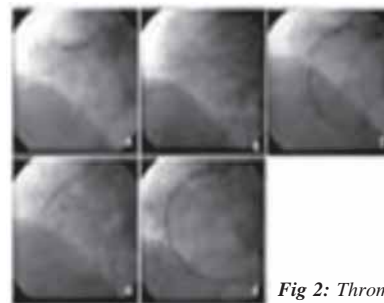


Fig 2: Thrombectomy

Local drug delivery viz Drug Eluting Balloons (DEB) have generated lots of interest lately. Rationale for the development of DEB derives mainly from the limitations of Drug Eluting Stents (DES). Nonstent-based local drug delivery using DEB maintains the antiproliferative properties of DES, but

without the limitations of DES. Moreover, DEB may be used in subsets of lesions where DES cannot be delivered or where DES do not perform well, such as in tortuous vessels, small vessels¹⁰, or long diffuse calcified lesions, which can result in stent fracture; or perhaps when scaffolding obstructs major side branches or in bifurcated lesions¹¹. The discovery that sustained drug release is not a requisite for the long-lasting antiproliferative effect of paclitaxel and the fact that the uptake of paclitaxel by vascular smooth muscle cells is rapid and can be retained up to 1 week, resulting in prolonged antiproliferation, have given rise to the concept of local paclitaxel delivery through coated balloons¹¹. The most appealing indication for paclitaxel-eluting balloons would be for the treatment of ISR¹². Fig 3 shows drug eluting balloon.

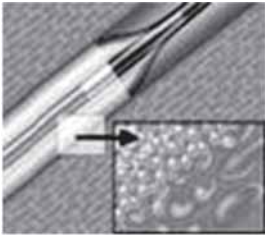


Fig 3: Drug eluting balloon

Additional potential advantages of DEB include (a) homogenous drug transfer to the entire vessel wall; (b) rapid release of high concentrations of the drug sustained in the vessel wall no longer than a week, with little impact on long-term healing; (c) absence of polymer could decrease chronic inflammation and the trigger for late thrombosis; (d) absence of a stent allows the artery's original anatomy to remain intact, notably in cases of bifurcation or small vessels, thereby diminishing abnormal flow patterns; and (e) with local drug delivery, overdependence on antiplatelet therapy could be curtailed¹¹.

Percutaneous coronary intervention (PCI) with bioabsorbable stents has created interest because the need for mechanical support for the healing artery is temporary, and beyond the first few months there are potential disadvantages of a permanent metallic prosthesis. Biodegradable stents contain a biodegradable polymer or are completely biodegradable. There are around twelve stents with biodegradable polymer. LEADERS STUDY¹³, an all comers trial, showed that biolimus eluting stent with a biodegradable polymer was non inferior when compared to sirolimus eluting stent with durable polymer at nine months, as regards safety, efficacy and angiographic outcomes. Potential advantages of having a completely biodegradable stent is that the stent would disappear from the treated site reducing or abolishing late stent thrombosis, improving lesion imaging with computed tomography or magnetic resonance, facilitation of repeat treatments (surgical or percutaneous) to the same site, restoration of vasomotion, and freedom from side-branch obstruction by struts and from strut fracture-induced restenosis. Some of completely biodegradable stents in various stages of development or trials are Igaki-Tamai Bioabsorbable Stent, BVS Everolimus-Eluting Bioabsorbable PLLA Stent, REVA Bioabsorbable Stent. Fig 4 shows pathological appearance with biodegradable stent.

Treatment of left main coronary stenosis by percutaneous means continues to evolve further. At one time a truly surgical domain is now increasingly

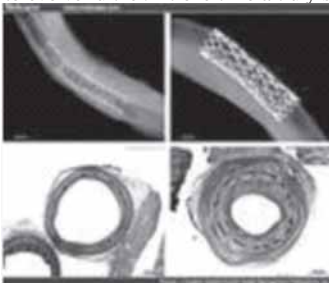


Fig 4 : Biodegradable stents

being treated with stents. In the landmark SYNTAX trial¹⁴ a subgroup of 705 patients with unprotected left main coronary artery disease (ULMCA) had similar rates of MACE, cardiac death, and MI. Stroke was significantly lower in PCI compared to CABG. However there was increased need for repeat revascularisation in the PCI subgroup. The MAIN compare¹⁵ trial also validated the findings of SYNTAX trial. The registry showed at 5 years there was no significant long term difference in death, MI or stroke but there was increased repeat revascularisation in the PCI group. However patient selection is the key to success. SYNTAX¹⁴ and EUROSCORE¹⁶ systems have emerged as important tools to risk stratify patients. A SYNTAX score of more than 34 indicates patient would be better off with CABG than with PCI.

Intervention for peripheral vascular disease has also improved with further expertise. CREST trial a head to head comparison of carotid endarterectomy with carotid stenting for carotid stenosis has shown that stenting is as good as endarterectomy and perhaps in certain patients those under seventy may be better¹⁷. Patients with symptomatic or asymptomatic carotid stenosis were randomized to undergo carotid-artery stenting or carotid endarterectomy. The primary composite end point was stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization. For 2502 patients over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary end point between the stenting group and the endarterectomy group (7.2% and 6.8%, respectively; hazard ratio with stenting, 1.11; 95% confidence interval, 0.81 to 1.51; P=0.51).

Till now management of valvular heart disease was mostly a surgical domain. Among the valve afflictions, valvular mitral regurgitation (MR) remains largely the purview of surgery. Recently, the potential for less invasively replicating these successful surgical procedures without the need for thoracotomy or cardiopulmonary bypass has generated considerable interest. For the most part, these new approaches are modeled after established surgical strategies. The Mitraclip device (Fig 5 Evalve, Inc, Menlo Park, Calif) has proven relatively safe and often effective. Using a multiaxial transeptal catheter system, a metallic clip is used to grasp and approximate the free edges of the 2 leaflets. The ongoing EVEREST registry includes EVEREST I and nonrandomized (roll-in) EVEREST II patients. Clip implantation was successful in 89% of 104 patients with MR grade reduced to ≥ 2 in 79 (76%)¹⁸. The type of valves suitable for such procedure would be those where the cause of regurgitation is because of annular dilatation as happens in many cases of ischemic MR. Annulus reduction techniques using rings inserted through coronary sinus encircling and hence reducing the annulus size are in various stages of development or trials¹⁹.



Fig 5: mitra clip

Surgical aortic valve replacement is the reference treatment standard for patients with symptomatic severe aortic valve stenosis. Despite the fact that the prognosis with medical management is poor, many patients do not undergo surgery because of an increased anticipated operative risk, driven by comorbidities such as severe obstructive pulmonary disease, porcelain aorta, etc²⁰. The results with balloon aortic valvuloplasty are beneficial in the acute phase with clinical improvements, but unfortunately only palliative and short lived²¹. Percutaneous aortic valve replacement (PAVR or TAVI) using stent-based prostheses has emerged as a promising new option in recent years and has been used by number of operators in different centers

with incremental success in line with procedural experience²². Initially starting with 22 French systems today, PAVR using the 18F CoreValve prosthesis. (Fig 6) is feasible and reliable in experienced hands with a high acute device success rate of about 97%. PAVR has been introduced to offer a safe treatment option for candidates in whom surgical aortic valve replacement is considered not to be safe, balancing perioperative operative risk versus the natural course of the disease/medical treatment. Therefore, mortality is the key safety parameter in all present PAVR studies. The results from recent PARTNER trial²³ are very encouraging. In this study 358 patients with severe aortic stenosis, whom surgeons considered not to be suitable candidates for surgery were randomized to standard therapy (including balloon aortic valvuloplasty) or transfemoral transcatheter implantation of a balloon-expandable bovine pericardial valve (sapien valve). The primary end point was the rate of death from any cause. At 1 year, the rate of death from any cause (Kaplan–Meier analysis) was 30.7% with TAVI, as compared with 50.7% with standard therapy (hazard ratio with TAVI, 0.55; 95% confidence interval [CI], 0.40 to 0.74; P<0.001. Among survivors at 1 year, the rate of cardiac symptoms (New York Heart Association class III or IV) was lower among patients who had undergone TAVI than among those who had received standard therapy (25.2% vs. 58.0%, P<0.001). The conclusion of study was that in patients with severe aortic stenosis who were not suitable candidates for surgery, TAVI, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular.

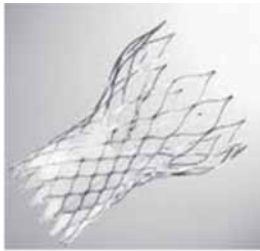


Fig 6: Core valve prosthesis

3. Stem Cell Therapy

Stem cell therapy as applied to cardiology has shown partial progress. A large number of patients with coronary artery disease experience angina with vessels that are not suitable for revascularization. The angina in so called end stage coronary artery disease is refractory to conventional medical therapy. Laboratory and preclinical studies have provided evidence for the safety and potential efficacy of autologous CD34+ stem cell therapies as treatment for angina. Clinical studies investigating intramyocardial transplantation of autologous CD34+ stem cells by catheter injection for patients with refractory angina show that this is safe and feasible. It remains unclear whether intracoronary infusion of CD34+ stem cells exerts beneficial effects in patients with angina as well. In a controlled clinical trial enrolling 112 patients²⁴ with refractory angina, no myocardial infarction was observed during intracoronary infusion. No serious adverse events occurred in either group. The reduction in the frequency of angina episodes per week 3 and 6 months after infusion was significantly higher in the treatment group (-14.6 ± 4.8 at 3 months and -15.6 ± 4.0 at 6 months) than in the control group (-4.5 ± 0.3 and -3.0 ± 1.2, respectively; p < 0.01). Other efficacy parameters such as nitroglycerine usage, exercise time and the Canadian Cardiovascular Society class also showed an improvement in the treatment group compared to the control group.

The REPAIR-AMI trial²⁵ involved 204 MI patients undergoing primary PCI following which some patients were randomized to receive bone marrow stem cells. The primary end point of this study was ejection fraction at four

months. This increased significantly more in the patients who received stem-cell infusions than in those given placebo infusions. Subgroup analysis further suggested that the benefit was greatest in patients suffering larger infarcts (those with lower ejection fractions at baseline) and those treated more than five days after their MI.

Role of stem cells in heart failure is also under evaluation. The star heart study²⁶ involved 391 patients with chronic heart failure following an MI experienced three to eight years previously. Of these patients, 191 accepted the stem-cell treatment while the other 200, who did not agree to the intervention, acted as controls. The therapy involved taking bone-marrow cells from the iliac crest and isolating mononuclear cells, which were cultivated, harvested, and then re administered via an intracoronary balloon catheter directly into the infarcted zone. Results at three months, 12 months, and five years after the bone-marrow-cell therapy showed significant improvement in left ventricular ejection fraction, cardiac index, exercise capacity, oxygen uptake, and left ventricular contractility. Controls, however, showed a deterioration in LV performance. Of particular note, there appeared to be a significant decrease in long-term mortality in the stem-cell-treated patients. Within a median follow-up time of 4.6 years, average mortality rate of 0.75% per year in treatment group compared to 3.68% in control groups. Table I shows current clinical approaches in stem cell therapy.

TABLE I. Current Clinical Approaches in Cardiac Stem Cell Therapy	
ABM injection (acute and chronic)	
• Transcatheter	
• Surgical	
ABM intracoronary infusion (acute)	
Stem cell mobilization/G-CSF (acute)	
Myoblast injection (chronic)	
• Transcatheter	
• Surgical	
ABM = autologous bone marrow; G-CSF = granulocyte colony stimulating factor	

Still it is very early to comment on how stem cell therapy will be incorporated into treatment protocols. It is something to look forward to.

4. Cardiac Imaging

Cardiac imaging has also undergone evolution especially for evaluation of coronary artery disease. Coronary CT angiography as per trials has an excellent negative predictive value but a suboptimal positive predictive value for stenosis in 50%-70% range due to overestimation²⁷. Additional functional testing using perfusion imaging is often necessary to assess physiological significance of these intermediate lesions. Recently concern has been raised regarding radiation exposure which can be minimized by ECG gating. The value of MDCT will be enhanced in future when left ventricular function and first pass myocardial perfusion can be evaluated²⁸. Fig 7 shows a representative coronary ct angiography.

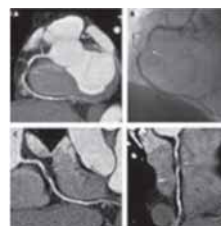


Fig 7: CT coronary angiography

FUTURE TRENDS

The future is always linked to the present. Among the technologies to be eagerly awaited the most important one is the availability and approval of completely biodegradable stents some of which are under development at present. The role of percutaneous intervention for left main stenosis may be accepted alternate to surgery in future but for that long term data is required. Another important advancement to look forward to is the refinement of trans aortic valve replacement hardware (presently 18 fr) and reduction in incidence of periprocedural strokes with further expertise. Stem cell therapy may be the answer to problem of left ventricular function recovery post primary intervention in acute myocardial infarction but needs to be proved conclusively in large scale trials.

CONCLUSION

The field of cardiology has undergone rapid changes in the last decade. We have more potent drugs, development of new diagnostic techniques, evolution of stent technology with more complex coronary anatomy being treated percutaneously. New valve therapies for high risk patients have emerged and likely to evolve further. Stem cells as always have been an area of active debate and research and continue to intrigue. It can be said that the future looks bright and there is much to look forward to.

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LITERATURE REVIEW

The incidence of renal artery stenosis in the patients referred for coronary artery bypass grafting

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Multivessel coronary disease or peripheral arterial disease is the clinical clue to diagnosis of renal artery stenosis (RAS). RAS is considered equivalent to coronary artery disease in terms of cardiovascular risk. In this study, we evaluated the incidence of RAS in the patients who were proposed to undergo coronary artery bypass grafting (CABG). Diagnostic evaluations of coronary arteriography and renal artery angiography were performed during the same procedure; the patients who were proposed for CABG in terms of CAD anatomy and clinical manifestation were enrolled. RAS was evaluated and a diameter stenosis of $\geq 50\%$ was considered as significant RAS; significant RAS patients were divided into five groups. The five groups of RAS were as follows: (1) unilateral RAS $\geq 50-70\%$, (2) unilateral RAS $\geq 70\%$, (3) bilateral RAS $\geq 50-70\%$, (4) one-renal-artery stenosis $\geq 50-70\%$, contralateral RAS $\geq 70\%$, and (5) bilateral renal artery stenosis $\geq 70\%$. A total of 151 patients were enrolled, and RAS ($\geq 50\%$ stenosis in either or both renal arteries) was identified in 47.02% (71/151) patients. Unilateral RAS $\geq 50-70\%$ was identified in 16.6% (25/151) patients, unilateral RAS $\geq 70\%$ in 4.6% (7/151) patients, bilateral RAS $\geq 50-70\%$ in 7.9% (12/151) patients, one-renal-artery stenosis $\geq 50-70\%$ and contralateral RAS $\geq 70\%$ in 7.9% (12/151) patients, and bilateral RAS $\geq 70\%$ was in 9.9% (15/151) patients. The incidence of RAS was 29.03% (18/62) in patients aged ≤ 60 years, 60% (36/60) in patients aged >60 and ≤ 70 years, and 58.62% (17/29) in patients aged >70 years. The incidence of RAS was significantly higher in patients aged $>60 - \leq 70$, and >70 years than patients aged ≤ 60 years ($P = 0.001$ and $P = 0.007$, respectively). There was a trend that the incidence of RAS in patients with hypertension [HTN, 50.40% (64/127)] was higher than those without HTN (29.17%, 7/24), with $P = 0.056$. The incidence of RAS was 47.02% in patients who were proposed for CABG; bilateral RAS of $\geq 70\%$ was 9.9%. Older age and HTN were associated with RAS in patients who were referred for CABG. This study indicates that the incidence of RAS was high in the patients referred for CABG, and the renal function should be taken care of.