Management of refractory angina in the contemporary era

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This editorial refers to ‘Long-term survival in patients with refractory angina’, by T.D. Henry et al., on page 2683

Refractory angina pectoris is a debilitating disease characterized by angina resistant to conventional therapies for coronary artery disease including drug therapy, percutaneous coronary interventions, and/or coronary artery bypass grafting. Individuals with refractory angina may suffer severely impaired quality of life, with recurrent and sustained chest pain, poor general health status, psychological distress, impaired role functioning and productivity, and restricted ability to perform activities. The European Society of Cardiology (ESC) Joint Study group on the Treatment of Refractory Angina emphasized that refractory angina is a clinical diagnosis (i.e. based on a combination of history, physical examination, and investigations) and states that refractory angina pectoris is a chronic condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery. The presence of reversible myocardial ischaemia should be clinically established to be the cause of the symptoms. Chronicity is defined as a duration of >3 months. The ESC Joint Study group further states that the diagnosis of refractory angina requires a cardiological and cardiothoracic surgical assessment that the patient has angina of ischaemic origin and that revascularization is not feasible. Despite these robust definitions, the diagnosis has a subjective component particularly with determining the suitability for either percutaneous or surgical revascularization based on availability of local expertise. Furthermore, the group of refractory angina patients who are deemed as having no option for revascularization is a heterogeneous entity with many different reasons for not being a suitable candidate for revascularization, i.e. diffuse coronary disease, poor target vessels, lack of conduits, advanced/multiple comorbidities, etc. Few data exist on the true prevalence of refractory angina and outcomes of this difficult to treat population.

Henry et al. have now reported on The OPTions In Myocardial Ischemic Syndrome Therapy (OPTIMIST) programme at the Minneapolis Heart Institute. This prospective clinical database of 1200 patients suggests that long-term mortality in patients with refractory angina is lower than previously reported. The authors further suggest that since survival is comparable with that of patients with stable chronic ischaemic heart disease, therapeutic options for this distinct and growing group of patients should focus on angina relief and improved quality of life. There have been only few previous studies on the natural history and predictors of mortality for patients with refractory angina, and none this size. One study from the Cleveland Clinic in 500 consecutive patients undergoing cardiac catheterization found that 59 (11.8%) patients had ischaemia but were ineligible for revascularization, and none this size. One study in the Cleveland Clinic series was quite high at ~17%. The Mediators of Social Support Study (MOSS), a longitudinal observational study of patients undergoing cardiac catheterization at Duke University between August 1992 and January 1996, similarly reported a high mortality (38% at 2.2-year mean follow-up) in 487 patients who did not undergo revascularization within 30 days. In contrast, 1-year mortality from the OPTIMIST study was ~4%. The obvious question is whether mortality has declined significantly in the last 15 years since the Cleveland Clinic and the Duke study or are we looking at very different patient populations. While differences in study cohort baseline characteristics cannot be entirely ruled out, it is likely that improved secondary prevention drugs such as more potent antiplatelet/antithrombotic agents, high-potency statins, optimal use of guideline-based medical therapies, and more advanced revascularization techniques, including wider use of left internal mammary artery graft to the left anterior descending, have contributed to a decline in mortality in patients with refractory angina, as has happened in other subset of patients with coronary artery disease. Despite some limitations of this study by Henry et al., including its observational nature and lack of a control group, this large study provides important clinical insights into changing epidemiology and outcomes of patients with refractory angina in the contemporary era.

As evident in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, medical therapy has made significant progress over the last decade and appears comparable with percutaneous coronary revascularization in reducing
the risk of death, myocardial infarction, or other major cardiovascular events in stable coronary artery disease. Similarly, among diabetics, traditionally considered a high-risk group, there was no significant difference in the rates of death and major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Based on proven benefits of contemporary medical therapy, it is important that clinicians have a standardized approach for the management of patients with refractory angina which should incorporate lifestyle modification, use of guideline-based medical therapies including newer agents such as ranolazine when indicated, and novel therapies such as EECP (enhanced external counterpulsation), spinal cord stimulation, laser revascularization, etc. as appropriate. Figure 1 outlines a simplified evidence-based approach for the management of patients with refractory angina. If, as is evident in this study, survival of patients with refractory angina is quite comparable with that of patients with stable ischaemic heart disease on optimal medical therapy, it would make clinical sense to target other outcomes such as angina relief and quality of life. However, we should not forget the lessons learnt from the Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis (VIVA) trial which showed that placebo may have a significant ameliorating effect on a subjective outcome such as angina pectoris. An important finding of the VIVA trial was the prominent placebo effect noted at day 60 with a 48 s improvement in exercise treadmill test time, 56% of patients improving at least one angina class, and a nearly 14-point improvement in the Seattle Angina Questionnaire angina frequency domain. It is therefore critically important to test new therapies for refractory angina in a randomized double blind design. For now, we cannot overemphasize the importance of optimal medical therapies in patients with refractory angina pectoris. Patients with refractory angina represent a high-risk group, where secondary prevention is likely to be particularly beneficial and cost-effective. Overall, refractory angina management

**Figure 1** Simplified approach to a patient presenting with refractory angina. BMI, body mass index; HbA1c, glycated haemoglobin.
requires an effective optimization of medical therapies with the use of different drugs in maximally tolerated doses, \(^{11}\) with judicious use of therapies such as transcutaneous electric nerve stimulation, spinal cord stimulation, EECP, and laser revascularization in selected cases for symptom relief. \(^{12}\)

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**References**


