Atherosclerosis: The 21st Century Epidemic
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Acute Myocardial Infarction: A Century of Progress

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The year 2010 marks the centenary of the first description of acute myocardial infarction (AMI). In 1910, Obraztsov and Strazhesko from Kiev in the Ukraine presented their landmark observation in five patients. Remarkably, in the very first paper on the subject, they described correctly the key clinical findings of this important condition. To quote them (translated from Ukranian):

> All patients noted an acute, sudden onset of the disease. Direct events often precipitated the disease; the infarct began in one case on climbing a high staircase, in another during an unpleasant conversation and in a third during emotional distress associated with a heated card game.

They stated that the symptoms were of three types:

1. Substernal pain with radiation to the neck, head and left hand
2. Shortness of breath, reaching such a severe degree that it did not permit the patients to lie or sleep
3. Heaviness and severe pressure in the epigastrium

Just three years later, Anitschkow and Chalatow (1913) produced atherosclerotic lesions in the arteries of healthy rabbits who were fed a diet containing large quantities of fat, thereby raising the cholesterol concentration in the circulating blood to approximately 1000 mg/dl.

From these two landmark observations – one clinical and the other experimental – the mechanism of obstruction of coronary arteries secondary to atherosclerotic changes, and the serious clinical consequences of such obstruction, were firmly established.

The pathophysiology of acute myocardial ischemia was studied experimentally by Tennant and Wiggers (1935). They occluded a coronary artery in anesthetized open chest dogs and observed that contraction of the myocardium in the distribution of the occluded vessel ceased immediately. If the occlusion was relieved rapidly (within 23 minutes) contractions returned. With longer occlusions contraction did not return. Several years later Blumgart and colleagues showed, also in dogs, that prolonged, although temporary, coronary artery occlusion caused myocardial necrosis (infarction). They stated that their 'observations afford evidence that temporary ischemia, if of sufficient duration, may cause myocardial infarction of the

same character and degree as that which occurs after permanent and complete occlusion of a [coronary] artery'. (Blumgart H.L. *et al.*, 1941)

During the first half of the twentieth century the number of patients in North America and Europe in whom the diagnosis of AMI was made increased rapidly and the short-term (30 day) mortality was prohibitive – approximately 30%. Indeed, by mid-century, AMI was identified as the most frequent cause of death in adults. In 1961 Desmond Julian, a trainee in cardiology in Edinburgh, published a landmark paper describing what would become the coronary care unit. (Julian, 1961) He recommended the creation of a specific area in the hospital for patients with AMI, an area that contained all of the equipment necessary for these patients (catheters, drugs, solutions, pacemakers, defibrillators, etc.) and where specially trained physicians and nurses were available at a moment's notice. Coronary care units sprang up almost immediately around the world and resulted in a reduction by half of the short-term mortality to approximately 15%. The coronary care unit was made possible by the four distinct advances shown in Table 1.

Myocardial oxygen consumption

Approaching the problem from a different perspective, my colleagues and I, beginning in 1955, in Stanley Sarnoff's laboratory at the National Heart Institute in Bethesda Maryland in the US, began to dissect out the determinants of myocardial oxygen consumption (Sarnoff *et al.*, 1958) (Figure 1). We found that there were at least eight separate functions of the heart which required oxygen (Braunwald *et al.*, 1969) (Table 2). The most important of these were myocardial tension development, myocardial contractility, as reflected in the velocity of myocardial shortening (V_{max}) and the frequency of contraction.

After moving from the NIH to the University of California, San Diego, my colleagues and I developed and tested the hypothesis that following coronary artery occlusion the fate of the ischemic myocardium in the distribution of the occluded artery was dependent on its balance of oxygen supply and demand. We found that early reperfusion of the ischemic muscle (increase in oxygen supply) and beta adrenergic blockade (lowering of oxygen demand) reduced the quantity of myocardium which became necrotic, i.e. reduced infarct size, while hypotension (reduction of coronary perfusion through collateral vessels), decreased oxygen supply and the administration of positive inotropic agents such as isoproterenol (augmentation of oxygen demand), increased infarct size. We speculated: 'In patients with myocardial ischemic injury resulting from coronary occlusion, measures designed for reduction of myocardial oxygen demands and improvement of coronary perfusion when effected promptly after a patient has

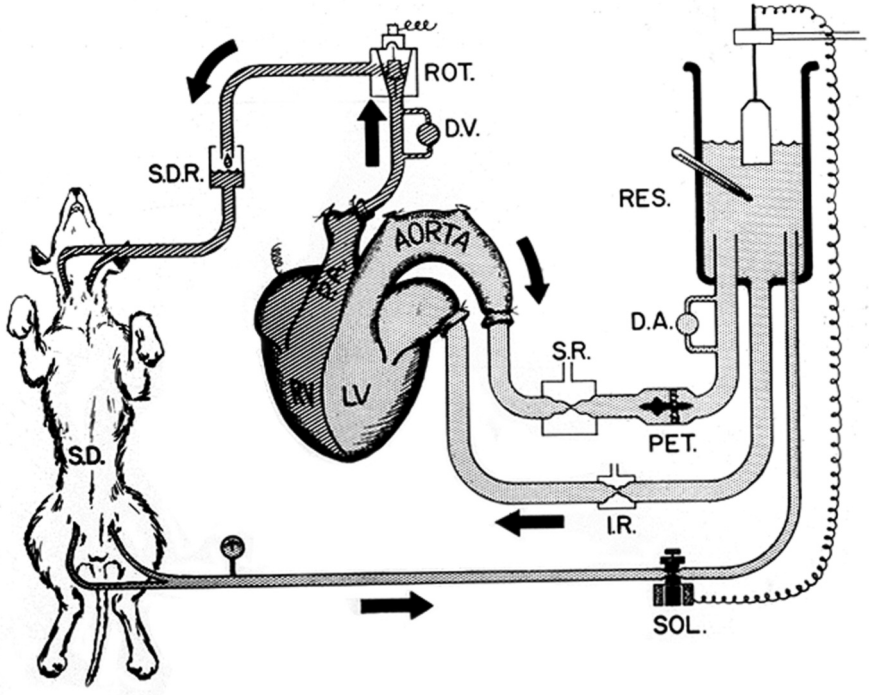

Figure 1 Schematic diagram of the isolated support heart (ISH) preparation. SR = air-filled Starling resistance. PET = Potter electroturbinometer. DA = arterial densitometer. RES = reservoir. LR = water-filled inflow Starling resistance. DV = venous densitometer. ROT = rotameter. SDR = support dog reservoir. SD = support dog. SOL = solenoid valve electrically operated by microswitch at top of reservoir float. From: Sarnoff, S.J., Braunwald, E., Welch, G.H., Jr., Case, R.B., Stainsby, W.N., Macruz, R. (1958) Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol* 192:148-56.

Technical	Continuous ECG monitoring with alarms
Clinical	Closed chest CPR
Administrative	Clustering of AMI patients
Social	Empowerment of nurses

CPR = cardiopulmonary resuscitation; AMI = acute myocardial infarction

Table 1. Advances Leading to the Development of the Coronary Care Unit

• Tension development • Contractility • Heart rate	} 92%
• Basal • Depolarization • Activation • Maintenance of active state • Shortening against a load – Fenn effect	

Table 2. Determinants of myocardial o_2 consumption. From Braunwald E. 13th Bowditch Lecture. The determinants of myocardial oxygen consumption. *The Physiologist* 1969;12:65-93.

been brought to a hospital, might reduce the ultimate size of the infarct' (Maroko *et al.*, 1971).

Successful reperfusion of patients with AMI using the fibrinolytic agent streptokinase injected into the occluded artery was first performed by Chazov and his collaborators in Moscow. Their work was published in a Soviet journal in 1976 (Chazov E.I. *et al.*, 1976) and was not adequately known or appreciated in the West for a number of years.

Percutaneous coronary intervention

In 1978 Gruntzig described percutaneous transluminal coronary angioplasty (PTCA) (Gruntzig *et al.*, 1978), which provided the foundation for rapid, complete reperfusion of ischemic myocardium. Indeed, several years later, Meyer and colleagues (Meyer J *et al.,* 1982) successfully treated a patient with AMI who was in cardiogenic shock with what later became known as 'pharmacoinvasive therapy'. This consisted of intracoronary streptokinase, which provided partial flow through the occluded artery, followed immediately by PTCA which resulted in full reperfusion.

In 1985, after development of the powerful fibrinolytic agent tissue recombinant plasminogen activator (rt-PA), the National Institutes of Health in the US established the Thrombolysis in Myocardial Infarction (TIMI) Study Group, which still remains active after 25 years and completing 50 trials. In our first trial, we compared the abilities of streptokinase and rt-PA

to open occluded coronary arteries in patients with AMI and found that the latter was superior (The TIMI Study Group, 1985) (Figure 2, see p. 183). We also observed that patients who achieved patency of the occluded artery had a considerably lower one year mortality rate than did those in whom the vessel remained occluded (Dalen JE *et al.*, 1988) (Figure 3, see p. 184). This provided support for the 'open artery hypothesis' in which we called attention to the concept that early opening of an occluded coronary artery in a patient with ischemic myocardium was highly desirable. We also observed that intravenously administered beta adrenergic receptor blockers in concert with fibrinolytic reperfusion were associated with reduction of reinfarction and of recurrent myocardial ischemia (Roberts *et al.*, 1971). An important step was taken by the ISIS Study Group which showed in 1988 that both streptokinase and the antiplatelet agent, aspirin, each independently reduced mortality. These benefits were additive when the two drugs were combined (ISIS-2 Collaborative Group, 1988) (Figure 4, see p. 185).

It was well known, before the development of the coronary care unit, that of the 70% of patients with AMI who survived the first month, an additional 20% died because of heart failure, thus leading to a 1 year survival of only about 50%. The development of angiotensin-converting enzyme inhibitors (ACE-i) made it possible to determine whether enlargement of the left ventricle and subsequent death in the increasing number of patients who were now surviving AMI could be reduced by the administration of these agents. Drs. Marc and Janice Pfeffer showed in rats in which the coronary arteries had been occluded that left ventricular remodeling and death could be reduced by the administration of an angiotensin converting enzyme inhibitor (Pfeffer *et al.*, 1985). We then extended this observation to patients in the Survival and Ventricular Enlargement (SAVE) trial (Figure 5, see p. 186), and showed that in patients with AMI the administration of an ACE-i begun at discharge from the hospital showed improved long-term survival benefit (Pfeffer MA *et al.*, 1992).

It had been demonstrated in the fibrinolytic trials that the reduction of mortality from reperfusion was greatly dependent on the duration of ischemia. As had been shown by both Tennant and Wiggers (1935) and by Blumgart *et al.* (1941), the earlier the reperfusion, the smaller the ensuing infarction. In 1993, the European Myocardial Infarction Project Group shortened the time from the onset of symptoms to reperfusion by administering the fibrinolytic agent in the ambulance rather than waiting until the patient reached the hospital. They concluded: 'Prehospital thrombolytic therapy for patients with suspected AMI is both feasible and safe when administered by well-equipped, well-trained mobile emergency medical staff.

Such therapy reduces mortality from cardiac causes' (The European Myocardial Infarction Project Group, 1993).

Reocclusion is reduced by the addition of heparin to the fibrinolytic agent. In the TIMI- 25 trial, Antman *et al.* demonstrated the superiority of the subcutaneous administration of a low molecular weight heparin when compared to intravenous administration of unfractionated heparin. (Figure 6, see p. 187) (Antman *et al.*, 2006). Building on the benefit of adding aspirin to streptokinase in the above-mentioned ISIS 2 trial (ISIS-2 Collaborative Group, 1988), Sabatine *et al.* showed, in the CLARITY-TIMI 28 trial, that the addition of a second anti-platelet agent, clopidogrel, to aspirin in patients with AMI treated with a fibrinolytic-heparin combination greatly increased myocardial perfusion and reduced death or recurrent myocardial infarction (Sabatine *et al.*, 2006) (Figure 7, see p. 188). Going a step further, the TRITON-TIMI 38 trial showed that prasugrel, a more powerful antiplatelet agent than clopidogrel, in patients with ST-segment elevation myocardial infarction (STEMI) treated by reperfusion reduced the incidence of cardiovascular death, recurrent MI and stroke (Figure 8, see p. 189) (Montalescot *et al.*, 2009). This more powerful antiplatelet agent also reduced by half the incidence of stent thrombosis, a serious complication of stent placement, although it did increase the severity of bleeding.

There are currently two methods of reperfusion of AMI – pharmacologic and mechanical, i.e. the percutaneous coronary intervention (PCI). (Antman *et al.*, 2008) (Figure 9, see p. 190). Each has advantages and disadvantages. Overall, PCI, when conducted early after the onset of AMI, is more effective than fibrinolysis in salvaging ischemic myocardium and has become the treatment of choice in Western Europe and North America and in selected populations elsewhere. However, immediate PCI is not yet widely available in much of the developing world, where fibrinolysis using the relatively inexpensive fibrinolytic streptokinase is still employed. These two techniques, i.e. PCI and fibrinolysis, can be used together in a technique known as 'rescue PCI'. A 2008 update of the American College of Cardiology/American Heart Association guidelines for the management of patients with ST-elevation myocardial infarction statement states: 'A strategy of coronary angiography with intent to perform rescue PCI is reasonable for patients in whom fibrinolytic therapy has failed (ST-segment elevation less than 50% resolved after 90 min following initiation of fibrinolytic therapy) and a moderate or large area of myocardium is at risk [anterior MI, inferior MI with right ventricular involvement or precordial ST-segment depression]' (Antman *et al.*, 2008).

An approach to using these two techniques together was tested in the TRANSFER AMI trial (Figure 10, see p. 191). This was a study of a phar-

macoinvasive strategy in 1059 high-risk patients with STEMI presenting to non-PCI-capable hospitals within 12 hrs of symptom onset. All patients were treated with a fibrinolytic agent and then randomized to a pharmacoinvasive strategy (fibrinolytic therapy followed by immediate transfer for PCI) or to standard treatment after fibrinolytic therapy (rescue PCI only for patients with ongoing chest pain and less than 50% resolution of ST-elevation hemodynamic instability at 60-90 minutes). The results indicated that when high risk STEMI patients present to hospitals without PCI-capability following treatment with a fibrinolytic agent, transfer to a PCI center to undergo coronary angiography and PCI should be initiated immediately, without waiting to determine whether reperfusion has occurred (Cantor WJ *et al.*, 2009).

Sudden cardiac death remains a most serious complication of AMI. Patients with impaired left ventricular function are at particular risk and should be treated with an implanted cardioverter defibrillator (ICD). The approach to preventing this complication is shown in Figure 11, p. 192 (Antman EM *et al.,* 2008).

Future directions

Cell therapy, most commonly intracoronary administration of autologous bone marrow cells, is a recent development in the treatment of AMI. A five year followup in one trial is shown in Figure 12, p. 193 (Yousef M, 2009). A second trial using mononuclear autologous bone marrow cells with favorable long term outcomes was also published recently. (Cao *et al.*, 2009) Efforts are now underway to use gene therapy in AMI (Hammond and Tang, 2009) (Figure 13, see p. 194). In addition, left ventricular assist devices are becoming smaller and much more reliable than heretofore and have become suitable for the heart failure that follows large STEMIs.

One can now foresee a five step approach to patients with AMI and cardiogenic shock, which remains a complication associated with a very high mortality. 1) Attempt immediate reperfusion by PCI; 2) Insert percutaneous left ventricular assist device; 3) harvest the patient's own bone marrow cells; 4) treat these cells and reinject them into the damaged myocardium; and 5) when these cells become functional, wean the patient from the left ventricular assist device and remove the device. An alternative, in place of, or in addition to, autologous bone marrow cells, i.e. steps 3 and 4 above, is to insert genes into cells which are viable but not contracting.

From a public health perspective, the next major goal is to prevent, rather than merely treat, AMI. A number of risk factors are associated with the development of AMI. These include elevations of blood pressure and low-density lipoprotein cholesterol, cigarette smoking, and the presence of diabetes mellitus.

Both primary and secondary prevention of MI can be accomplished by improving lifestyle (discontinuation of cigarette smoking, exercise and weight loss in overweight and obese subjects) and pharmacologic control of diabetes mellitus, hypertension and hypercholesterolemia. The recent discovery of genetic risk factors for the development of AMI now allows greater precision in the assessment of risk (Figure 14, see p. 195) (Kathiresan *et al.*, 2009).

Summary

It has been an extraordinary century in the history of AMI. The condition was described in 1910 and by the middle of the twentieth century it was recognized to be the most common cause of adult death in the industrialized world. Intensive research into the causes and the management of AMI has reduced the one year mortality from about 50% to 10%. The number of patients with AMI has declined markedly during the past two decades. However, AMI remains a serious condition, especially in the developing world. There has been progress both in identifying subjects at high risk of developing AMI and of lowering this risk in order to reduce its incidence. At the same time, high technology approaches to the management of patients who develop serious complications are being pursued actively. A major challenge now is to apply what has been learned about AMI – both its prevention and treatment – to the developing world, and to do so at costs that are realistic in their economies.

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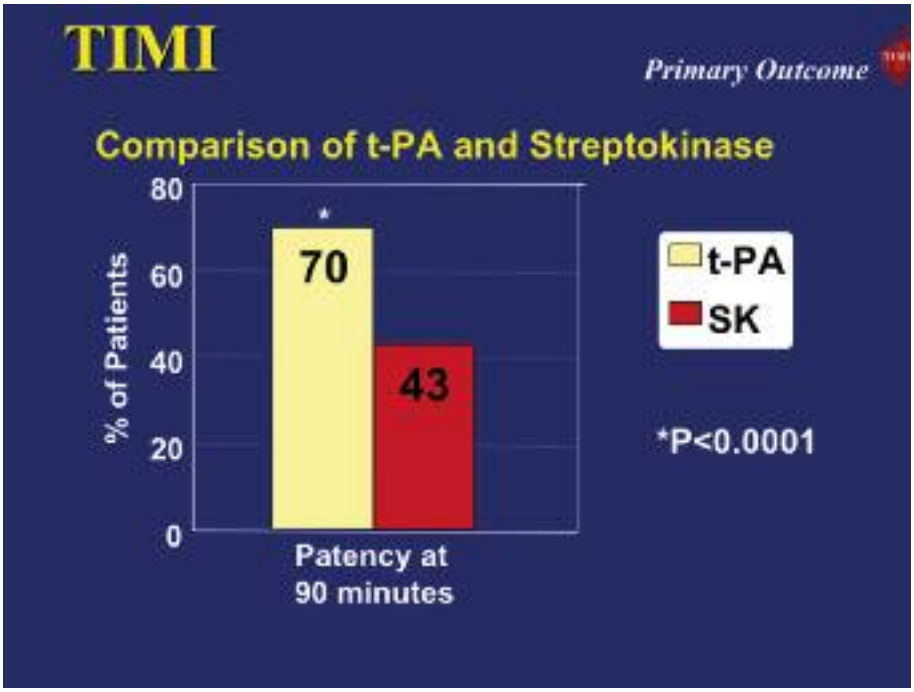

Figure 2. Data from: The TIMI Study Group. (1985) The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med* 312:932-6.

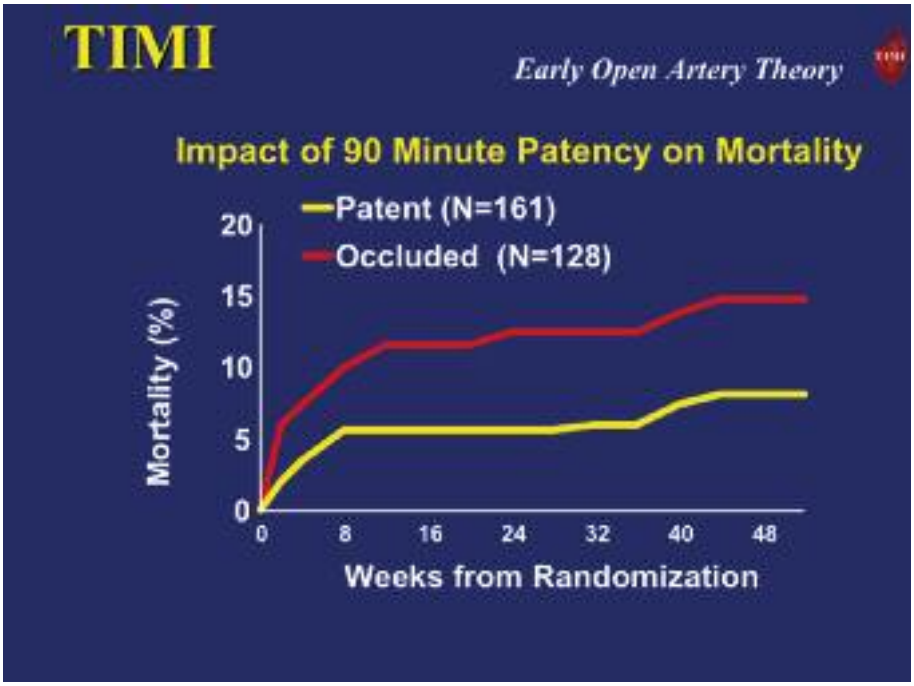

Figure 3. TIMI Phase I: Life table cumulative mortality rates by perfusion status at 90 minutes. From: Dalen, J.E., Gore, J.M., Braunwald, E., *et al*. (1988) Six and twelve-month follow-up of the Phase I Thrombolysis in Myocardial Infarction (TIMI) Trial. *Am J Cardiol* 62:179-85.

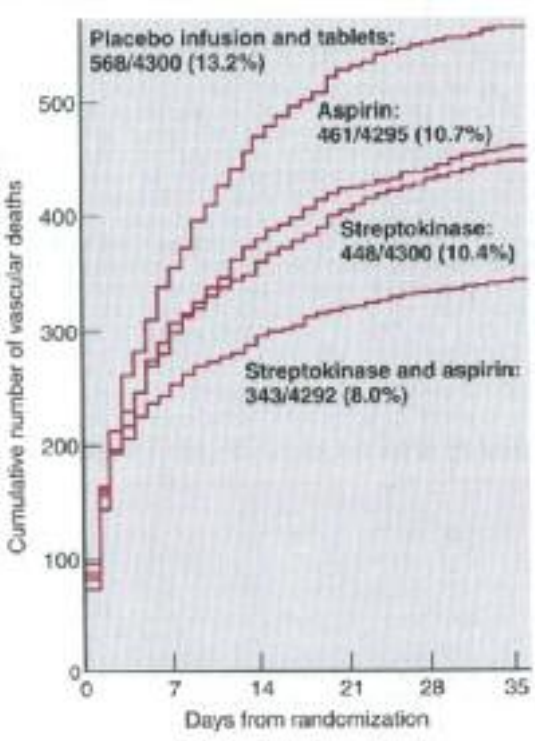

Figure 4. Cumulative vascular mortality in days 0-35. Patients allocated (i) active streptokinase only, (ii) active aspirin only, (iii) both active treatments, and (iv) neither. From: ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. (1988) Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 2:349-60.

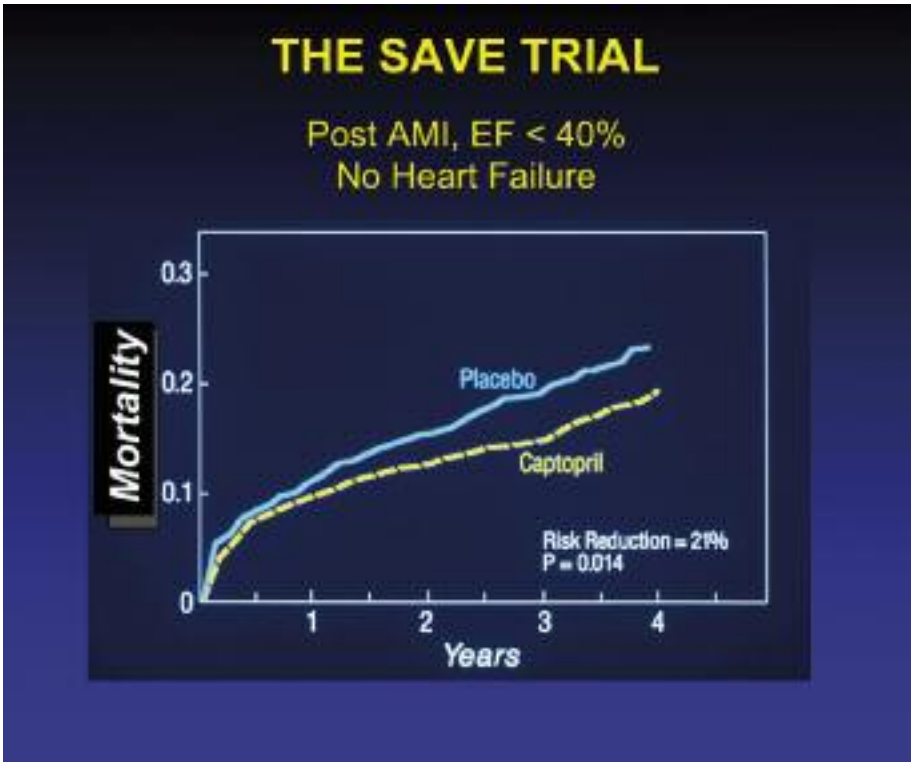

Figure 5. Cumulative mortality from all causes in the SAVE trial. From: Pfeffer MA, Braunwald E, Moye LA, *et al*. (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 327:669-77.

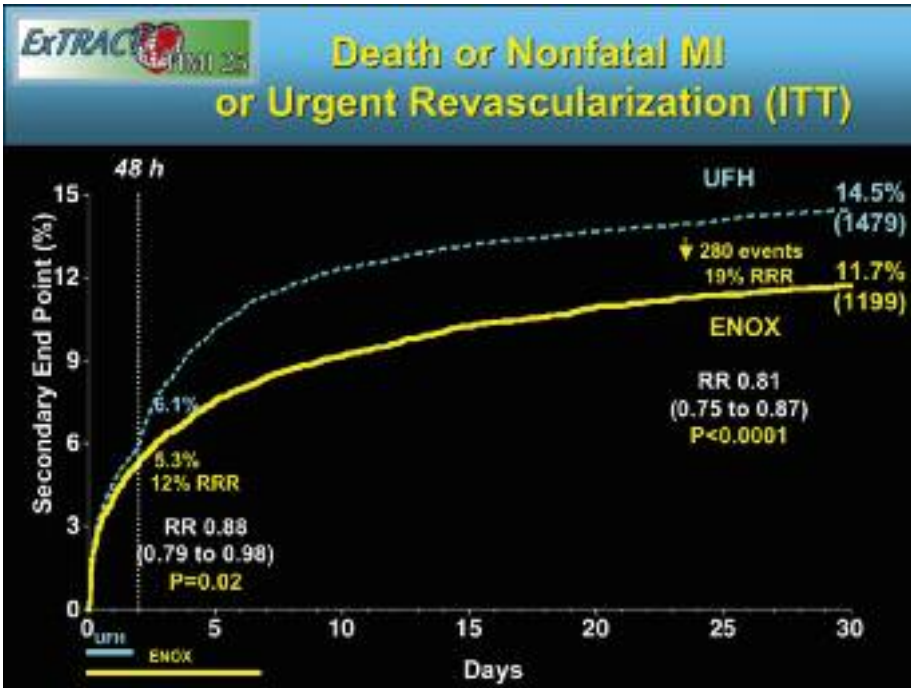

Figure 6. Death, non-fatal myocardial infarction or urgent revascularization, comparing ENOX (enoxaparin) and UFH (unfractionated heparin). ITT = intention to treat. From: Antman, E.M., Morrow, D.A., McCabe, C.H., *et al*. (2006) Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 354:1477-88.

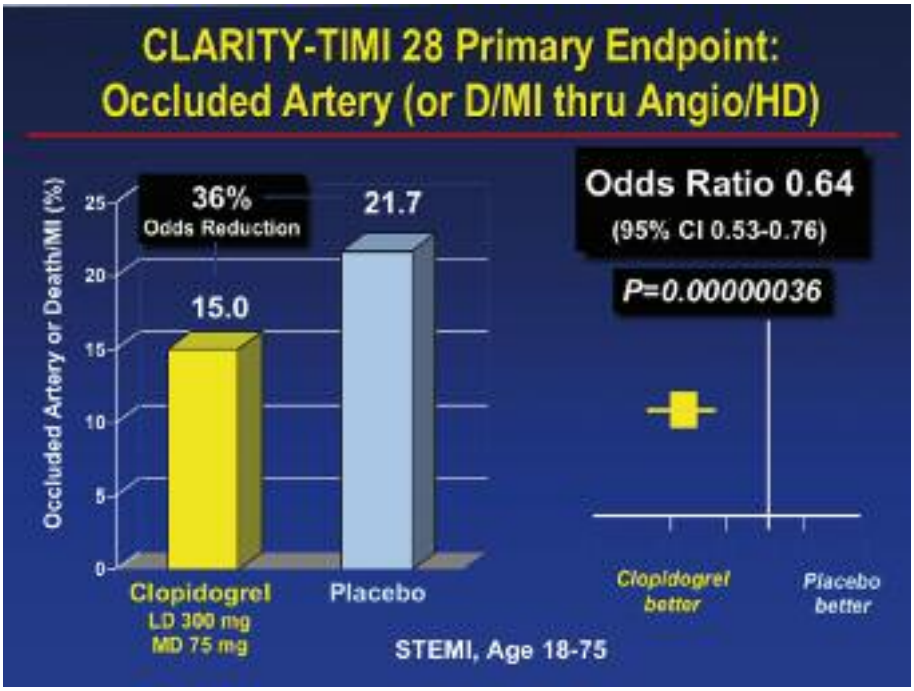

Figure 7. LD = loading dose. MD = daily maintenance dose. From: Sabatine, M.S., Cannon, C.P., Gibson, C.M. *et al*. (2006) Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352:1179-89.

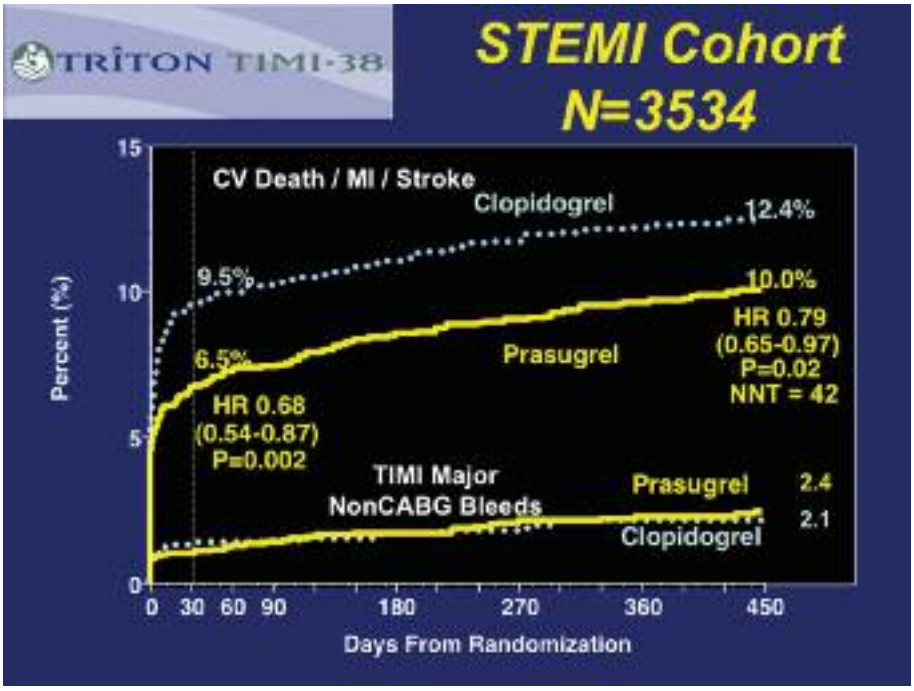

Figure 8. From: Montalescot, G., Wiviott, S.D., Braunwald, E., *et al*. (2009) Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomized controlled trial. *Lancet* 373:723-31.

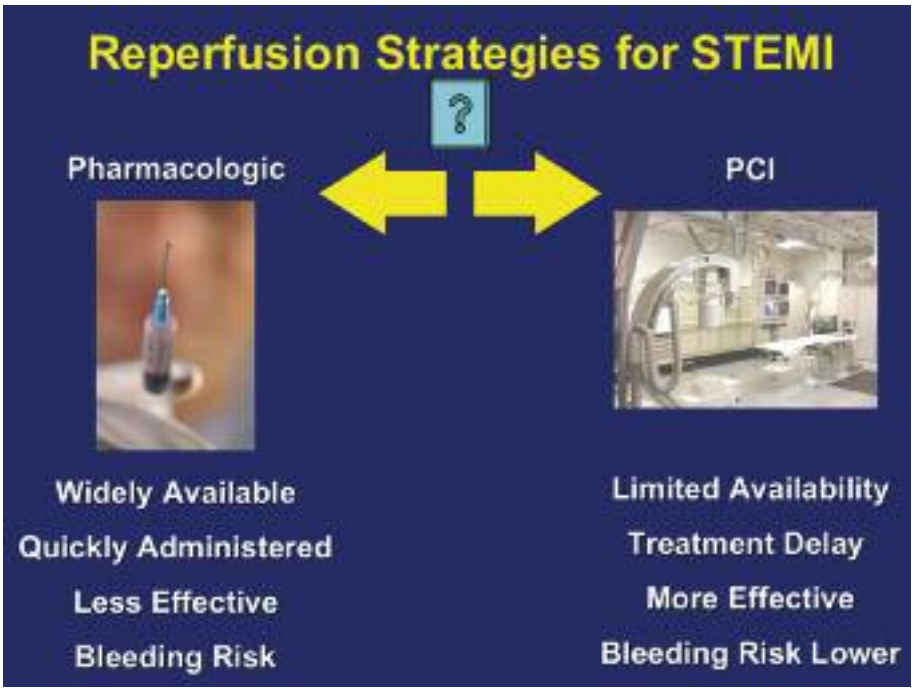

Figure 9. Comparison of the two approaches to reperfusion in ST-elevation myocardial infarction (STEMI). The advantages and disadvantages of each approach are outlined at the bottom. PCI = percutaneous coronary intervention. From: Antman, E.M. (2008) ST-elevation myocardial infarction, in Libby, P. *et al.* (eds): *Braunwald's Heart Disease*, 8th ed. Philadelphia: Elsevier. pp 1233-1299.

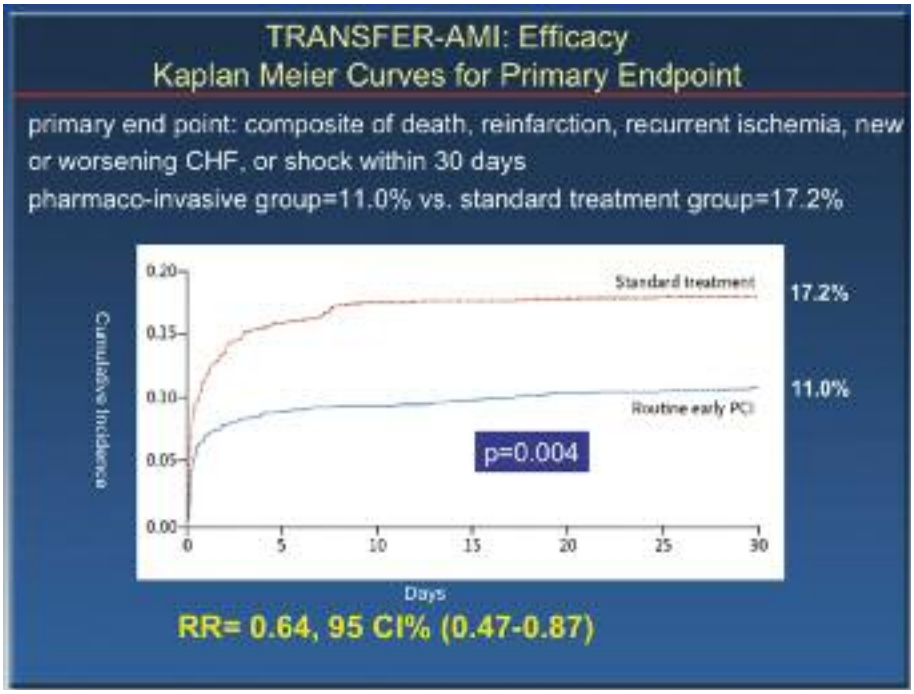

Figure 10. Kaplan-Meier curves for the primary endpoint at 30 days. The primary end point was the composite of death, reinfarction, worsening heart failure, or cardiogenic shock within 30 days. (see text) PCI denotes percutaneous coronary intervention. CHF = congestive heart failure. From: Cantor, W.J., Fitchett, D., Borgundvaag, B., *et al*. (2009) Routine Early Angioplasty after Fibrinolysis for Acute Myocardial Infarction. *N Eng J Med* 360:2705-18.

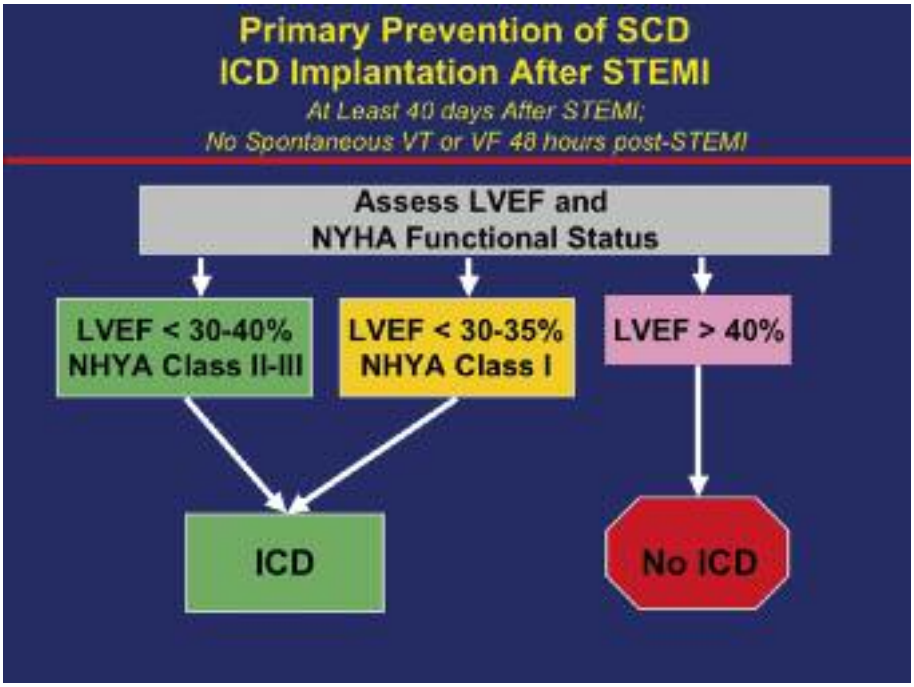

Figure 11. Algorithm for implantation of an implantable cardioverter defibrillator. (ICD) in ST-elevation myocardial infarction (STEMI) patients without ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) more than 48 hours after STEMI. The appropriate management path is based on measurement of left ventricular ejection fraction (LVEF). EF measurements obtained 3 days or less after STEMI should be repeated before proceeding with the algorithm. Patients with EF less than 30 to 40 percent at least 40 days post-STEMI are referred for insertion of an ICD if they are in New York Heart Association (NYHA) Classes II or III. Patients with a more depressed LVEF less than 30 to 35 percent are referred for ICD implantation even if they are NYHA Class I. Patients with preserved left ventricular function (LVEF ›40 percent) do not receive an ICD post-STEMI. From: Antman, E.M. (2008) ST-elevation myocardial infarction, in Libby, P. *et al*. (eds): *Braunwald's Heart Disease*, 8th ed. Philadelphia: Elsevier, pp 1233-1299. *Modified from:* Zipes, D.P. *et al*. (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden death. *Circulation* 114:e385-484.

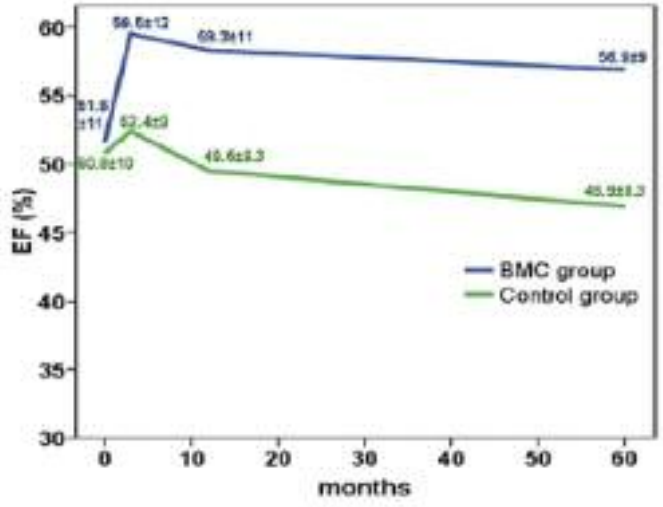

Figure 12. Ejection Fraction over the course of time after bone marrow cell (BMC) therapy in patients with AMI in comparison with the control group. Ejection fraction (EF) improves significantly in the BMC group. The initial beneficial effect of BMC therapy, as evidenced by a significant improvement of EF after 3 months, was longstanding after 60 months. In contrast, the EF decreases in the control group. AMI = acute myocardial infarction. From: Yousef, M., Schannwell, C.M., Köstering, M., *et al*. (2009) The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. *J Am Coll Cardiol* 53:2262-9.

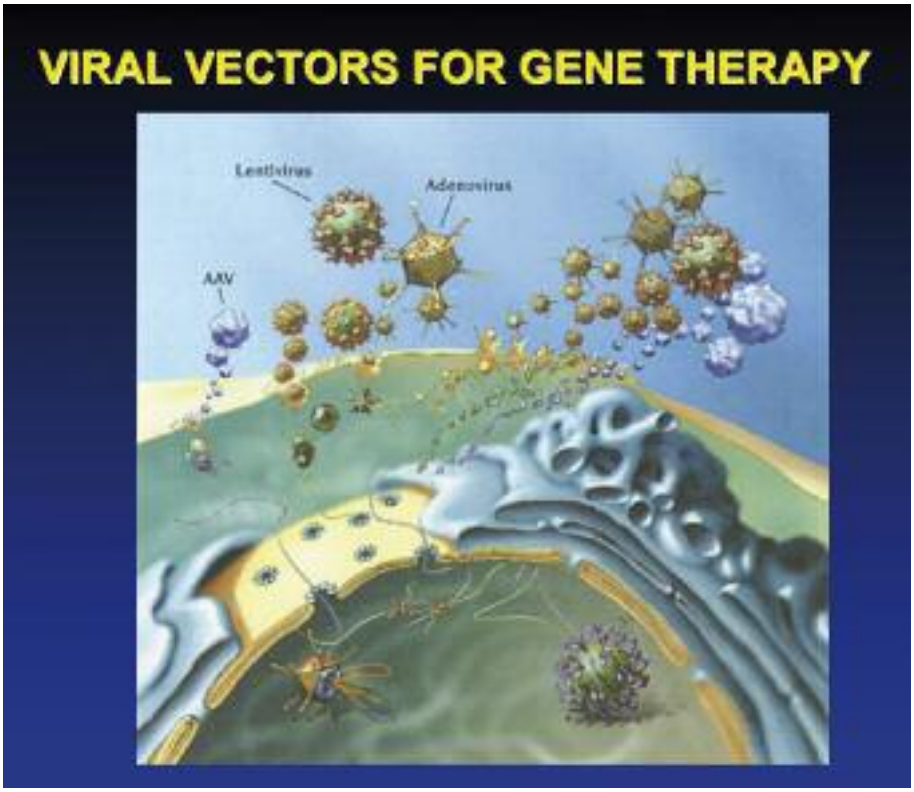

Figure 13. Virus-mediated gene transfer. The figure depicts the three major virus vectors used for cardiac gene therapy. Once the vector has gained access to the cardiac interstitium, the vectors attach to cell surface receptors or integrins, enter the cell by vesicular transport, traverse the cytoplasm, and enter the nucleus. Adeno-associated virus (AAV) and lentivirus provide persistent transgene expression, as the transgene becomes integrated into the host chromosome. Adenovirus provides extrachromosomal expression. From: Hammond, H.K., Tang, T. (2009) Gene therapy for myocardial infarction–associated congestive heart failure: how far have we got? *Dialogues CV Medicine* 14:29-36. *Modified from*: Perkel, J.M., Slayden, C., Swift, A. Viral mediated Gene Delivery, Poster. www.sciencemag.org/products/posters/GeneDeliveryPoster.PDF Washington DC, American Association for the Advancement of Science.

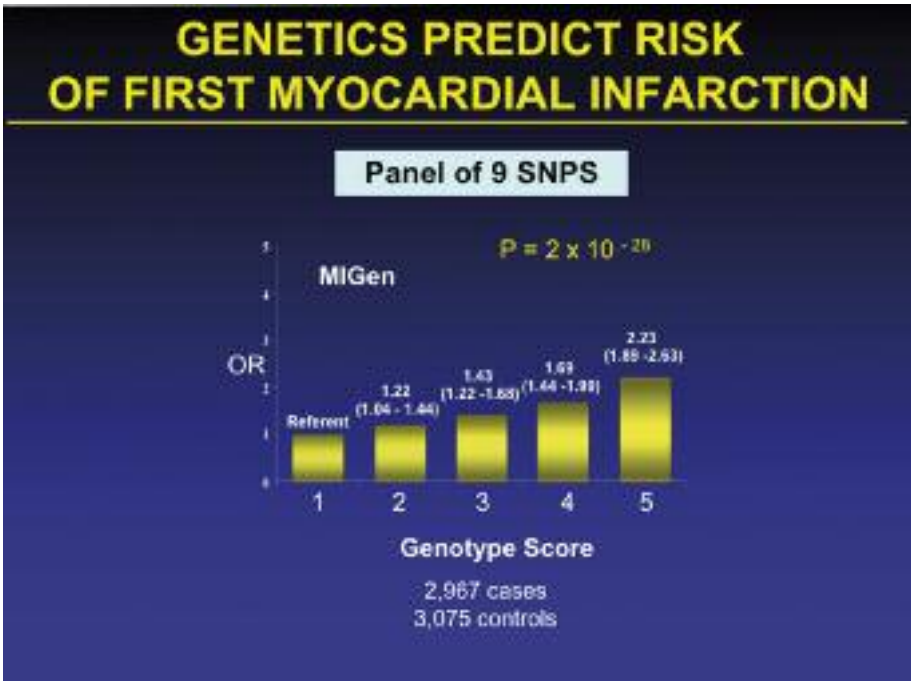

Figure 14. Genetic risk prediction of first myocardial infarction. O.R. = odds ratio; SNP = single nucleotide polymorphism. From: Kathiresan, S., Voight, B.F., Purcell, S., *et al*. (2009) Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nature Genetics*. 41:334-41.