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New Era of Genetic Risk Variants, Genetic Risk Score and Gene Therapy for Management of Coronary Artery Disease

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Abbreviation: GRS: Genetic Risk Score; CAD: Computer-Aided Design; NNT: Number Needed to Treat; DNA: Deoxyribonucleic Acid; VEGF: Vascular Endothelial Growth Factor; FGF: Fibroblast Growth Factor

Introduction

Recent substantial progress in genomic medicine, guided by great breakthroughs in laboratory technology and computing power, provides us with a golden opportunity to understand the genetic basis of CAD. Improved application of established primary prevention strategies undoubtedly has the potential to further reduce the incidence of CAD. Collectively, these strategies are able to reduce the incidence of CAD by almost 50% in high-risk populations [1]. Much awaited clinical application for genetic risk variants predisposing to CAD is to be able to improve ability to risk-stratify individuals. A large pool of individuals with incident events carries either only 1 modifiable risk factor or only borderline risk factor. Recent epidemiological studies involving unrelated individuals provided the first clues that non Mendelian common presentations of CAD in middle to late adulthood were heritable. Studies have documented 2.5- to 4-fold higher rates of CAD among individuals with a family history compared with those with no family history when adjusting only for age and sex. Familial aggregation studies prove that a stronger family history or an earlier age of onset of disease in a family member further increases the risk for close relatives [2].

Improving our ability to better predict a particular set of women with similar risk factors will experience an event through the addition of a novel biomarker, such as one's genetic susceptibility to CAD, would be expected to improve outcomes through more efficient application of established primary prevention therapies. The use of GRS in clinical practice has been slow to materialize for several reasons, including the high cost of genotyping, the more modest effects of genetic variants on the risk of CAD than originally anticipated, and the challenge of improving a clinical risk score, such as the Framingham or ACC/AHA risk score, that already performs quite well. The most practical way to currently integrate genetics into risk prediction models, such as the Framingham Risk Score or the ACC/AHA pooled cohorts calculator, is through the calculation of a genetic risk score (GRS) for individuals. 42 A GRS is a single variable that summarizes one's exposure to variants that increase risk for CAD. Though family history serves as a substitute for genetic risk, yet individual variants, as well as GRS of CAD, have been shown to predict clinical complications of CAD independent of family history [3,4].

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GRS involving 27 variants previously proven to be associated with CAD was constructed after genotyping DNA bio banked at baseline from participants in 1 community-based cohort study (the Malmo Diet and Cancer Study), 2 primary prevention trials of statins (JUPITER and ASCOT), and 2 secondary prevention trials assessing the efficacy of statin therapy (CARE and PROVE ITTIMI 22).4 In primary prevention trials number needed to treat (NNT) to prevent 1 such event in 10 years was 66 in people at low genetic risk, 42 in those at intermediate genetic risk and 25 in those at high genetic risk in JUPITER, and 57, 47, and 20, respectively, in ASCOT. GRS served as a prognostic marker and also as a marker to predict response to single most important primary and secondary therapy already available. The absolute risk reduction estimated a roughly 3-fold decrease in the number needed to treat (NNT) to prevent 1 CAD event in the primary prevention trials [4].

The rapid translations for loci such as PCSCK9 offer some optimism that such developments are possible. This is likely to provide us with innovative opportunities to further reduce and possibly eliminate CAD in times to come. These new resources and techniques have already provided important mechanistic insights for several novel susceptibility loci for CAD, including those regions harboring the genes CDKN2B, SORT1, TCF21, ADAMTS7, SMAD3, and other loci. 4 this knowledge has yet to be applied to therapeutic agents to target these loci. Current knowledge pertaining to 60 susceptibility loci identified for CAD confirms the importance of established risk factors and many novel causal pathways. This will surely improve our understanding of genetic basis of CAD and hopefully open the door to development of new therapeutic agents in the future. Genetic risk scores of CAD are important both as prognostic and predictive markers. This may also change the approach to delivery of established prevention strategies.

Gene therapy describes the transfer of genes to a target cell or organ to treat or prevent disease. Successful delivery of a gene to the target is paramount to therapeutic efficacy. In some cases, this can be as simple as transduction of a few cells to secrete a hormone or growth factor; in more stringent cases, the requirement may be as extensive as transduction of most or all cells in the target organ. A number of gene delivery methods have been developed using both viral- and non-viral-based vectors (Figure 1).

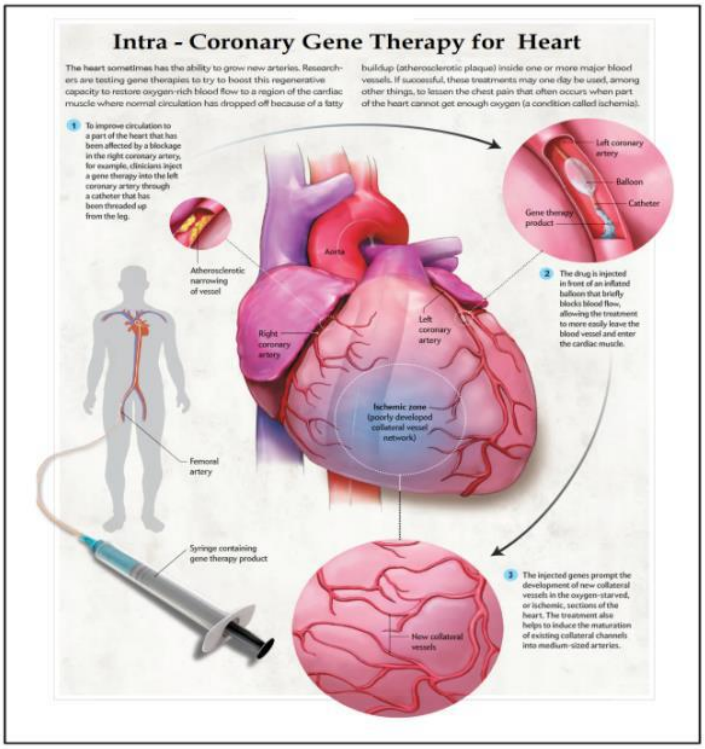

Figure 1: Intra-Coronary Gene Therapy for Heart.

Intracoronary Perfusion

Intracoronary perfusion of gene transfer vectors has been reported by percutaneous catheterization, open-chest aortic cross-clamp with left ventricular cavity infusion, and cardiopulmonary bypass with direct coronary arterial perfusion. Gene transfer to the myocardium is considerably less efficient by intracoronary infusion than by intramyocardial injection. The principle limitation is escape from the vasculature to access cardiac myocytes [5]. Long-term survival of patients with coronary disease has increased because of advances in pharmacologist and revascularization techniques. However, a group of patients who are refractory to conventional therapy has emerged. These patients suffer from severe angina pectoris despite maximal medical therapy and are no longer treatable with percutaneous coronary intervention or coronary artery bypass graft surgery. An alternative treatment option is being developed, termed therapeutic angiogenesis. The therapy involves administration of genes for angiogenic growth factors to augment collateral vessel development [6].

Preclinical angiogenesis studies investigated a variety of angiogenic growth factors including VEGF, FGF, hepatocyte growth factor, platelet-derived growth factor, and hypoxia-inducible factor, among others. A competing issue within these trials was a strong placebo effect. When subgroups were analyzed or VEGF-treated patients compared with themselves at follow-up, improvements were noticed, but when the active treatment arm was compared with the placebo arm in these trials, no significant differences were generally found [7]. The goal of gene therapy is to modify a gene or genetic pathway to provide therapeutic value and prevent or reduce disease. It is important to develop a method that is safe and effective for the treatment of human disease. Important issues such as tolerance and ease of administration need to be translated to the clinic. For cardiovascular disease, gene therapy has been limited due to vectors and delivery to the target cell. Long-term expression with ADs is limited, and inflammation as a result of host recognition is a problem.

Clinical studies have shown limited efficacy but no long-term adverse events with angiogenic gene therapy and suggestions of efficacy and safety with early-stage heart failure gene therapy. Modification of multiple genes may be necessary. Genetic modulation in cardiovascular disease is the forefront of new therapeutic options and, with additional development and rigorous testing, could become the paradigm for first-round treatment options in the clinic. Preclinical work is currently ongoing for arrhythmia applications. For gene therapy to be successful, the right gene needs to be targeted in the setting of the correct disease. With multiple disease mechanisms for individual diseases, finding the molecule to target is daunting.

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