Current Perspectives in Cardiovascular Medicine

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Abstract: Cardiovascular disease (CVD) is the leading cause of death in the United States accounting for approximately 31% of all deaths. There have been significant accomplishments in the diagnosis and treatment of CVD; however, these advances have mostly occurred in the application of cutting edge technology, pharmacotherapy, and surgical techniques to treat the manifestations and symptoms of the disease. Developments in outcomes research and those in atherosclerosis and genetics, as well as in the control of risk factors for CVD are discussed.

Keywords: Obesity, *polypill*, cardiovascular, atherogenesis, genetics.

According to recent American Heart Association statistics [1-3] there are approximately 85.6 million adult Americans (>1 in 3) with cardiovascular disease (CVD) and stroke. Of these, 43.7 million are ≥60 years of age. It is the leading cause of death in the United States, accounting for nearly 786,641 deaths, or 31.3% of all deaths. CVD claims more lives each year when compared to deaths from cancer. More than 2150 Americans die of heart disease every day, on an average 1 death every 40 seconds. Of interest is the fact that 34% of deaths occur before the age of 75 years, which is below the life expectancy of 78.7 years. However, there has been a decline in death rates attributable to CVD by 30.8%, and a relative decline in stroke death by 36%. It is noteworthy that if all forms of CVD were eliminated, life expectancy would rise by 7 years; whereas if all forms of cancer were eliminated, 3 additional years would be added [1]. The direct and indirect cost of CVD for 2011 was estimated at approximately $320.1 billion for those with heart conditions, stroke, peripheral artery disease, and high blood pressure [1]. CVD costs more than any other diagnostic condition.

I will focus on two aspects on recent developments in CVD: 1) research, and 2) control of risk factors.

RESEARCH

There have been great accomplishments in the diagnosis and treatment of CVD in the last four decades; however, most if not all of these advances have been in the application of cutting edge technology, pharmacotherapy, and surgical techniques to treat the manifestations and symptoms of the disease. However, in many disease states the best approach towards treating an illness and its manifestations remains controversial. This holds true for such common entities such as atrial fibrillation, coronary artery disease (CAD), infarct-size modulation immediately post myocardial infarction, heart failure and cardiomyopathies. In this regard, outcome research utilizing different approaches, such the ongoing Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) [4] to determine which method affords the best outcome in terms of symptomatic relief and survival, but also quality of life measures and cost are needed. Recently, a prospective randomized study (FREEDOM) [5] showed that coronary bypass surgery was superior to stents in patients with diabetes. The study also found a better outcome including mortality in patients undergoing coronary artery bypass than those undergoing stents. Over the long run, surgery was also more cost effective. It is of considerable interest that a recent study [6] showed that Transcatheter Aortic Valve Replacement (TAVR) is the preferred method relative to surgical replacement in high risk elderly patients. However, long term benefit (> 1year), stroke and silent brain infarcts, and quality of life improvement, expansion of indications to include patients with intermediate risk, need to be addressed.

Atherogenesis and Plaque Modulation [7-17]

Atherosclerosis, a condition wherein fat is deposited in the arteries, is the cause of coronary artery disease and peripheral vascular disease. It can also affect the

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arterial system throughout the body including the brain and kidney. The critical biochemical event in atherosclerosis is the deposition of apolipoprotein-B (apoB) containing lipoproteins within the wall of an artery. This process leads to local responses that result in an accumulation of macrophages that consume the retained lipoproteins. Unfortunately, these macrophages fail to emigrate from the site, and are intricately involved in the formation of the atheromatous plaque, which when it ruptures sets up a cascading blood clotting process that results in thrombosis and myocardial infarction. At this moment in time we have no ability to regress the atheroma with the use of drugs that lower the low density lipoproteins and arrest the development of an atheromatous plaque. Studies in animals have shown that statin drugs that reduce the levels of low density lipoproteins also have the ability to cause some regression of the plaque; however, animal models are not close to or akin to the intact human heart. Although, statins are known to improve survival and reduce the incidence of heart attacks in man, perhaps by altering the vulnerable plaque (by lipid removal and deposition of fibrous tissue and calcium), the exact mechanism of how they work remains poorly defined. Current and future research towards identification of plaque characteristics (vulnerable plaque) with the use of imaging modalities such as optical coherence tomography (OCD), near-infrared spectroscopy (NIRS), magnetic resonance imaging (MRI), and positron emission tomography (18F-FDG PET) could provide valuable information. Furthermore, it may be possible by using the latter techniques to study the effects of drugs on “plaque regression” with attention devoted to the macrophages. Better understanding of the biochemistry and biophysics of the “atheromatous plaque,” may lead to the development of new drugs to prevent the cascade of events that result in atherosclerosis. Recent studies (DESCARTES and MENDEL – 2) of an investigational agent, evolocumab, a monoclonal antibody that targets proprotein convertase subtilisan/kenin type 9 (PCSK9) given by monthly injection proved highly effective in lowering LDL-C and increasing HDL-C. However, the long term benefit of these agents in preventing coronary events and mortality has yet to be determined. There is no doubt that biologicals, currently in use in rheumatology, oncology, and skin diseases such as psoriasis, have the potential of a paradigm shift in the management of atherosclerotic disease. However, it is noteworthy that in the future alternate genetic pathways might be discovered independent of the lipid hypothesis.

Genetic Interventions [18-29]

Advances in management once the disease has taken hold does not address the root cause of illness. The cause of many diseases including CVD and cancer has a genetic basis (inherited or mutated) with secondary interaction of the environment. As far as heart rhythm abnormalities are concerned, such entities like the Long QT Syndrome, the Brugada Syndrome, Right Ventricular Dysplasia, and catecholaminergic polymorphic ventricular tachycardia (CVPT), have solely a genetic basis. Even sudden cardiac death in patients with acute myocardial infarction might have an inherited basis. On the other hand the genetic basis of coronary artery disease is likely pleomorphic with involvement of a multitude of genes not yet defined. In a recent study in Iceland, a gene was found with a strong link to cardiovascular disease.

Not surprising, genomic and genetic research has received considerable attention in recent years. Ultimately correction of the genetic abnormality will be the tour-de-force except in mechanical abnormalities such as valve dysfunction. However, the ambitious undertaking of altering or *fixing* ones genetics is probably eons away. Three areas that are the subject of intense investigation could produce some dividends in the future, if not revolutionize the field of CVD over the long run. These include: 1) Gene therapy: gene transfer to restore heart muscle viability and improve function of damaged myocardium following myocardial infarction has potential benefits. Here stem cells from donors and patients own bone marrow cells have been injected into the diseased heart muscle. In a recent study, injection of mesenchymal stem cells was associated with some improvement in functional capacity, quality of life and remodeling. A more recent multicenter study comparing different bone marrow derived stem cells approaches compared with standard therapy in patients with reperfused ST elevation myocardial infarction was disappointing. No improvement of left ventricular ejection fraction and left ventricular end systolic volume occurred in the stem cells groups when compared to standard treatment. Thus, the type of stem cells and their benefit in improving heart function has remained controversial. Moreover, some authorities feel that the whole area is premature and too hyped. Nonetheless, phase II-III studies for c-kit cells, mesenchymal stem cells and cardiosphere-derived cells are needed. Delivering targeted biological agents to stimulate progenitor cell populations rather than injecting cells maybe another option.

Takahashi and Yamanaka induced pluripotent stem cells (iPS cells) from a non-pluripotent cell, typically an adult somatic cell by inducing a forced expression of specific genes. These cells could have the potential in differentiating into cardiac myocytes in damaged infarcted heart muscle. Additionally, these cells, which are obtained from the patients themselves, could be a source of fertile investigation in those with proven genetic abnormalities such as the Long QT Syndrome, and other inherited or mutated entities, leading to the correction of proteonomic genetic abnormalities. 2) It is well known in medicine that drugs affect human beings both in terms of efficacy and toxicity, rather differently. Thus one of the promising outcomes of genomic research is to establish to what extent genetic differences account for drug responses. Recently, geneticists assayed hundreds of thousands of genetic markers covering the entire human genome to search for and identify genes that cause disease. This *genome-wide association study* (GWAS) assayed ~326,000 markers in 1,053 Swedish patients to identify genes that alter response to the anticoagulant drug warfarin, since patients vary widely in the dose of the drug to prevent clotting. This study detected two genes (*VKORC1*, *CYP2C9*) already known to cause ~40% of the variability in warfarin dose and discovered a new gene (*CYP4F2*) contributing 1%–2% of the variability. Thus it is possible that patients might benefit from individualized dose forecasting based on a patient's genetic makeup. This approach may provide clinical benchmarks for drug use in the foreseeable future. The GWAS study also established the heritable nature of AF. Polymorphism within the chromosome 4q25 confers risk of AF. Future studies are needed to further identify genetic and molecular causal variants in AF.3) There are a host of other approaches such as the study of proteins encoded by genes, and gap junctions between myocardial cells and transplanted embryonic and stem cells that should be the subject of future investigation.

CONTROL OF RISK FACTORS

High Blood Pressure [1-3]

Nearly 32.6% of US adults ≥20 years of age have high blood pressure, accounting for an estimated 80 million US adults with hypertension. Although the prevalence of high blood pressure is nearly equal between the sexes, African American adults have among the highest rates of hypertension, a whopping 44%. Nearly ≈82% are aware of their condition, 75% are on blood pressure lowering drugs, but only 53% of those are aware that their blood pressure is under control. Needless to say, education about the consequences of uncontrolled high blood pressure in the causation of heart disease, kidney disease, and stroke particularly in the American-African community, and to reduce the intake of dietary sodium are of paramount importance. Primary care clinics directed at prevention, and universal health care should go a long way in controlling high blood pressure and its consequences. However, the control of blood pressure with drugs and its benefits regarding organ damage and mortality on the long run is not established in all population groups, and despite a host of studies, still remains controversial. Indeed, recent guidelines [30] have modified what we term as hypertension from 140/90 to 150/90 in patients over 60 years of age. The definition of what constitutes hypertension for treatment purposes in the age group below 60 years is less well established. Although there was insufficient medical evidence to support systolic blood pressure threshold for drug treatment in people younger than 60 years of age, the guideline committee opined that the current threshold of lower than 140 systolic should stand.

New modalities of therapy such as sympathetic denervation of the renal arteries remain highly controversial. A recent multi-center study negated the findings of previous studies of sympathetic denervation in patients with high blood pressure difficult to control with drugs alone [31].

Cigarette Smoking [1-3]

There is no doubt that significant progress has been made to curtail smoking in the United States. It is no longer permissible on public transportation including airplanes, buses and trains and places of public gathering including restaurants and parks and even city streets. Despite four decades of progress in curtailing smoking, in 2012, 20% of American men and 16% of women >18 years of age have continued cigarette smoking. In 2013, 22% of students from grades 9 through 12 reported tobacco use. Fortunately, the percentage of current cigarette smokers declined by 26% since 1998. Similarly, secondhand smokers, declined by 40% from 2007 to 2008. Hopefully, there will be a further decline in these figures because of current restrictions in smoking, and taxation on cigarettes imposed in most states.

Cholesterol and Diabetes [1-3]

An estimated 30.9 million adults (13%) ≥20 years of age have total serum cholesterol levels ≥240 mg/ld.

Abnormal lipid levels among youth 12 to 19 years of age are around 20%; however, 42.9% of obese youth have ≥ one abnormal lipid level. Cholesterol levels, and particularly low density lipoproteins, have been shown to increase the risk for coronary artery disease. In 2010, an estimated 19 million Americans had diagnosed diabetes mellitus, representing 8% of the adult population. An additional 8 million had undiagnosed diabetes mellitus, and 38% had pre-diabetes, with abnormal fasting glucose levels. African Americans, Mexican Americans, Hispanic/Latino individuals, and other ethnic minorities bear a strikingly disproportionate burden of diabetes mellitus in the United States. Needless to say, aggressive weight control with diet and exercise are needed to control the metabolic syndrome, which is characterized by truncal obesity, diabetes, high blood pressure, high cholesterol, and insulin resistance. The intake of excessive amount of carbohydrates, a sedentary life style, and undue stress likely plays a dominant role in individuals with the metabolic syndrome (incidence, age adjusted = 23%). We now know that the requirement of both drugs and insulin go substantially down in those who lose weight and in those who have bariatric surgery, where weight reduction is significant.

It is unfortunate that the prevalence of obesity and the metabolic syndrome is increasing in developing countries. Unfortunately, a higher standard of living, better socio-economic standard and more people entering the middle class is associated with a greater sedentary life style, fast foods, and a fast paced life style, all detrimental to cardiovascular health.

In subjects who have a strong family history of coronary artery disease, diet, control of cholesterol and exercise should be considered at an early age. Furthermore, control of such risk factors like high blood pressure, high cholesterol and diabetes in patients who have had symptoms of coronary artery disease and a heart attack is of paramount importance. Recent guidelines [32] sponsored by the American Heart Association and the American College of Cardiology for the use of high dose statins for secondary and primary prevention of CAD have met with substantial controversy. These guidelines recommend statin treatment intensity (i.e., high or moderate) rather than specific LDL cholesterol goals levels (in contrast to guidelines released in 2001), to guide clinicians' treatment of persons most likely to benefit from statin therapy (e.g., people with existing CVD or high risk of developing CVD).

It is noteworthy that control of risk factors with the use of drugs has produced mixed results. Barely 40% of patients in developed countries and 10% in developing countries continue to take their medication on a long term basis [33]. In 2003, Wald and Law [34] introduced the concept of the *polypill* as a new method for the global prevention of CVD. The idea proposed to develop a single pill composed of a fixed combination of pharmacological drugs that have individually been shown to effectively treat risk factors such as high cholesterol, hypertension, the clotting mechanism, and folic acid to lower serum homocystine levels. They reasoned that this single polypill would reduce coronary artery disease by 88% and strokes by 80% if taken by everyone above the age of 55 years irrespective of the risk profile, and everyone with existing CAD. A recent multicenter study, The UMPIRE Randomized Clinical Trial [35] studied 2004 participants with established CVD or at risk of CVD in India and Europe. These participants were taking multiple medications for high blood pressure and high cholesterol prior to enrollment. The polypill group were given a combination of two blood pressure medications (lisinopril 10 mg and atenolol 50 mg) plus one lipid lowering agent (simvastatin 40 mg), and aspirin (75 mg), while the usual care group continued individual medications as usual. The study found significantly improved medication adherence at 15 months in those with or at high risk of CVD who were taking the polypill with small improvements in blood pressure and LDL cholesterol. There was a higher rate of cardiovascular events in the polypill group as compared to those in the usual group (5.0% vs. 3.5%); however, these differences were not statistically significant.

Although the idea of the polypill sounds interesting particularly in adhering to drug therapy for the secondary prevention of CAD, there are several aspects that raise questions. These include: insurmountable costs that could run in billions of dollars if this approach is used for primary prevention; the drugs/dosages used will not likely be equally effective in everyone, there could be side effects from one or more drugs in the pollypill, and perhaps importantly, many will be tempted to continue their habits thinking that the medications will protect them. "Pills" or "drugs" are not necessarily the solution to risk modification. Lifestyle changes focusing on exercise, a healthy diet, and relaxation should be at the forefront of risk modification.

The Obesity Epidemic and its Consequences [1-3]

It is estimated that 155 million representing about 68% of the US populations (≥20 years of age) is overweight. Obesity (body mass index ≥30 kg/m^2) was present in approximately 35% of US adults. Both sexes of all races and ethnic groups are affected by the epidemic of overweight and obesity. What is even more disturbing is the prevalence of overweight and obesity in children between the ages of 2 to 19 years. Approximately 32% are overweight and obese (which represents 24 million children), of which 17% are obese (13 million children). Among the ethnic groups, Mexican American boys and girls, and African American girls are disproportionately affected. It is disturbing that over the past three decades, the prevalence of obesity in children has increased dramatically from ≈4% to 19%.

The proportion of youth (≤18 years of age) engaging in no regular physical activity is high, and the proportion increases with age. The American Heart Association and 2008 federal guidelines on physical activity (PA) recommended that children get at least 60 minutes of PA daily, and adults get at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity per week as well as perform muscle-strengthening activities at least 2 days per week. On the basis of survey interviews, performed in 2011 and 2012, approximately 36% of children and 44% of adults met these criteria.

Between 1971 and 2004, average total energy consumption among US adults increased by 22% in women (from 1542 to 1886 kcal/d) and by 10% in men (from 2450 to 2693 kcal/d). The increases in calories consumed during this time period are primarily attributable to an increase in carbohydrate intake, in particular: starches, refined grains, and sugars. Undoubtedly, other factors that have played a role and continue to do so include larger portion sizes, greater food quantity and calories per meal, and increased consumption of sugar-sweetened beverages, snacks, fast food meals, and higher energy-density foods. It is unclear what impact the use of hormones and antibiotics in poultry and cattle have on human obesity.

Obesity is associated with excess mortality and morbidity. It results in the development of diabetes mellitus, CVD end points (including coronary heart disease, atrial fibrillation, stroke, and heart failure), high blood pressure and other health conditions, including asthma, cancer, degenerative joint disease, and sleep apnea. The prevalence of diabetes mellitus alone shows an exponential increase over time, in parallel with the increases in prevalence of overweight and obesity.

There is no question that obesity in youth as well as in adults is related to a sedentary life style and diet. However, there may be genetic factors, and more recent studies in mice and humans have implicated intestinal bacteria in the role of obesity [36].

Undoubtedly, the entire American culture regarding our eating habits needs an overhaul. It is *not* in the interest of industry (food or beverage), to make these changes. Public awareness of these issues should be fostered by the Surgeon General and such organizations as the American Heart association and the American College of Cardiology. However, only the power of the Federal Government, as was the case with smoking can deliver these changes. A recent example is Mayor Michael Bloomberg of New York City who limited the size of sugary drinks to 16 ounces or less at restaurants, street carts, entertainment and sports venues. However, one day before the law went into effect, the Supreme Court in Manhattan called the limits “arbitrary and capricious” and struck down the law. An Appeals Court unanimously upheld the decision striking down the restriction. Of course some argue that controls infringes on freedom. However, freedom to put on weight, to be obese, to develop diabetes and high blood pressure and bankrupt state and federal coffers is not freedom. It is self-destruction.

REFERENCES

[1] Mozaffarian D, Benjamin EJ, Go AS, *et al*. Heart Disease and Stroke Statistics–2015 Update: A Report from the American Heart Association. Circulation 2015; 131: 29-322. http://dx.doi.org/10.1161/CIR.0000000000000152

[2] Go AS, Mozaffarian D, Roger VL, *et al*. Heart Disease and Stroke Statistics– 2014 Update: A Report from the American Heart Association. Circulation 2014; 128: 01-267.

[3] Roger VL, Go AS, Lloyd-Jones DM, *et al*. AHA Statistical Update: Heart Disease and Stroke Statistics-2011 Update: A report from the American Heart Association. Circulation 2012; 127: e6-e245.

[4] Packer DL. Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation. https://clinicaltrials.gov/ct2/show/NCT00911508

[5] Farkouh ME, Domanski M, Sleeper ScD, *et al* for the FREEDOM Trail Investigators: Strategies for Multivessel Revascularization in patients with Diabetes. N Engl J Med 2012; 367: 2375-84. http://dx.doi.org/10.1056/NEJMoa1211585

[6] Adams DH, Popma JJ, Reardon MJ, *et al*. Transcatheter Aortic – Valve Replacement with a Self-Expanding Prosthesis. N Engl J Med 2014; 370(19): 1790-98. http://dx.doi.org/10.1056/NEJMoa1400590

[7] Blankenhorn DH, Hodis HN. George Lyman Duff Memorial Lecture. Arterial imaging and atherosclerosis reversal. Arterioscler Thromb, 1994; 14: 177-92. http://dx.doi.org/10.1161/01.ATV.14.2.177

[8] Schell WD, Myers JN. Regression of atherosclerosis: a review. Prog Cardiovasc Dis 1997; 39: 483-96. http://dx.doi.org/10.1016/S0033-0620(97)80041-2

[9] Stein Y, Stein O. Does therapeutic intervention achieve slowing of progression or bona fide regression of atherosclerotic lesions? Arterioscler Thromb Vasc Biol 2001; 21: 183-8. http://dx.doi.org/10.1161/01.ATV.21.2.183

[10] Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993; 362: 801-9. http://dx.doi.org/10.1038/362801a0

[11] Wissler RW, Vesselinovitch D. Studies of regression of advanced atherosclerosis in experimental animals and man. Ann N Y Acad Sci 1976; 275: 363-78. http://dx.doi.org/10.1111/j.1749-6632.1976.tb43368.x

[12] Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. J Clin Invest 1990; 85: 1234-41. http://dx.doi.org/10.1172/JCI114558

[13] Feig JE, Shang Y, Rotllan N, *et al.* Statins Promote the Regression of Atherosclerosis *via* Activation of the CCR7-Dependent Emigration Pathway in Macrophages. PLoS One 2011; 6(12): e28534. http://dx.doi.org/10.1371/journal.pone.0028534

[14] Nissen SE, Nicholls SJ, Sipahil, *et al.* Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295: 1556-65. http://dx.doi.org/10.1001/jama.295.13.jpc60002

[15] Miyamoto Y. Okura H, Kume T, *et al.* Plaque characteristics of thin-cap fibroatheroma evaluated by OCT and IVUS. JACC Cardiovasc Imaging 2011; 6: 638-46. http://dx.doi.org/10.1016/j.jcmg.2011.03.014

[16] Dixon SR, Grines CL, Munir A, *et al.* Analysis of target lesion length before coronary artery stenting using angiography and near-infrared spectroscopy versus angiography alone. Am J Cadiol 2012; 109: 60-6. http://dx.doi.org/10.1016/j.amjcard.2011.07.068

[17] Feig JE, Vengrenyuk Y, Reiser V, *et al.* Regression of atherosclerosis is characterized by broad changes in the plaque macrophage transcriptome. PLoS One 2012; 7: e39790. http://dx.doi.org/10.1371/journal.pone.0039790

[18] Kass RS. The channelopathies: novel insights into molecular and genetic mechanisms of human disease. J Clin Invest 2005; 115 (8): 1980-6. http://dx.doi.org/10.1172/JCI26011

[19] Martin CA, Matthews GDK, Huang CJ-H. Sudden cardiac death and inherited channelopathy: the basic electrophysiology of the myocyte and myocardium in ion channel disease. Heart 2012; 98: 536-43. http://dx.doi.org/10.1136/heartjnl-2011-300953

[20] Napolitano C, Bloise R, Monteforte N, Priori SG. Sudden cardiac Death and Ion Channelopathies. Long QT, Brugada, Short QT, catecholaminergic Polymorphic Ventricular Tachycardia and Idipathic Ventricular Fibrillation. Circulation 2012; 125: 2072-34. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.055947

[21] Gudbjartsson DF, Helgason H, Gudjonsson S, *et al.* Large-scale whole-genome sequencing of the Icelandic population. Nature Genetics 2015; 47: 435-44. http://dx.doi.org/10.1038/ng.3247

[22] Hare JM, Traverse JH, Henry TD, *et al.* A Randomized, Double-Blind Placebo-Controlled, Dose-Escalation Study of Intravenous Adult Human Mesenchymal Stem Cells (prochymal) After Myocardial Infarction. J Am Coll Cardiol 2009; 54: 277-86. http://dx.doi.org/10.1016/j.jacc.2009.06.055

[23] Hare JM, Fishman JE, Gerstenblith G, *et al.* Comaparison of Allogenicvs Autologous Bone marrow-Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients with Ischemic Cardiomyopathy. The Poseidon Randomized Trial. JAMA 2012; 308(22): E1-E7. http://dx.doi.org/10.1001/jama.2012.25321

[24] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblasts cultures by defined factors. Cell 2006; 126(4): 663-76. http://dx.doi.org/10.1016/j.cell.2006.07.024

[25] Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. Nature 2007; 228(7151): 313-7. http://dx.doi.org/10.1038/nature05934

[26] San Roman JA, Sanchez PL, Villa A, *et al.* Comparison of different Bone Marrow derived Stem Cells approaches in Reperfused STEMI. JACC 2015; 65(22): 2372-2382. http://dx.doi.org/10.1016/j.jacc.2015.03.563

[27] Yaniz–Galende E, Chen J, Chemaly E, *et al.* Stem cell factor gene transfer promotes cardiac repair after myocardial infarctionvia in situ recruitment and expansion of c-kit cells. Circ Res 2012; 111: 1434-1445. http://dx.doi.org/10.1161/CIRCRESAHA.111.263830

[28] Takeuchi F, McGinnis R, Bourgeous S, *et al.* A genome – Wide Association Study Confirms VKORC1, CYP2C9 and CYP4F2 as Principal Genetic Determinants of Warfarin Dose. PLoS Genet 2009; 5(3): e1000433. http://dx.doi.org/10.1371/journal.pgen.1000433

[29] Lenfant C. Cardiovascular Research: A look into Tomorrow Circulation Research 2001; 88: 253-55.

[30] James PA, Oparil S, Carter BL, *et al.* Evidence-Based Guideline for the Management of High Blood Pressure in Adults. JAMA 2014; 312(3): 507-520. http://dx.doi.org/10.1001/jama.2013.284427

[31] Bhatt DL, Kandzari DE, O'Neill WW, *et al.* A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014; 370: 1393-1401. http://dx.doi.org/10.1056/NEJMoa1402670

[32] Stone NJ, Robinson JG, Lichtenstein AH, *et al.* 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Circ 2014; 129: 51-S45. http://dx.doi.org/10.1161/01.cir.0000437738.63853.7a

[33] Sang G, Fuster V. Prevention. Polypill for cardiovascular prevention: a step forward? Nat Rev Cardiol 2013; 10: 683-4. http://dx.doi.org/10.1038/nrcardio.2013.157

[34] Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003; 326(7404): 1419-23. http://dx.doi.org/10.1136/bmj.326.7404.1419

[35] Thom S, Poulter N, Field J, *et al.* Effects of a Fixed Dose Combination Strategy on adherence and Risk factors in patients with or at high risk of CVD. The UMPIRE Randomized Clinical Trial. JAMA 2013; 310 (9): 918-929. http://dx.doi.org/10.1001/jama.2013.277064

[36] Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Human gut microbes associated with obesity. Nature 2006; 444: 21-28. http://dx.doi.org/10.1038/4441022a

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