Diet and Cardiovascular Diseases: Heart Failure

Part I: Plant Based Diet, Beneficial Macronutrients

Abstract

Diet is a major modifiable factor in the prevention and management of cardiovascular diseases. Optimal body weight with a BMI between 20 and 24.9 (18.5 to 24.9 for Asians), and a diet rich in non-starchy vegetables, fruits, whole grains, legumes, moderate in consumption of nuts, seafood, lean meats, low-fat dairy products, and unsaturated vegetable oils, and limited in saturated fats, sodium, red meat, refined carbohydrates, and sugar-sweetened beverages is cardiovascular protective. Trans fats are extremely unhealthy. The benefit of a healthy diet extends to heart failure (HF). Dairy, coffee, tea, and chocolate may also be vascular friendly. Alcohol has a U-shaped relationship, with low to moderate intake cardiovascular healthy, while heavy intake usually causes harm. Some minerals and vitamins are also helpful in the prevention and management of HF. HF is increasing in incidence and prevalence in most world countries. It is associated with severe disability and is a major cause of death globally. The impact of a healthy diet on the development and progression of HF is discussed in this manuscript (in 2 parts).

Keywords: heart failure, plant-based diet, processed red meat, Mediterranean diet, DASH diet

Introduction

Heart failure (HF) is a common global disease[1], affecting between 1% and 2% of all adults[2]. There were 56.2 million prevalent cases of HF in 2019[3] with the older population is disproportionately affected[4]. The risk of developing HF at age 55 is around 33% for men and 28% for women[5]. With growing aging population and increasing worldwide obesity, the prevalence of HF is projected to increase by nearly 50% between 2012 and 2030[6]. HF results from an abnormality of cardiac structure or function[7]. The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) defines HF into three subtypes depending on the left ventricular ejection fraction: HF with a reduced EF (HFrEF) [EF is < 40%], HF with a mid-range or mildly reduced EF (HFmrEF) [EF 40–49%], and HF with preserved EF (HFpEF) [EF ≥ 50%][8]. HFrEF is the most common type in men, whereas HFpEF is the most common type in women[9]. In HFrEF, the systolic function is impaired, while in HFpEF, the diastolic function is abnormal. Several conditions act as etiologies for HF – these include hypertension (HTN)[10], coronary artery disease (CAD)[11], dilated cardiomyopathy[12], hormonal dysfunction[13], infections (such as Chagas' disease)[14], and drug use[15]. The pathological processes leading to structural abnormalities and functional problems involved include hemodynamic stress[16], neuro-endocrine activation[17], and inflammation[18].

Despite significant advances in the prevention and treatment of HF having developed in the last decades[19], life continues to be difficult for these patients. Forward failure results in HF patients

complaining of excessive fatigue, due to reduced aerobic capacity, decreased muscle strength, and limited exercise intolerance[20]. With increasing reduction in peripheral circulation, signs of cardiac cachexia develop. Backward failure due to volume or pressure overload leads to high pulmonary pressure and pulmonary congestion, leading to dyspnea. Liver congestion, ascites, and edema develop in the chronic stage due to volume overload, partly resulting from the permanent activation of compensatory neurohumoral systems[21]. Consequently, HF patients have a poor quality of life[22]. They are frequently hospitalized[23]. It is estimated that 83% of HF patients are hospitalized at least once, and almost 45% are hospitalized four times or more times[2]. HF is also associated with a high frequency of disability[24] and increased mortality[25]. Almost 32.9% of patients with decompensated HF die within one year following hospital discharge[26]. HF patients also frequently have multiple cardiovascular and non-cardiovascular comorbidities, which contribute to poor outcomes, increased rates of hospitalization, and higher mortality[27,28]. HF is responsible for extremely high healthcare costs globally[29,30].

Discussion

According to estimates by the World Health Organization (WHO), about three-quarters of deaths from cardiovascular disease (CVD) can be prevented by changes in lifestyle[31]. Diet is an established modifiable risk factor involved in the prevention, development, and management of CVDs[32]. Healthy dietary patterns are associated with lower cardiovascular morbidity[33], lower disability[34], and improved quality of life (QOL)[35]. A healthy diet also lowers CVD mortality rates[36]. Heart failure patients are no exception. In a prospective cohort study of 20,900 healthy men, healthy lifestyle habits significantly decreased the lifetime risk of heart failure[37]. Lack of exercise, smoking, excessive alcohol intake, obesity and a poor diet are major modifiable risk factors for HF[38-40]. Modification of diet remains an easy, cheap, non-drug, and non-interventional method of beneficially impacting HF. This manuscript discusses the various benefits and harms of different dietary patterns in the development and progression of HF. A healthy diet helps improve many features of HF[41]. Diet also plays a significant role in affecting the several risk factors for HF, including hyperlipidemia, HTN, and diabetes mellitus (T2DM)[42].

Plant-Based Diet

Several meta-analyses have reported that diets rich in fruits, vegetables, whole grains, nuts, seeds, and other plant-based foods reduce the risk of heart disease, including heart failure[43-45]. In the Physicians' Health Study of 20,900 healthy male physicians, greater consumption of fruits and vegetables was associated with a decreased risk of HF[46]. In a study of 38,075 Finnish people for a median of 14.1 years, higher consumption of vegetables was associated with a lower incidence of HF in men, but not in women[47]. In a prospective cohort from Sweden of 34,319 women without CVD and cancer at initial assessment, after a follow up period of 12.9 years, greater fruit and vegetable consumption was associated with a lower rate of HF[48]. In the Reasons for Geographic and Racial Differences in Stroke study (cohort of 15,569 people with no CAD or HF diagnosis at enrollment, showed in a subset analysis that after a median follow-up of more than 7 years, patients with closer adherence to plant-based dietary patterns had a lower risk of incident HF[49]. The beneficial role of plant-based diets in improving ejection fraction and positively remodeling the cardiac muscle is now well accepted[50,51]. Plant-based diets reduce

inflammation[52], decrease oxidative stress[53], reduce blood pressure (BP)[54], lower Hba1c[55], produce less trimethylamine-N-oxide (TMAO)[56], and lower serum lipid levels[57].

Vegetables and Fruits

Fruits and vegetables contain several micronutrients that help protect against HF. In a cross-sectional study, Polidori et al. found lower plasma concentrations of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene. and β-carotene in patients with heart failure compared with healthy controls[58]. A retrospective study reported marked decreases in HF incidence with increasing tomato consumption[59]. Tomatoes like papaya and watermelon have high levels of lycopene, and lycopene is cardio protective[60]. Several subsequent studies have confirmed the clinical implications of high fruit and vegetable consumption in HF[46,47]. In a study of middle-aged and older women followed for >10 years, there was an inverse association between higher fruit and vegetable intake (esp. >5 servings/day) and the rate of HF incidence[48]. Rautianen et al,. in a study published in 2015, reported that the consumption of apples, pears, and berries as well as green leafy vegetables, was inversely associated with HF risk in a dose-response manner[48]. Moderate vegetable (about 1 cup of green leafy vegetables (providing about 60 mg/day of vegetable nitrate) intake was associated with a 15% reduction in HF[61]. Besides the benefits mentioned before[52-57], fruits and vegetables also increase ejection fraction[62] and improve functional capacity[63]. These studies support recommendations of intake of five servings per day of fruit and vegetables, for good HF health.

Chocolate

A meta-analysis showed that chocolate consumption in moderation may be associated with a decreased risk (16% less) of HF[64]. However, higher amounts may lead to weight gain as chocolate, especially milk chocolate, often has a high calorie content[65]. Obesity is a known risk factor for developing HF[66,67].

Fish

Several prospective studies have reported that fish consumption is associated with decreased HF risk[68-73]. A meta-analytic study reported an inverse association between HF risk and oily fish consumption[74]. Fried fish, however, increases the risk of HF[68,75]. It is postulated that unfried fish is beneficial due to its high content of omega-3 fatty acids[76].

Eggs

Prospective studies have reported an increased incidence of HF (28–64 %) with egg consumption[77,78]. A 2017 meta-analysis reported a 25 % increase in the risk of incident HF in those with the highest compared to the lowest egg consumption[79]. Another recent study showed that intake of one egg per day was associated with an increased risk of heart failure when compared to no consumption[80]. The risk increased as the number of eggs consumed per week increased – for 7 eggs [summary relative risk or SRR = 1.15), for 8 eggs per week (SRR = 1.19 and for 9 eggs per week (SRR = 1.23) especially in men[80]. The American Heart Association guidelines consider one egg per week safe for patients who are healthy[81].

Alcohol

Most epidemiologic data is consistent with the potential benefits of moderate drinking on the risk of HF[82]. This relationship has been frequently studied. In the Framingham Heart Study, there was a 59% lower risk of HF in men consuming 8 to 14 drinks per week when compared to abstainers[83]. The Cardiovascular Health Study reported a 34% lower risk of HF in people who consumed 1 to 6 drinks per week (Hazard Ratio=0.66) when compared with abstainers[84]. Klatsky et al. found that light-to-moderate alcohol consumption was associated with a 40% to 50% lower risk of HF in individuals with antecedent myocardial infarction (MI)[85]. In another large study, compared with abstainers, US male physicians reporting alcohol consumption of 7 or more drinks per week had a 38% lower risk of HF[86]. More recently, Larsson et al., in meta-analysis, (total of 13 prospective studies, with 13,738 HF cases and 355,804 participants), reported that light alcohol drinking (0.1-7 drinks/week) was inversely associated with the risk of HF (Risk Ratio or RR=0.86)[87]. They found that compared with non-drinkers, the RR across levels of alcohol consumption was 0.90 for 3 drinks/week, 0.83 for 7 drinks/week, 0.84 for 10 drinks/week, 0.90 for 14 drinks/week, and 1.07 for 21 drinks/week[87]. This study demonstrated that the risks of HF go up as the amount of alcohol consumed increases. Two other meta-analyses confirmed that high levels of alcohol consumption increase the risk of heart failure[88,89]. In the United States, one "standard" drink is 12 ounces of regular beer, which is usually about 5% alcohol, 5 ounces of wine, which is typically about 12% alcohol, and 1.5 ounces of distilled spirits, which is about 40% alcohol[90]. The detrimental effects HF were reported in 2005 by Klatsky and collegues[85]. They determined that the risk of HF without antecedent MI among heavy drinkers was 1.7-fold higher than in abstainers. In the most recent meta-analysis, it was noted that the dose–response relationship between alcohol consumption and HF appeared to be curvilinear[87]. Compared to non-drinkers, the risk for 1–84 g per week, 85–168 g per week, 168–336 g per week, and >336 g per week was RR = 0.86, 0.88, 0.91, and 1.16, respectively. In the United States, a ‘standard drink’ (as described earlier) contains 14 g of pure alcohol[91]. Larsson et al., based on a meta-analysis of eight studies, concluded that former drinkers were at a higher risk for HF compared to lifetime abstainers (RR = 1.22)[87]. Klatsky et al. found no association between beverage types (beer, wine, or spirits) and HF[85]. Moderate alcohol intake also reduces the risk of two major risk factors for HF - MI and T2DM[92,93]. The beneficial effects are mediated through raising high-density lipoprotein cholesterol[94], improving insulin sensitivity[95,96], raising plasma levels of adiponectin[97], inhibiting inflammation[98], improving endothelial function[99], influencing platelet aggregation[100], coagulation factors[101], and fibrinolysis[102,103], and increasing the plasma concentration of atrial natriuretic peptide[104].

Whole Grain

Whole grain (kernel) is made up of three key edible parts – the bran, the germ, and the endosperm – covered by an inedible husk. The husk protects the kernel from external assaults such as sunlight, pests, water, and disease. Whole grains contain all three edible parts of the kernel. Whole grain is rich in biologically active compounds, such as fiber, vitamins, minerals, antioxidants, and other beneficial plant compounds including lignans and phytosterols[105-107]. These biological compounds help the cardiovascular system by several mechanisms, including

altering glucose homoeostasis, lipids, and lipoproteins, and endothelial function[108]. Several prospective cohort studies and their meta-analyses have reported a lower risk of CVD with a higher consumption of whole grains[109]. Refined grains have the bran and germ removed and, as a result, lack several beneficial ingredients. The benefit of whole grain intake has been reported in HF. A prospective study of individuals consuming seven servings of whole grain breakfast cereal weekly, during a 19.6-year follow-up period, reported a 29 % decrease in HF risk when compared to individuals with no intake of these cereals[110]. A subsequent prospective study confirmed the beneficial effects and reported a 7 % decrease in HF risk with each additional wholegrain serving[111].

Dairy

There is a sparsity of studies on the effect of dairy on heart failure. A prospective study done in 2008 reported that dairy intake was associated with an 8 % increase in HF risk[111,112]. However, a recent systematic review and meta-analysis of prospective studies noted an inverse relationship between biomarkers of dairy intake and HF incidence[113].

Nuts

Nuts (such as almonds, Brazil nuts, cashews, hazelnuts, macadamias, peanuts, pecans, pine nuts, pistachios, and walnuts) are rich sources of mono and poly unsaturated fatty acids, protein, fiber, several minerals (e.g., magnesium, potassium, and zinc), vitamin E, folic acid, and other bioactive micronutrients such as phenolics and phytosterols[114]. Meta-analyses of prospective studies have shown that nut consumption is beneficial for cardiovascular diseases[115-117]. Data from prospective studies on nut consumption in relation to heart failure is, however, limited[111,118,119]. Observational studies and clinical trials have shown cardiovascular benefits of nut consumption. Compared to non-consumers, one study reported that walnut consumption was associated with better diastolic function in young to middle-aged adults[120]. Nut consumption is also associated with a decrease in BP[121]. HTN is known to increase the risk of HF by 2–3 fold[122]. Nut intake also helps to reduce the risk of T2DM[123] which is also a risk factor for HF[124]. There is also a helpful weight loss with nut intake, provided the intake is not high[125]. Two earlier prospective studies found no association between nut consumption and HF incidence[118,119]. However, in a recent study, nut consumption was inversely related to heart failure. Compared with no nut consumption, for heart failure, the corresponding Hazard Ratio for (frequency of nut consumption: none;1–3/month;1–2/week; ≥3/week were 0.87, 0.80, and 0.98 respectively[126]. The reduced risk of heart failure associated with moderate but not high nut consumption might be related to the fact that high nut consumption increases rather than decreases body weight.

Nut consumption may favorably influence cardiovascular health by improving blood lipid levels[127,128], and its anti-inflammatory[129], and antioxidant effects[130]. It also helps improve endothelial function[131].

Coffee/Tea

It is estimated that 400 million cups of coffee are drunk every day in the US. An 8-ounce cup of coffee contains 80 to 100 mg of caffeine, while an 8-ounce cup of decaf coffee typically has only 2-15 milligrams. The FDA cites four to five cups of coffee (about 400 mgs) per day as a safe amount of consumption[132]. Studies have found that this amount of intake is not associated with any increased risk of heart failure[133]. Even consumption at higher levels – up to 600 mg/day, although may be associated with some cardiovascular symptoms, these are mild, transient, and reversible, with no lasting adverse effects[133]. The ARIC study reported that increased coffee consumption also appears to correlate with a reduced risk of developing HF later in life (even after controlling for known risk factors)[134]. Kolb et al. in 2020 even suggested that filtered coffee, without sugar or other additives, may be considered analogous to whole grains and vegetables as a dietary source of phenolic phytochemicals that could offer antioxidant protection in HF[135]. There is some suggestion that increasing decaffeinated coffee consumption may increase HF risk, but the data is limited[136].

Conclusion

There is growing evidence that nutrition may play a critical role in HF development and progression. A plant-based diet is high in antioxidants, micronutrients, dietary nitrate, and fiber but low in saturated/trans fats and sodium. These diets are associated with decreased HF incidence and severity. They contribute to decreased oxidative stress, lower homocysteine levels, and reduced inflammation as well as to higher nitric oxide bioavailability and a better gut microbiome. Part II of this manuscript covers the relationship between HF and harmful macronutrients, obesity, and its relationship with several special diets.

References

1. Spinar J, Spinarova L, Vitovec J. Pathophysiology, causes and epidemiology of chronic heart failure. Vnitr Lek 2018;64:834–8.
2. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. . Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. (2018) 137:e67–e492. 10.1161/cir.0000000000000558.
3. Zahra Aryan, Sahar Saeedi Moghaddam, Farshad Farzadfar. Abstract 6933: Mapping the Global Trends of Heart Failure Burden and its Contributing Factors from 1990 to 2019. QCOR at sessions. 8 Nov 2021Circulation. 2021;144:A6933.
4. Russo CA, Elixhauser A (2006) Hospitalizations in the elderly population, 2003: statistical Brief #6. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs Rockville.
5. Ponikowski P., Voors A.A., Anker S.D., et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur. Heart J. 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128.
6. https://www.heart.org/en/news/2018/05/01/heart-failure-projected-to-increase-dramatically-according-to-new-statistics. Accessed November 29, 2021.

7. Task A, Members F, Mcmurray JJ V, Uk C, Germany SDA, Auricchio A, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration. 2012;1787–1847.
8. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128.
9. Riet EES Van, Hoes AW, Limburg A, Landman MAJ, Hoeven H Van Der, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail. 2014; 16(7):772-7.
10. Djoussé L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. JAMA. 2009 Jul 22;302(4):394-400. doi: 10.1001/jama.2009.1062.
11. Sulo G, Igland J, Vollset SE, Nygård O, Ebbing M, Sulo E, Egeland GM, Tell GS. Heart failure complicating acute myocardial infarction; burden and timing of occurrence: a nation-wide analysis including 86 771 patients from the cardiovascular disease in Norway (CVDNOR) project. J Am Heart Assoc 2016; 5: e002667.
12. Caviedes Bottner P, Córdova Fernández T, Larraín Valenzuela M, Cruces Romero Presentación de Casos Clínicos P. Dilated cardiomyopathy and severe heart failure. An update for pediatricians. Arch Argent Pediatr. 2018 Jun 1;116(3):e421-e428. English, Spanish. doi: 10.5546/aap.2018.eng.e421.
13. Gencer B, Collet TH, Virgini V, et al. Thyroid Studies Collaboration. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation. 2012 Aug 28;126(9):1040-9. doi: 10.1161/CIRCULATIONAHA.112.096024.
14. Martinez F, Perna E, Perrone SV, Liprandi AS. Chagas Disease and Heart Failure: An Expanding Issue Worldwide. Eur Cardiol. 2019 Jul 11;14(2):82-88. doi: 10.15420/ecr.2018.30.2.
15. Robert L. Page II, Cindy L. O'Bryant, Davy Cheng, et al. Drugs That May Cause or Exacerbate Heart Failure. A Scientific Statement From the American Heart Association15hh Circulation. 2016;134:e32–e69. DOI: 10.1161/CIR.0000000000000426.
16. Modesti P.A., Vanni S., Bertolozzi I., Cecioni I., Polidori G., Paniccia R. Early sequence of cardiac adaptations and growth factor formation in pressure- and volume-overload hypertrophy. Am J Physiol Heart Circ Physiol. 2000;279(3):H976–H985.
17. Gajarsa J.J., Kloner R.A. Left ventricular remodeling in the post-infarction heart: a review of cellular, molecular mechanisms, and therapeutic modalities. Heart Fail Rev. 2011;16(1):13–21.
18. Yndestad A., Damas J.K., Oie E., Ueland T., Gullestad L., Aukrust P. Systemic inflammation in heart failure–the whys and wherefores. Heart Fail Rev. 2006;11(1):83–92.

19. Jhund P.S., MacIntyre K., Simpson C.R., Lewsey J.D., Stewart S., Redpath A., Chalmers J.W., Capewell S., McMurray J.J. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: A population study of 5.1 million people. Circulation. 2009;119:515–523. doi: 10.1161/CIRCULATIONAHA.108.812172.
20. Kaminsky LA, Tuttle MS. Functional assessment of heart failure patients. Heart Fail Clin. 2015 Jan;11(1):29-36. doi: 10.1016/j.hfc.2014.08.002.
21. Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther. 2021 Feb;11(1):263-276. doi: 10.21037/cdt-20-302.
22. Pereira Sousa J, Neves H, Lobao C, Goncalves R, Santos M. The effectiveness of education on symptoms recognition in heart failure patients to manage self-care: a systematic review protocol. Prof Inferm. 2019 Jan-Mar;72(1):50-54. English. doi: 10.7429/pi.2019.721050.
23. Klein L, Grau-Sepulveda MV, Bonow RO, et al. Quality of care and outcomes in women hospitalized for heart failure Circ Heart Fail 2011; 4: 589–598.
24. Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abdulkader RS, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet. 2017;390(10100):1260–1344. doi: 10.1016/S0140-6736(17)32130-X.
25. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006 Mar 21;113(11):1424-33. doi: 10.1161/CIRCULATIONAHA.105.584102.
26. Lassus J., Gayat E., Mueller C., et al. Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: The Multinational Observational Cohort on Acute Heart Failure (MOCA) study. Int. J. Cardiol. 2013;168:2186–2194. doi: 10.1016/j.ijcard.2013.01.228.
27. van Deursen VM, Urso R, Laroche C, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail. 2014 Jan;16(1):103-11. doi: 10.1002/ejhf.30.
28. Paolillo S, Scardovi AB, Campodonico J. Role of comorbidities in heart failure prognosis Part I: Anaemia, iron deficiency, diabetes, atrial fibrillation. Eur J Prev Cardiol. 2020;27(2_suppl):27-34. doi:10.1177/2047487320960288.
29. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. AHA statistical update executive summary: heart disease and stroke statistics — 2015 update a report from the American Heart Association Writing Group Members. 2015;434–441.
30. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol. 2014 Feb 15;171(3):368-76. doi: 10.1016/j.ijcard.2013.12.028.
31. Simão A.F., Précoma D.B., de Andrade J.P., Filho H.C., Saraiva J.F.K., Oliveira G.M.M. I diretriz brasileira de prevenção cardiovascular. Arq. Bras. Cardiol. 2014;102:420–431. doi: 10.5935/abc.2013S012.

32. Yu E, Malik VS, Hu FB. Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series. J Am Coll Cardiol. 2018 Aug 21;72(8):914-926. doi: 10.1016/j.jacc.2018.02.085.
33. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet. 2020 Mar 7;395(10226):795-808. doi: 10.1016/S0140-6736(19)32008-2.
34. Devries S, Dalen JE, Eisenberg DM, et al. A deficiency of nutrition education in medical training. Am J Med. 2014;127(9):804–806.
35. Galilea-Zabalza I, Buil-Cosiales P, Salas-Salvadó J, et al. PREDIMED-PLUS Study Investigators. Mediterranean diet and quality of life: Baseline cross-sectional analysis of the PREDIMED-PLUS trial. PLoS One. 2018 Jun 18;13(6):e0198974. doi: 10.1371/journal.pone.0198974
36. Sidney S., Quesenberry C.P., Jaffe M.G. Recent trends in cardiovascular mortality in the United States and public health goals. JAMA Cardiol. 2016;1(5):594–599.
37. Djoussé L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. JAMA. 2009;302:394–400.
38. Lloyd-Jones D.M., Larson M.G., Leip E.P., Beiser A., D'Agostino R.B., Kannel W.B. Lifetime risk for developing congestive heart failure: The Framingham Heart Study. Circulation. 2002;106:3068–3072. doi: 10.1161/01.CIR.0000039105.49749.6F.
39. Nichols G.A., Gullion C.M., Koro C.E., Ephross S.A., Brown J.B. The incidence of congestive heart failure in type 2 diabetes: An update. Diabetes Care. 2004;27:1879–1884. doi: 10.2337/diacare.27.8.1879.
40. He J., Ogden L.G., Bazzano L.A., Vupputuri S., Loria C., Whelton P.K. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch. Intern. Med. 2001;161:996–1002. doi: 10.1001/archinte.161.7.996.
41. Alasmre FA, Alotaibi HA. Plant-Based Diet: A Potential Intervention for Heart Failure. Cureus. 2020;12(5):e8282. Published 2020 May 25. doi:10.7759/cureus.8282.
42. Khatibzadeh S, Farzadfar F, Oliver J, Ezzati M, Moran A. Worldwide risk factors for heart failure: a systematic review and pooled analysis. Int J Cardiol. 2013;168:1186–1194.
43. García-Conesa M.T., Chambers K., Combet E., et al. Meta-analysis of the effects of foods and derived products containing ellagitannins and anthocyanins on cardiometabolic biomarkers: Analysis of factors influencing variability of the individual responses. Int. J. Mol. Sci. 2018;19:694. doi: 10.3390/ijms19030694.
44. Viguiliouk E., Glenn A.J., Nishi S.K., et al. Associations between Dietary Pulses Alone or with Other Legumes and Cardiometabolic Disease Outcomes: An Umbrella Review and Updated Systematic Review and Meta-analysis of Prospective Cohort Studies. Adv. Nutr. 2019;10:S308–S319. doi: 10.1093/advances/nmz113.
45. Kwok C.S., Gulati M., Michos E.D., Potts J., Wu P., Watson L., Loke Y.K., Mallen C., Mamas M.A. Dietary components and risk of cardiovascular disease and all-cause mortality: A review of evidence from meta-analyses. Eur. J. Prev. Cardiol. 2019;26:1415–1429. doi: 10.1177/2047487319843667.

46. Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. JAMA. (2009) 302:394–400. 10.1001/jama.2009.1062.
47. Wang Y, Tuomilehto J, Jousilahti P, et al. Lifestyle factors in relation to heart failure among Finnish men and women. Circ Heart Fail. (2011) 4:607–12. 10.1161/circheartfailure.111.962589.
48. Rautiainen S, Levitan EB, Mittleman MA, Wolk A. Fruit and vegetable intake and rate of heart failure: a population-based prospective cohort of women. Eur J Heart Fail. (2015) 17:20–6. 10.1002/ejhf.191.
49. Lara KM, Levitan EB, Gutierrez OM, Shikany JM, Safford MM, Judd SE, et al. Dietary patterns and incident heart failure in U.S. Adults without known coronary disease. J Am Coll Cardiol. (2019) 73:2036–45. 10.1016/j.jacc.2019.01.067.
50. Alasmre FA, Alotaibi HA. Plant-Based Diet: A Potential Intervention for Heart Failure. Cureus. 2020;12(5):e8282. Published 2020 May 25. doi:10.7759/cureus.8282.
51. Allen KE, Gumber D, Ostfeld RJ. Heart Failure and a Plant-Based Diet. A Case-Report and Literature Review. Front Nutr. 2019;6:82. Published 2019 Jun 11. doi:10.3389/fnut.2019.00082.
52. Watzl B. Anti-inflammatory effects of plant-based foods and of their constituents. Int J Vitam Nutr Res. (2008) 78:293–8. 10.1024/0300-9831.78.6.293.
53. Kim MK, Cho SW, Park YK. Long-term vegetarians have low oxidative stress, body fat, and cholesterol levels. Nutr Res Pract. (2012) 6:155–61. 10.4162/nrp.2012.6.2.155.
54. Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, et al. Vegetarian diets and blood pressure: a meta-analysis. JAMA Intern Med. (2014) 174:577–87. 10.1001/jamainternmed.2013.14547.
55. Barnard ND, Cohen J, Jenkins DJ, Turner-Mcgrievy G, Gloede L, Jaster B, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care. (2006) 29:1777–83. 10.2337/dc06-0606.
56. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. . Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. (2013) 19:576–85. 10.1038/nm.3145.
57. Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D. Effects of vegetarian diets on blood lipids: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. (2015) 4:e002408. 10.1161/jaha.115.002408.
58. Polidori MC, Savino K, Alunni G, Freddio M, Senin U, Sies H, Stahl W, Mecocci P. Plasma lipophilic antioxidants and malondialdehyde in congestive heart failure patients: relationship to disease severity. Free Radic Biol Med 2002; 32: 148– 152.
59. Wood N, Johnson RB. The relationship between tomato intake and congestive heart failure risk in periodontitis subjects. J Clin Periodontol. 2004;31:574–80. doi: 10.1111/j.1600-051X.2004.00531.x.
60. Biddle M, Moser D, Song EK et al. Higher dietary lycopene intake is associated with longer cardiac event-free survival in patients with heart failure. Eur J Cardiovasc Nurs. 2013;12:377–84. doi: 10.1177/1474515112459601.

61. Bondonno CP, Dalgaard F, Blekkenhorst LC, et al. Vegetable nitrate intake, blood pressure and incident cardiovascular disease: Danish Diet, Cancer, and Health Study. Eur J Epidemiol. 2021 Apr 21. doi: 10.1007/s10654-021-00747-3.
62. Polidori MC, Savino K, Alunni G et al. Plasma lipophilic antioxidants and malondialdehyde in congestive heart failure patients: relationship to disease severity. Free Radic Biol Med. 2002;32:148–52. doi: 10.1016/S0891-5849(01)00782-1.
63. Serdar A, Yesilbursa D, Serdar Z et al. Relation of functional capacity with the oxidative stress and antioxidants in chronic heart failure. Congest Heart Fail. 2001;7:309–11. doi: 10.1111/j.1527-5299.2001.00261.x.
64. Gong F, Yao S, Wan J, Gan X. Chocolate Consumption and Risk of Heart Failure: A Meta-Analysis of Prospective Studies. Nutrients. 2017 Apr 20;9(4):402. doi: 10.3390/nu9040402.
65. Greenberg J.A., Manson J.E., Buijsse B., et al. Chocolate-candy consumption and 3-year weight gain among postmenopausal U.S. women. Obesity. 2015;23:677–683. doi: 10.1002/oby.20983.
66. Gupta P.P., Fonarow G.C., Horwich T.B. Obesity and the obesity paradox in heart failure. Can. J. Cardiol. 2015;31:195–202. doi: 10.1016/j.cjca.2014.08.004.
67. Carbone S., Lavie C.J., Arena R. Obesity and heart failure: Focus on the obesity paradox. Mayo Clin. Proc. 2017;92:266–279. doi: 10.1016/j.mayocp.2016.11.001.
68. Mozaffarian D, Bryson CL, Lemaitre RN et al. Fish intake and risk of incident heart failure. J Am Coll Cardiol. 2005;45:2015–21. doi: 10.1016/j.jacc.2005.03.038.
69. Yamagishi K, Iso H, Date C et al. Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. J Am Coll Cardiol. 2008;52:988–96. doi: 10.1016/j.jacc.2008.06.018.
70. Levitan EB, Wolk A, Mittleman MA. Fatty fish, marine omega-3 fatty acids and incidence of heart failure. Eur J Clin Nutr. 2010;64:587–94. doi: 10.1038/ejcn.2010.50.
71. Belin RJ, Greenland P, Martin L et al. Fish intake and the risk of incident heart failure: the Women's Health Initiative. Circ Heart Fail. 2011;4:404–13. doi: 10.1161/CIRCHEARTFAILURE.110.960450.
72. Wilk JB, Tsai MY, Hanson NQ et al. Plasma and dietary omega-3 fatty acids, fish intake, and heart failure risk in the Physicians' Health Study. Am J Clin Nutr. 2012;96:882–8. doi: 10.3945/ajcn.112.042671.
73. R.J. Belin, P. Greenland, L. Martin, et al. Fish intake and the risk of incident heart failure: the Women's Health Initiative. Circ Heart Fail, 4 (2011), pp. 404-413.
74. Li YH, Zhou CH, Pei HJ et al. Fish consumption and incidence of heart failure: a meta-analysis of prospective cohort studies. Chin Med J (Engl) 2013;126:942–8.
75. Belin RJ, Greenland P, Martin L et al. Fish intake and the risk of incident heart failure: the Women's Health Initiative. Circ Heart Fail. 2011;4:404–13. doi: 10.1161/CIRCHEARTFAILURE.110.960450.
76. Wang C, Xiong B, Huang J. The role of omega-3 polyunsaturated fatty acids in heart failure: a meta-analysis of randomised controlled trials. Nutrients. 2016. pp. 9–E18.

77. Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians? Health Study. Circulation. 2008;117:512–6. doi: 10.1161/CIRCULATIONAHA.107.734210.
78. Larsson SC, Åkesson A, Wolk A. Egg consumption and risk of heart failure, myocardial infarction, and stroke: results from 2 prospective cohorts. Am J Clin Nutr. 2015;102:1007–13. doi: 10.3945/ajcn.115.119263.
79. Khawaja O, Singh H, Luni F et al. Egg Consumption and incidence of heart failure: a meta-analysis of prospective cohort studies. Front Nutr. 2017;4:10. doi: 10.3389/fnut.2017.00010.
80. Godos J, Micek A, Brzostek T, et al. Egg consumption and cardiovascular risk: a dose-response meta-analysis of prospective cohort studies. Eur J Nutr. 2021 Jun;60(4):1833-1862. doi: 10.1007/s00394-020-02345-7.
81. Carson JAS, Lichtenstein AH, Anderson CAM, Appel LJ, Kris-Etherton PM, Meyer KA, Petersen K, Polonsky T, Van Horn L; on behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Peripheral Vascular Disease; and Stroke Council. Dietary cholesterol and cardiovascular risk: a science advisory from the American Heart Association. Circulation. 2020;141:e39–e53) https://doi.org/10.1161/CIR.0000000000000743.
82. Abramson JL, Williams SA, Krumholz HM, Vaccarino V. Moderate alcohol consumption and risk of heart failure among older persons. JAMA. 2001;285:1971–1977.
83. Walsh CR, Larson MG, Evans JC, et al. Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med. 2002;136:181–191.
84. Bryson CL, Mukamal KJ, Mittleman MA, et al. The association of alcohol consumption and incident heart failure: the Cardiovascular Health Study. J Am Coll Cardiol. 2006;48:305–311.
85. Klatsky AL, Chartier D, Udaltsova N, et al. Alcohol drinking and risk of hospitalization for heart failure with and without associated coronary artery disease. Am J Cardiol. 2005;96:346–351.
86. Djousse L, Gaziano JM. Alcohol consumption and risk of heart failure in the Physicians' Health Study I. Circulation. 2007;115:34–39.
87. Larsson SC, Wallin A, Wolk A. Alcohol consumption and risk of heart failure: Meta-analysis of 13 prospective studies. Clin Nutr. 2018 Aug;37(4):1247-1251. doi: 10.1016/j.clnu.2017.05.007,
88. Larsson S.C., Orsini N., Wolk A. Alcohol consumption and risk of heart failure: A dose-response meta-analysis of prospective studies. Eur. J. Heart Fail. 2015;17:367–373. doi: 10.1002/ejhf.228.
89. Padilla H., Gaziano J.M., Djoussé L. Alcohol Consumption and Risk of Heart Failure: A Meta-Analysis. Null. 2010;38:84–89. doi: 10.3810/psm.2010.10.1812.
90. https://www.niaaa.nih.gov/alcohols-effects-health/overview-alcohol-consumption/what-standard-drink.

91. Kalinowski A., Humphreys K. Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries. Addiction 2016; 111: 1293–1298.
92. Flesch M, Rosenkranz S, Erdmann E, Bohm M. Alcohol and the risk of MI. Basic Res Cardiol. 2001;96:128–135.
93. Koppes LL, Dekker JM, Hendriks HF, et al. Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. Diabetes Care. 2005;28:719–725.
94. Gaziano JM, Buring JE, Breslow JL, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of MI. N Engl J Med. 1993;329:1829–1834.
95. Greenfield JR, Samaras K, Hayward CS, et al. Beneficial postprandial effect of a small amount of alcohol on diabetes and cardiovascular risk factors: modification by insulin resistance. J Clin Endocrinol Metab. 2005;90:661–672.
96. Hendriks HF. Moderate alcohol consumption and insulin sensitivity: observations and possible mechanisms. Ann Epidemiol. 2007;17:S40–S42.
97. Beulens JW, van Loon LJ, Kok FJ, et al. The effect of moderate alcohol consumption on adiponectin oligomers and muscle oxidative capacity: a human intervention study. Diabetologia. 2007;50:1388–1392.
98. Imhof A, Woodward M, Doering A, et al. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Augsburg, Glasgow, Lille) Eur Heart J. 2004;25:2092–2100.
99. Shai I, Rimm EB, Schulze MB, et al. Moderate alcohol intake and markers of inflammation and endothelial dysfunction among diabetic men. Diabetologia. 2004;47:1760–1767.
100. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet. 1992;339:1523–1526.
101. Dimmitt SB, Rakic V, Puddey IB, et al. The effects of alcohol on coagulation and fibrinolytic factors: a controlled trial. Blood Coagul Fibrinolysis. 1998;9:39–45.
102. Torres Duarte AP, Dong QS, Young J, et al. Inhibition of platelet aggregation in whole blood by alcohol. Thromb Res. 1995;78:107–115.
103. Booyse FM, Pan W, Grenett HE, et al. Mechanism by which alcohol and wine polyphenols affect coronary heart disease risk. Ann Epidemiol. 2007;17:S24–S31.
104. Djousse L, Hunt CS, Eckfeldt JH, et al. Alcohol consumption and plasma atrial natriuretic peptide (From The HyperGEN Study) Am J Cardiol. 2006;98:628–632.
105. Belobrajdic DP, Bird AR. The potential role of phytochemicals in wholegrain cereals for the prevention of type-2 diabetes. Nutr J 2013;12:62. 10.1186/1475-2891-12-62,
106. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet 2019;393:434-45. 10.1016/S0140-6736(18)31809-9.
107. Kyrø C, Tjønneland A. Whole grains and public health. BMJ 2016;353:i3046. 10.1136/bmj.i3046.

108. Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: a meta-analysis. Nutr Metab Cardiovasc Dis 2008;18:283-90. 10.1016/j.numecd.2006.12.008.
109. Bechthold A, Boeing H, Schwedhelm C, et al. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr 2019;59:1071-90. 10.1080/10408398.2017.1392288.
110. Djoussé L, Gaziano JM. Breakfast cereals and risk of heart failure in the physicians' health study I. Arch Intern Med. 2007;167:2080–5. doi: 10.1001/archinte.167.19.2080,
111. Nettleton JA, Steffen LM, Loehr LR et al. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. J Am Diet Assoc. 2008;108:1881–7. doi: 10.1016/j.jada.2008.08.015.
112. Wannamethee SG, Jefferis BJ, Lennon L, Papacosta O, Whincup PH, Hingorani AD. Serum Conjugated Linoleic Acid and Risk of Incident Heart Failure in Older Men: The British Regional Heart Study. J Am Heart Assoc. 2018 Jan 6;7(1):e006653. doi: 10.1161/JAHA.117.006653.
113. Liang J, Zhou Q, Kwame Amakye W et al. Biomarkers of dairy fat intake and risk of cardiovascular disease: A systematic review and meta analysis of prospective studies. Crit Rev Food Sci Nutr. 2016;21:1–9. doi: 10.1080/10408398.2016.1242114.
114. Ros E. Health benefits of nut consumption. Nutrients 2010;2:652–82. 10.3390/nu2070652.
115. Aune D, Keum N, Giovannucci E, et al. . Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. BMC Med 2016;14:207 10.1186/s12916-016-0730-3.
116. Mayhew AJ, de Souza RJ, Meyre D, et al. . A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. Br J Nutr 2016;115:212–25. 10.1017/S0007114515004316.
117. Grosso G, Yang J, Marventano S, et al. . Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies. Am J Clin Nutr 2015;101:783–93. 10.3945/ajcn.114.099515,
118. Mohammadifard N, Ghaderian N, Hassannejad R, et al. Longitudinal Association of Nut Consumption and the Risk of Cardiovascular Events: A Prospective Cohort Study in the Eastern Mediterranean Region. Front Nutr. 2021 Jan 21;7:610467. doi: 10.3389/fnut.2020.610467.
119. Djoussé L, Rudich T, Gaziano JM. Nut consumption and risk of heart failure in the Physicians' Health Study I. Am J Clin Nutr 2008;88:930–3. 10.1093/ajcn/88.4.930.
120. Steffen LM, Yi SY, Duprez D, Zhou X, Shikany JM, Jacobs DR Jr. Walnut consumption and cardiac phenotypes: The Coronary Artery Risk Development in Young Adults (CARDIA) study. Nutr Metab Cardiovasc Dis. 2021 Jan 4;31(1):95-101. doi: 10.1016/j.numecd.2020.09.001.

121. Mohammadifard N, Salehi-Abargouei A, Salas-Salvadó J, Guasch-Ferré M, Humphries K, Sarrafzadegan N. The effect of tree nut, peanut, and soy nut consumption on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials. Am J Clin Nutr. 2015 May;101(5):966-82. doi: 10.3945/ajcn.114.091595.
122. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'agostino RB, Kannel WB, et al. . Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. (2002) 106:3068–72. 10.1161/01.CIR.0000039105.49749.6F.
123. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA. 2002;288:2554–60.
124. Rosano GM, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. CFR. (2017) 3:52–5. 10.15420/cfr.2016:20:2.
125. Bess-Rastrollo M, Sabate J, Gomez-Gracia E, Alonso A, Martinez JA, Martinez-Gonzalez MA. Nut consumption and weight gain in a Mediterranean cohort: The SUN study. Obesity (Silver Spring) 2007;15:107–16.
126. Larsson SC, Drca N, Björck M, Bäck M, Wolk A. Nut consumption and incidence of seven cardiovascular diseases. Heart. 2018 Oct;104(19):1615-1620. doi: 10.1136/heartjnl-2017-312819.
127. Ros E. Health benefits of nut consumption. Nutrients 2010;2:652–82. 10.3390/nu2070652.
128. Del Gobbo LC, Falk MC, Feldman R, et al. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. Am J Clin Nutr 2015;102:1347–56. 10.3945/ajcn.115.110965.
129. Siracusa R, Fusco R, Peritore AF, et al. The Antioxidant and Anti-Inflammatory Properties of Anacardium occidentale L. Cashew Nuts in a Mouse Model of Colitis. Nutrients. 2020; 12(3):834. https://doi.org/10.3390/nu12030834.
130. Xiao Y, Huang W, Peng C, et al. . Effect of nut consumption on vascular endothelial function: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr 2017. 10.1016/j.clnu.2017.04.011.
131. Mozaffarian D, Hao T, Rimm EB, et al. . Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404. 10.1056/NEJMoa1014296.
132. https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much.
133. Turnbull D, Rodricks JV, Mariano GF, Chowdhury F. Caffeine and cardiovascular health. Regul Toxicol Pharmacol. 2017 Oct;89:165-185. doi: 10.1016/j.yrtph.2017.07.025.
134. Stevens LM, Linstead E, Hall JL, Kao DP. Association Between Coffee Intake and Incident Heart Failure Risk: A Machine Learning Analysis of the FHS, the ARIC Study, and the CHS. Circ Heart Fail. 2021 Feb;14(2):e006799. doi: 10.1161/CIRCHEARTFAILURE.119.006799.
135. Kolb H, Kempf K, Martin S. Health effects of coffee: mechanism unraveled?Nutrients. 2020; 12:1842–1856.

136. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation. 2014; 129:643–659. doi: 10.1161/CIRCULATIONAHA.113.005925.