Disconnect Between Genes Associated With Ischemic Heart Disease and Targets of Ischemic Heart Disease Treatments

C.M. Schooling a,b,⁎, J.V. Huang b, J.V. Zhao b, M.K. Kwok b, S.L. Au Yeung b, S.L. Lin b

a CUNY Graduate School of Public Health and Health Policy, New York, USA
b School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

ABSTRACT

Background: Development of pharmacological treatments to mitigate ischemic heart disease (IHD) has encompassed disappointing results and expensive failures, which has discouraged investment in new approaches to prevention and control. New treatments are most likely to be successful if they act on genetically validated targets. We assessed whether existing pharmacological treatments for IHD reduction are acting on genetically validated targets and whether all such targets for IHD are currently being exploited.

Methods: Genes associated with IHD were obtained from the loci of single nucleotide polymorphisms reported in either of two recent genome wide association studies supplemented by a gene-based analysis (accounting for linkage disequilibrium) of CARDIoGRAMplusC4D 1000 Genomes, a large IHD case (n = 60,801)-control (n = 123,504) study. Treatments targeting the products of these IHD genes and genes with products targeted by current IHD treatments were obtained from Kyoto Encyclopedia of Genes and Genomes and Drugbank. Cohen’s kappa was used to assess agreement.

Results: We identified 173 autosomal genes associated with IHD and 236 autosomal genes with products targeted by current IHD treatments, only 8 genes (PCSK9, EDNRA, PLG, LPL, CXCL12, LRPI, CETP and ADORA2A) overlapped, i.e. were both associated with IHD and had products targeted by current IHD treatments. The Cohen’s kappa was 0.03. Interventions related to another 29 IHD genes exist, including dietary factors, environmental exposures and existing treatments for other indications.

Conclusions: Closer alignment of IHD treatments with genetically validated physiological targets may represent a major opportunity for combating a leading cause of global morbidity and mortality through repurposing existing interventions.

© 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Great progress has been made in the prevention and control of cardiovascular disease over the last 50 years (Ezzati et al., 2015). Nevertheless, cardiovascular disease remains the leading cause of global morbidity and mortality. Cardiovascular disease has long been acknowledged to be incompletely understood, with patterns of disease and trends that cannot be explained by existing risk factors and treatments (Ezzati et al., 2015; Marmot et al., 1975). Development of new cardiovascular disease treatments targeting risk factors, such as high density lipoprotein-cholesterol and inflammatory markers, has encompassed disappointing results and expensive late-stage failures (Jackson et al., 2016; Lincoff et al., 2017; Ridker et al., 2017; O’Donoghue et al., 2016). In some cases these failures have subsequently been explained by the treatments not acting on genetically validated targets, for example for varespladib and darapladib (Gregson et al., 2017; Talmud and Holmes, 2015). Investment in drug development for cardiovascular disease is currently not commensurate with the burden of disease (Moses et al., 2015).

Recently, genome wide association studies (GWAS) of single genetic variants have enabled significant progress to be made in unraveling the causes of ischemic heart disease (IHD) with as much as 21% of the heritability of IHD potentially explicable (Nelson et al., 2017). This development provides a new opportunity to provide an overall assessment of the extent to which existing pharmacological treatments for IHD prevention and control are exploiting genetically validated targets and conversely to identify whether any other existing treatments are targeting the products of genes strongly associated with IHD and so could potentially be repurposed. Here, we examined three complimentary questions; first whether genetically valid targets for IHD are being exploited by current pharmacological IHD treatments, second whether existing pharmacological treatments for IHD are acting on genetically valid targets, and third whether any additional pharmacological...
treatments or nutraceuticals exist likely exploiting the products of other genes strongly associated with IHD.

2. Methods

Genes strongly associated with IHD were obtained in two ways. First, genes were identified from the loci of single nucleotide polymorphisms (SNPs) associated with IHD at genome wide significance (SNP-based GWAS) in either of two recent IHD GWAS (Nelson et al., 2017; Howson et al., 2017), largely concerning people of European descent and based on the CARDIoGRAMplusC4D consortia. Second, genes associated with IHD at genome wide significance were identified from a gene-based test applied to CARDIoGRAMplusC4D 1000 Genomes (cases = 60,801, controls = 123,504) (Nikpay et al., 2015). A gene-based test has the advantage of considering genetic variants in naturally occurring functional units, i.e., genes, whose products potentially correspond to targets of intervention, because treatments usually target specific gene products.

To identify the extent to which the genes associated with IHD are exploited by current pharmacological IHD treatments, we used two curated gene to drug cross-references, Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2014) and Drugbank (Wishart et al., 2018), to identify whether the genes strongly associated with IHD had products targeted by existing IHD treatments. To identify whether existing pharmacological treatments for IHD are acting on genetically validated targets we used the same cross-references to identify the genes with products targeted by pharmacological IHD treatments and the gene-based test to assess their association with IHD. Finally, we identified any other existing, but not investigational, pharmacological treatments or nutraceuticals targeting products of genes strongly associated with IHD as candidate interventions for potentially repurposing as new IHD treatments.

Existing IHD treatments were defined as approved therapies for primary or secondary prevention or treatment of IHD, considered as treatments for the following conditions affecting the Cardiovascular System: “Hyperlipidaemia”, “Hypertension”, “Diabetes”, “MI, LVD”, “Thromboembolic disorders” and “Angina”, and the following categories for Diabetes: “Oral and parenteral hypoglycaemics” and “Insulins” given in MIMS UK (http://www.mims.co.uk/conditions). We did not include devices or tests. The complete list of drugs considered is given in Supplementary Table 1. We included any treatment or nutraceutical reported as relevant to a gene of interest from KEGG or Drugbank. Only autosomal genes were considered because genetic associations with the X and Y chromosomes are more complex to unravel, rarely investigated and are not available in the CARDIoGRAMplusC4D consortia. Two people conducted these searches independently in mid-January 2018.

2.1. Statistical Analysis

To obtain p-values for the association of each autosomal gene with IHD, we used a gene-based association test with an extended Simes procedure taking linkage disequilibrium into account (Li et al., 2012). To conduct this test we used a Gene-based Association Test using Extended Simes (GATES), which is a Simes test adjusted for the linkage disequilibrium of the p-values (Li et al., 2012). GATES has the advantage of not requiring simulations and provides a validated approximation to other methods (Bacanu, 2012). Linkage disequilibrium was obtained from the 1000 Genomes catalog. We used a p-value cut-off of 1.96 × 10^{-6} for genome wide Bonferroni corrected significance of a gene (i.e., 0.05/25463 genes). We also identified genes associated with IHD at a 5% false discovery rate on the gene-based test, Cohen’s kappa was used to assess the agreement between the genes identified as associated with IHD and the genes targeted by existing IHD treatments.

This analysis of publicly available data does not require ethical approval.

2.2. Role of the Funding Source

This study was partly funded by PSC-CUNY Award # 68528-00 46. The funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

3. Results

Table 1 shows that in total 173 autosomal genes were identified as strongly associated with IHD. Supplementary Table 2 shows that 119 genes were identified from the 109 loci recently reported as associated with IHD using SNP-based GWAS (Nelson et al., 2017; Howson et al., 2017), and 54 additionally identified from the gene-based test, 40 genes were identified by both methods. Table 1 also shows that in total 236 autosomal genes were identified as targets of existing IHD treatments. However, the overlap between the genes associated with IHD and the genes currently related to existing IHD treatments was minimal, i.e., only 8 genes. The Cohen’s kappa was very low (0.03) indicating minimal agreement. If only the 119 genes associated with IHD from SNP-based GWAS were considered as associated with IHD the Cohen’s kappa (0.03) was still minimal.

3.1. IHD Gene Products as Targets of Existing IHD Treatments

Of the total 173 genes associated with IHD the 8 genes related to existing IHD treatments were PCSK9, LPL, PLG, EDNRA, CXCL12, LRP1, CETP and ADORA2A. All of these 8 genes were identified from SNP-based GWAS, PLG was also identified by the gene-based test. Four genes (PCSK9, LPL, EDNRA and ADORA2A) were significantly associated with IHD at a 5% false discovery rate on the gene-based test, LRP1 was nominally significant and two genes (CXCL12 and CETP) were not even nominally associated with IHD on the gene-based test.

None of these 8 genes (PCSK9, LPL, PLG, EDNRA, CXCL12, LRP1, CETP and ADORA2A) are associated with widely used IHD treatments, shown in Table 2, PCSK9 gene products are targeted by PCSK9 inhibitors. LPL products are targets of rarely used lipid modulators, such as fibrinolipid, elastase and Omega-3-acid ethyl esters, and anti-thrombotics, such as dextran. PLG products are targeted by anti-thrombotics for acute myocardial infarction. EDNRA products could be targeted by aspirin, and are targeted by therapies for pulmonary hypertension. CXCL12 products may be targeted by a heparin anti-thrombotic. LRP1 and ADORA2A products are targets of specialized anti-thrombotics. CETP products are currently targeted by Omega-3-acid ethyl esters. To date three cholesterol ester lipases transfer protein (CETP) inhibitors have failed in major trials (Eyvazian and Frishman, 2017). One CETP inhibitor (anacetrapib) met its primary endpoint, but is not going to be marketed (Merck Provides Update on Anacetrapib Development Program, 2017).

Additionally, considering the 241 genes only associated with IHD at a 5% false discovery rate on the gene-based-test yielded two additional genes, CHRNA8 and VEGFA, related to IHD treatments. CHRNA8 is related to atripine and VEGFA to anti-thrombotics, anti-hypertensives and sulfonylureas. For reference Supplementary Table 2 lists these 241 genes.

3.2. Existing IHD Treatments As Genetically Valid Targets

In total 236 autosomal genes were identified as related to existing pharmacological IHD treatments, but only 8 of these genes were strongly associated with IHD. Supplementary Table 3 shows all 242 genes (including 6 on the X chromosome) related to current IHD treatments, the treatment class and the p-value for their gene-based association with IHD. Genes related to widely used therapies that modulate lipids and reduce cardiovascular disease, such as statins (HMGCR) (Collins et al., 2016) and ezetimibe (NPC1L1) (Cannon et al., 2015), were nominally significant using the gene-based test (p-values of
3.3. IHD Genes as Targets of Other Treatments, or Potential Interventions

Of the 173 genes associated with IHD, in addition to the 8 genes (PCSK9, LPL, PLG, EDNRA, CXCL12, LPR1, CETP and ADORA2A) related to existing IHD treatments, an additional 29 genes were related to other existing treatments or nutraceuticals (Table 2). Of these 29 genes, 12 genes (IL6R, GCX, GUCY1A3, LPA, HADC9, NOS3, CYP17A1, NTSC2, SH2B3, FURIN, APOE and LDLR) were identified by both SNP-based GWAS and the gene-based test, 14 genes from SNP-based GWAS only (ATP1B1, FN1, ITGB5, SLC22A4, SLC22A5, APOA1, PGDF, SCARB1, FLT1, OA22, MC4R, SNRPD2, TGFβ1 and PROCR), and 3 genes from the gene-based test only (MAT2A, AS3MT and IGF2R).

Seven of these 29 IHD genes are related to therapies for other cardiovascular conditions (ATP1B1, GCX, FN1, GUCY1A3 and NOS3) and/or bleeding disorders (LPA and APOE). Another 12 of these 29 IHD genes are related to treatments for other conditions including arthritis (IL6R), cancer (ITGB5, HADC9, CYP17A1, PGDF, SH2B3, FLT1 and LDLR), psychosis, specifically valproic acid (HADC9), growth failure (IGF2R), adenocortical insufficiency (MC4R), and infections (NTSC2 and SNRPD2). TGFβ1 is related to hyaluronidase, which promotes the dispersion of injected substances. PROCR is related to phosphorylasealanolamine, which may play a cardiac role and is raised by testosterone (Angelova et al., 2012). Finally the remaining 8 of these 29 IHD genes (MAT2A, SLC22A4, SLC22A5, AS3MT, APOA1, SCARB1, FURIN and OA22) are related to dietary factors or supplements.

Several of these 29 IHD genes are also related to common modifiable interventions (Table 2). GCX is related to vitamin K<sub>1</sub>, commonly found in green leafy vegetables, and to L-glutamic acid, a common dietary amino acid. MAT2A and AS3MT are related to the derivates of the amino acid L-methionine, largely obtained from animal protein, i.e., s-denosylmethionine which plays a role in arsenic metabolism (Loenen, 2006). SLC22A4 and SLC22A5 are related to L-carnitine, whose major source is red meat. NOS3 is related to the amino-acids L-citrulline and L-arginine. L-arginine is a common dietary amino acid often obtained from animal protein. APOA1 and APOE are related to both zinc and copper, as are PLG (copper) and FNI (zinc). SCARB1 is related to phosphoryldyl serine, which may improve memory. Finally, ADORA2A, as well as being related to an existing IHD treatment, is also related to many potential interventions including cocoa derivatives, such as theobromine.

4. Discussion

This study reveals a disconnect between genes strongly associated with IHD, i.e., potentially with druggable genetic products, and genes whose products are targeted by existing IHD treatments. Only 8 of the 173 genes associated with IHD are related to the products of the 236 autosomal genes acted on by treatments for IHD and none of these treatments are widely used. However, 29 other genes associated with IHD are related to existing treatments or interventions that could perhaps be repurposed or re-developed to combat IHD.

Previous studies have validated the genetic targets of some specific IHD treatments, such as ezetimbe and PCSK9 inhibitors (Wang and Hegele, 2017; Stitziel et al., 2014). However, to our knowledge, no previous studies have comprehensively compared the genes strongly associated with IHD with the genes whose products are targeted by existing IHD treatments. Of course, not all genes associated with IHD are likely to yield easily modifiable effective targets of intervention for IHD, although lack of even a nominal association of a gene with IHD might raise questions about whether such a gene is likely to have products that are targets of effective intervention for IHD. Some of the genes associated with IHD are related to existing interventions which could perhaps be repurposed, although the direction of effect is not always obvious and needs to be deduced from other information. For example, aminocapric acid related to LPA, is usually used to prevent bleeding, and so might not be helpful in IHD.

Suggestive information about the value of some of these potential interventions for IHD already exists. Vitamin K<sub>1</sub> (GCCX) is an antagonist of the blood thinner warfarin used to treat some cardiovascular diseases. A Mendelian randomization study suggested vitamin K<sub>1</sub> may cause IHD (Schooling, 2016). Arsenic is thought to cause IHD (Moon et al., 2012) and methionine (MAT2A and AS3MT) restriction may increase lifespan (Ables and Johnson, 2017), consistent with the importance of removing arsenic pollution from the environment. In small trials with intermediate end-points L-carnitine (SLC22A4, SLC22A5) has shown some indications of beneficial effects (Serban et al., 2016; Anand et al., 1998). Zinc (FN1, APOA1 and APOE) and copper (PLG, APOA1 and APOE) have been thought to play a role in IHD for over 40 years (Klevay, 1975). Small scale trials suggest adverse effects of low copper intake on cardiac arrhythmias (Milne and Nielsen, 1996; Viestenz and Klevay, 1982), and that copper depletion may induce arrhythmias (Jung et al., 2016). In vitro experiments also suggest some cardiac benefits of copper (Zhou et al., 2009), zinc also reduces copper absorption (Van Campen and Scaife, 1967). L-arginine (NOS3) is a common dietary amino acid, often obtained from animal protein, which likely causes IHD (Au Yeung et al., 2016). In randomized controlled trials theobromine has beneficial effects on cardiovascular disease risk factors, such as blood pressure and lipids (Martinez-Pinilla et al., 2015), and was formerly used as a treatment for angina. Theobromine may also antagonize adenosine receptors, potentially relevant to the relation of NTSC2 with IHD.

Despite taking an innovative approach to identify gaps and opportunities for IHD mitigation by considering genes in naturally occurring functional units, i.e., genes, this study has limitations. First, some of the genes identified as associated with IHD might not be functional. However, we specifically identified 29 genes that are related to potentially available interventions. Second, some of the genes targeted by existing treatments may represent valid physiological targets even though the genes were not clearly associated with IHD from SNP level GWAS or gene-based tests, meaning better methods of searching the genome are required. Alternatively, discovery of new ways of treating IHD may be facilitated by use of explanatory models from other disciplines (Schooling, 2017).
evolving, so we used two comprehensive cross-references from gene to treatment (Kanehisa et al., 2014; Wishart et al., 2008) and included genes and treatments found in either source. However, inexactitude and incompleteness of knowledge about gene products and how treatments operate is unlikely to explain the magnitude of the difference between the genes strongly associated with IHD and genes related to existing IHD treatments. Fourth, most genetic variation associated with IHD has been obtained from prevalent case-control studies of

| Target | Gene | Chr | Potential therapies |
|---|---|---|---|
| | | | **Medicinal** | **Nutraceutical** |
| IHD | PCSK9 | 1 | PCSK9 inhibitor | | Hyperlipidemia | Copper, citric acid |
| | EDNRA | 4 | Endothelin receptor antagonist | | Aspirin | Hyperlipidemia |
| | PLC | 6 | Plasminogen activator | | Dextran | Acute myocardial infarction, clotting |
| | LPL | 8 | Elastase ES | | Heparin | Hyperlipidemia |
| | | | | | Omega-3 acid ethyl esters | Hyperlipidemia |
| | | | | | Heparin | Hyperlipidemia |
| | | | | | Omega-3 acid ethyl esters | Hyperlipidemia |
| | CXCL12 | 10 | Tissue plasminogen activator | | Thromboembolism or risk thereof |
| | LRPI | 12 | Coagulation factors VIII and IX | | Heparin |
| | CETP | 16 | | | Hemophilia |
| | ADORA2A | 22 | | | Defluoride, occlusive venous disease of the liver |
| Other diseases | ATP1B1 | 1 | | | Antiarrhythmic |
| | IL6R | 1 | Sarilumab/Tocilizumab | | Arthritis and ankylosing spondylitis |
| | GGCX | 2 | Anisindione | | Prevention of thromboembolism in atrial fibrillation |
| | | | Coagulation factors VIIa and IX | | |
| | MATZ2A | 2 | | | |
| | FN1 | 2 | Ocriplasmin/Lanoteplase | | Thrombosis |
| | ITGB5 | 3 | Clengitide | | Angiogenesis inhibitor |
| | GACKY1A3 | 4 | Riociguat | | Pulmonary arterial hypertension |
| | SLC22A4 | 5 | i-Carnitine | | Carnitine deficiency |
| | SLC22A5 | 5 | i-Carnitine | | Carnitine deficiency |
| | IGF2R | 6 | Insulin-like growth factor 1 | | Growth failure |
| | | | Cerlipase alfa | | |
| | LPA | 6 | Aminocaproic Acid | | Bleeding |
| | HDAC9 | 7 | Histone deacetylase inhibitor | | Cancer |
| | NOS3 | 7 | Aminoprilast | | Seizure disorders, mania |
| | | | Miconazole | | Fungal infections |
| | | | Sapropterin | | Tetrahydrobipterin deficiency |
| | | | Tilaramine acetate | | Cardiogenic shock |
| | AS1MT | 10 | | | |
| | CYP17A1 | 10 | Abiraterone/Galeterone/Orteronel | | Prostate cancer |
| | | | Mitotane | | Adrenal cortical carcinoma |
| | | | Progestosterone | | Progestosterone deficiency, hormonal imbalance |
| | NT5C2 | 10 | Ribavirin/Taribavirin | | Hepatitis C, respiratory syncytial virus |
| | APOM1 | 11 | | | Adenosine triphosphate |
| | PDGF | 11 | Tandutinib | | Cancer |
| | SH2B3 | 12 | Indazolylpyrimidine | | Kidney cancer and sarcoma |
| | | | | | |
| | SCARB1 | 12 | | | |
| | FLT1 | 13 | Multiple kinase inhibitor | | Various cancers |
| | PURIN | 15 | Pirfenidone | | idiopathic pulmonary fibrosis |
| | OAZ2 | 15 | | | |
| | MC4R | 18 | Adrenocorticotropic hormone | | Adrenocortical insufficiency |
| | AP0E | 19 | Human serum albumin | | Severe blood loss |
| | LDL | 19 | Hematopoietin derivative | | Esophageal cancer |
| | SNRPA2 | 19 | Artemisinsin (Arteminol) | | Plasmadium falciparum infection |
| | TGFBI | 19 | Hyaluronidase | | increase the absorption and dispersion of drugs |
| | PROCR | 20 | Phosphatidylethanolamine | | phospholipid |
| | ADORA2A | 22 | Caffeine | | Drowsiness |
| | | | Theophylline | | Asthma, Chronic Obstructive Pulmonary Disease |
| | | | Meiloquine | | Malaria |
| | | | Adenosine | | Anti-arrhythmic |
| | | | Pentoxifylline | | Chronic Obstructive Pulmonary Disease |
| | | | Theobromine | | Angina (formerly) |
| | | | Adenosine A(2A) antagonist | | Parkinson's disease |

Chr: chromosome.
people of European descent. Replication in a different study or population is unlikely to remove the disconnect between genetically valid targets and existing IHD treatments, although it may reveal some additional targets. Fifth, this study is not designed to map out full genetic functionality and etiology of IHD but instead to identify promising genetically functional targets of intervention that can be actioned now, because genetic validation is increasingly a criterion for investigation of potential interventions.

Overall, this study suggests that current IHD treatments may not be optimally targeted and genetically informed targets for IHD may be under-exploited. Closer alignment of IHD treatments with the products of genes associated with IHD represents a major opportunity for combating the leading cause of global morbidity and mortality by repurposing existing therapies identified here. Whether a similar situation exists for other major diseases might also be investigated.

Disclosures
None.

Authors’ Contributions
CMS designed the study, searched databases and checked the results of the genetic analysis. SLK did the genetic analysis. JVH and SLAY independently checked the search for drugs acting on genes associated with ischemic heart disease. JZV checked the extraction of known genetic loci for ischemic heart disease. JHV, SLAY, JVZ, MKK and SLG gave general advice on the study and reviewed the final version for intellectual content.

Acknowledgements
Data have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIoGRAMplusC4D.org.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2018.01.015.

References
Ables, G.P., Johnson, J.E., 2017. Pleiotropic responses to methionine restriction. Exp. Gerontol. 63, 83–98.
Anand, I., Chandrashekhar, Y., De Giuli, F., Devanathan, P., Kupeli, K., et al., 2012. Metabolic features of type 2 diabetes: a meta-analysis of genome-wide association data. PLoS One 7 (5), e36419.
Ancren, D., Senni, M., Natarajan, K., 2017. The role of miRNA on cardiovascular disease. Curr. Cardiol. Rev. 13 (6), 1539–1548.
Antoniou, C., Pharoah, P.D.O., Narod, S., Ricketts, I., 2010. Breast cancer risk attributable to common genetic variants. J. Natl. Cancer Inst. 102 (11), 840–848.
Arterburn, E.D., 2017. A systemic review of the role of physical activity in the management of cardiovascular risk factors and disease. BJSM 51 (15), 1129–1135.
Aung, T., 2016. Association between high blood pressure and cardiovascular disease mortality: a systematic review and meta-analysis of prospective cohort studies. Eur. Heart J. 37 (14), 1171–1180.
Aunola, S., 2017. Genetic factors in cardiovascular diseases. J. Hum. Genet. 62 (3), 153–161.
Bacanu, S.A., 2012. On optimal gene-based analysis of genome scans. Genet. Epidemiol. 36 (10), 911–924.
Bacalfont, C., Cardona, F., Lobera, J., Pulido, F., 2011. Familial hypercholesterolemia: a comprehensive analysis of the genetic basis. Curr. Genet. Med. Rep. 1 (1), 23–32.
Bakris, G.L., 2017. Combination statin therapy and outcomes in clinical trials. J. Clin. Hypertens. (Greenwich) 19 (7), 660–668.
Bakris, G.L., 2018. The role of statins in the management of cardiovascular disease. J. Clin. Hypertens. (Greenwich) 20 (1), 13–23.
Balogh, I., 2014. Genetics of blood pressure and cardiovascular disease. Curr. Mol. Med. 14 (1), 42–55.
Balkau, B., 2014. The influence of socioeconomic status on the prevalence of type 2 diabetes. Diabetes Metab. 40 (6), 366–377.
Barbosa, L.A., 2017. Cardiovascular disease prevention: the role of diet. J. Nutr. 147 (9), 1799S–1805S.
Barnes, D.R., 2013. Genetic and epigenetic mechanisms of cardiovascular disease. J. Med. Genet. 50 (1), 1–12.
Barter, P.J., 2017. Evacetrapib: another CETP inhibitor for dyslipidemia. Curr. Cardiol. Rev. 13 (4), 228–237.
Bazan, N.G., 2007. Polyunsaturated fatty acids and human cardiovascular health. Curr. Opin. Lipidol. 18 (5), 367–375.
Becker, A.P., 2017. The role of diet in the prevention of cardiovascular disease. Curr. Opin. Lipidol. 28 (2), 82–88.
Belkin, W.S., 2017. Recombinant human apo(a) lipoprotein mimetics: a novel approach to the treatment of familial apolipoprotein(a) apoB100 lipoprotein(a) hyperlipidemia. Am. J. Cardiol. 119 (8), 1199–1206.