Genetic invalidation of Lp-PLA$_2$ as a therapeutic target:

large-scale study of five functional Lp-PLA$_2$ lowering alleles

John M. Gregson* PhD; Daniel F. Freitag* PhD; Praveen Surendran PhD; Nathan O. Stitziel MD PhD; Rajiv Chowdhury MD; Stephen Burgess PhD; Stephen Kaptoge PhD; Pei Gao PhD; James R. Staley MSc; Peter Willeit MD, PhD; Sune F. Nielsen PhD; Muriel Caslake PhD; Stella Trompet PhD; Linda M. Polfus PhD; Kari Kuulasmaa PhD; Jukka Kontto MSSc; Markus Perola MD, PhD; Stefan Blankenberg MD; Giovanni Veronesi PhD; Francesco Gianfagna MD, PhD; Satu Männistö ; Akinori Kimura MD, PhD.; Honghuang Lin PhD; Dermot F. Reilly PhD; Mathias Gorski; Vladan Mijatovic on behalf of the CKDGen consortium; Patricia B. Munroe PhD; Georg B. Ehret MD on behalf of the International Consortium for Blood Pressure; Alex Thompson PhD; Maria Uria-Nickelsen PhD; Anders Malarstig PhD; Abbas Dehghan MD PhD on behalf of the CHARGE inflammation working group; Thomas F. Vogt PhD; Taishi Sasaoka MD, PhD; Fumihiko Takeuchi PhD; Norihiro Kato MD, DPhil; Yoshiji Yamada MD, PhD; Frank Kee MD; Martina Müller-Nurasyid PhD; Jean Ferrières MD; Dominique Arveiler MD; Philippe Amouyel MD; Veikko Salomaa MD, PhD; Eric Boerwinkle PhD; Simon G. Thompson FMedSci; Ian Ford PhD; J. Wouter Jukema MD; Naveed Sattar MD; Chris J. Packard PhD; Abdulla al Shafi Majumder MD; Dewan S Alam MD, PhD; Panos Deloukas PhD; Heribert Schunkert MD; Nilesh J. Samani FMedSci; Sekar Kathiresan MD on behalf of the MICAD Exome consortium; Børge G. Nordestgaard MD; Danish Saleheen* MD; Joanna M.M. Howson* PhD; Emanuele Di Angelantonio* MD; Adam S. Butterworth* PhD; John Danesh* FMedSci on behalf of the EPIC-CVD consortium and the CHD Exome$^+$ consortium

*denotes equal contribution; work was conducted at the University of Cambridge; Author's affiliations are provided in the appendix

Correspondence: Dr Freitag or Professor Danesh
Department of Public Health and Primary Care
University of Cambridge
Strangeways Research Laboratory
Cambridge CB1 8RN
UK
john.danesh@phpc.cam.ac.uk
Tel: +44 1223 748 655

ABSTRACT (248 words)

Aims: Darapladib, a potent inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2), has not reduced risk of cardiovascular disease outcomes in recent randomized trials. We aimed to test whether Lp-PLA_2 enzyme activity is causally relevant to coronary heart disease (CHD).

Methods: In 72,657 patients with CHD and 110,218 controls in 23 epidemiological studies, we genotyped five functional variants, four rare loss-of-function mutations (c.109+2T>C[rs142974898], Arg82His[rs144983904], Val279Phe[rs76863441], Gln287Ter[rs140020965]) and one common modest-impact variant (Val379Ala[rs1051931]) in *PLA2G7*, the gene encoding Lp-PLA_2. We supplemented de-novo genotyping with information on a further 45,823 CHD patients and 88,680 controls in publicly available databases and other previous studies. We conducted a systematic review of randomized trials to compare effects of darapladib treatment on soluble Lp-PLA_2 activity, conventional cardiovascular risk factors, and CHD risk with corresponding effects of Lp-PLA_2-lowering alleles.

Results: Lp-PLA_2 activity was decreased by 64% ($p=2.4\times10^{-25}$) with carriage of any of the four loss-of-function variants, by 45% ($p<10^{-300}$) for every allele inherited at Val279Phe, and by 2.7% ($p=1.9\times10^{-12}$) for every allele inherited at Val379Ala. Darapladib 160mg once-daily reduced Lp-PLA_2 activity by 65% ($p<10^{-300}$). Causal risk ratios for CHD per 65% lower Lp-PLA_2 activity were: 0.95 (0.88-1.03) with Val279Phe; 0.92 (0.74-1.16) with carriage of any loss-of-function variant; 1.01 (0.68-1.51) with Val379Ala; and 0.95 (0.89-1.02) with darapladib treatment.

Conclusions: None of a series of Lp-PLA_2–lowering alleles was related to CHD risk, suggesting that Lp-PLA_2 is not a valid therapeutic target.

KEY WORDS: Human genetics, target validation, coronary heart disease, Lipoprotein-associated phospholipase A_2, darapladib

ABBREVIATIONS

CHD = Coronary Heart Disease

CI = Confidence Interval

HDL = High-density lipoprotein

LDL = Low-density lipoprotein

Lp-PLA_2 = Lipoprotein-associated phospholipase A_2

MI = Myocardial infarction

SD = Standard deviation

Word count: 3003 (excluding references and abstract (248 words))

3 main figures, 2 tables, 1 Appendix

Supplement (comprising a supplementary note and 6 tables, 4 figures)

INTRODUCTION

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), an enzyme expressed by inflammatory cells in atherosclerotic plaques, is carried in the circulation bound predominantly to low-density-lipoprotein (LDL)[1]. Lp-PLA_2 (also called platelet-activating factor acetyl hydrolase) hydrolyzes oxidized phospholipids to yield pro-inflammatory products implicated in endothelial dysfunction, plaque inflammation, and formation of necrotic core in plaque[1]. Observational[2] and experimental studies in humans and animals have suggested that Lp-PLA_2 could be a valid therapeutic target, postulating this enzyme to link oxidative modification of LDL and development of inflammatory responses to arterial intima[1]. Previous studies have investigated genetic variants altering Lp-PLA_2 function in relation to coronary heart disease (CHD) risk[3, 4]. However, these studies have generally yielded inconclusive, or conflicting results[3, 4], perhaps due to limited statistical power and to limited knowledge about variants altering Lp-PLA_2 function (i.e., previous studies have been able to consider only one loss-of-function variant in *PLA2G7*, the gene encoding Lp-PLA_2).

However, two phase 3 randomized trials of darapladib, a potent inhibitor of Lp-PLA_2 activity, have not shown reductions in cardiovascular risk[5, 6]. These results could, at least in part, have been due to features of the trials. One of the phase 3 trials was restricted to patients recently hospitalized with acute coronary syndromes[5], yet many cardiovascular events occurring early after acute coronary syndromes may relate to thrombotic mechanisms and not be modifiable through Lp-PLA_2 inhibition. Trials used statins as background therapy, so any Lp-PLA_2 inhibition achieved with statins could have reduced any incremental benefits of darapladib. Trials could not assess the effects of prolonged Lp-PLA_2 inhibition because they recorded only about 3-4 years of median follow-up[5, 6].

An alternative explanation is that darapladib did not reduce cardiovascular risk because Lp-PLA_2 is not a causal risk factor in cardiovascular disease. We tested this possibility by investigating natural loss of Lp-PLA_2 activity. Studies of Lp-PLA_2–lowering alleles should complement randomized trials of darapladib because genotypes are fixed at conception, avoiding potential distorting effects of pre-existing disease and medication usage. Furthermore, Lp-PLA_2–lowering alleles should produce lifelong, rather than shorter-term, Lp-PLA_2 inhibition.

In over 260,000 participants of European, South Asian, or East Asian ancestries, we studied five functional variants in *PLA2G7*. We compared effects of Lp-PLA_2-lowering alleles on soluble Lp-PLA_2 activity, conventional cardiovascular risk factors, and CHD risk with corresponding effects of darapladib, using results from randomized trials.

METHODS

Study design

Figure 1 summarises the study approach. **Table 1** provides definitions and sources of data used. First, we identified four loss-of-function mutations and one missense variant in *PLA2G7* suggested by previous experimental and bioinformatics studies, thereby developing an allelic series for Lp-PLA_2 activity. Second, we assessed associations of these variants ─ both singly and in combination ─ with soluble Lp-PLA_2 activity, conventional cardiovascular risk factors, and CHD risk in people of European, South Asian, or East Asian continental ancestries. Third, we compared associations of Lp-PLA_2–lowering alleles with the aforementioned traits and CHD risk with the effects of darapladib treatment through a systematic review of randomized trials.

Genetic variants

We defined loss-of-function variants as non-synonymous variants with *in vitro* or *in vivo* evidence demonstrating complete lack of Lp-PLA_2 activity or sequence changes expected to abolish Lp-PLA_2 function (e.g., nonsense variants or mutations in essential splice sites). We selected variants through a systematic search for loss-of-function variants using the UniProt database[7], the Exome Aggregation Consortium database (Cambridge, MA, USA; URL: http://exac.broadinstitute.org; [accessed November 2014])[8], studies of site-directed mutagenesis[9-11] and results from targeted gene sequencing[12]. Among the full set of variants identified (**eTable1**), we selected the following variants that could be detected in the 1000 Genomes[13] or the Exome sequencing[14] projects (and, hence, potentially studied at the population level): the splice site mutation 109+2T>C (rs142974898); two non-synonymous variants ─ Arg82His (rs144983904) and Val279Phe (rs76863441); and the nonsense variant Gln287Ter (rs140020965). These loss-of-function variants are rare in European and South Asian ancestry populations, whereas carriage of 279Phe is common in East Asian ancestry populations and abolition of Lp-PLA_2 activity is well documented[15]. Additionally, we studied Val379Ala (rs1051931), a functional variant common in European ancestry populations, which lowers Lp-PLA_2 activity only modestly[9, 16], in contrast with the substantial Lp-PLA_2–lowering achieved by the loss-of-function variants described above.

Samples and data for genetic studies

We aimed to maximise study power and comprehensiveness by using the following complementary approaches to generate new data on, as well as to collate systematically existing relevant information about, the *PLA2G7*

variants mentioned above: (1) we conducted de-novo genotyping for 72,657 CHD patients and 110,218 controls (the majority of whom also had information available on some cardiovascular risk factors); (2) we accessed non-overlapping summary-level data from the only known global genetics consortium of CHD[17], yielding information on a further 35,735 CHD patients and 73,481 controls; (3) we conducted a systematic review (supplemented by provision of tabular data from each study investigator) of published East Asian CHD studies of Val279Phe because these studies were not represented in the global CHD consortium, yielding information on a further 10,088 CHD cases and 15,199 controls; (4) we accessed summary-level data from the largest available global genetics consortium on each of several relevant cardiovascular risk factors (eg, Lp-PLA_2 activity, conventional lipids, blood pressure), yielding information on 489,045 participants. Each of these sources of information is summarised below and in **Table 1**.

Coronary heart disease outcomes For CHD outcomes, we had access to data for a total of 92,995 patients and 162,228 controls. For 182,875 of these participants (72,657 CHD patients, 110,218 controls), we did de-novo genotyping of the four loss-of-function variants (c.109+2T>C, Arg82His, Val279Phe, Gln287Ter) and Val379Ala using customized Exome arrays (Illumina, California, USA) by technicians masked to the phenotypic status of the participants' samples. For 35,829 CHD cases, 44,948 controls in eight studies, we had access to individual-participant data. The eight studies were: the Bangladesh Risk of Acute Vascular Events Study (BRAVE)[18], Copenhagen City Heart Study (CCHS)[19], Copenhagen Ischemic Heart Disease/Copenhagen General Population Study (CIHDS/CGPS)[19], European Prospective Investigation into Cancer and Nutrition-Cardiovascular Disease Study (EPIC-CVD)[20], MONICA Risk, Genetics, Archiving, and Monograph (MORGAM) study[21, 22], Pakistan Risk of Myocardial Infarction Study (PROMIS)[23], Pravastatin in elderly individuals at risk of vascular disease (PROSPER) trial[24] and the West of Scotland Coronary Prevention Study (WOSCOPS)[25] (these eight studies are collectively called the "CHD Exome+ consortium"). For 15 additional studies (collectively called the "MICAD consortium"), we used similar genotyping methods to those described above but did not genotype c.109+2T>C and had access only to study-level data. We supplemented de-novo data on Val379Ala with non-overlapping consortium-level results from a further 35,735 CHD patients and 73,481 controls in the transatlantic Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM)[26] and Coronary Artery Disease Genetics (C4D)[27] consortia (**Table 1**). We obtained tabular data on Val279Phe from seven East Asian studies involving a total of 10,088 CHD cases and 15,199 controls, identified through systematic review (**eTable 5** and **Supplement**). About 90% of CHD patients in our genetic

analysis had myocardial infarction or other major acute coronary events; the remainder had angiographic evidence alone (eg, >50% coronary stenosis; **eTables 2 & 5**).

Lp-PLA$_2$ activity For 13,835 participants, we had information on functional variants in *PLA2G7* and Lp-PLA$_2$ activity, using data from de-novo genotyping in MORGAM[21, 22] and PROSPER[24], supplemented by published data from the CHARGE Consortium (ie, from the Atherosclerosis Risk in Communities [ARIC] Study[28], Cardiovascular Health Study[16], Framingham Heart Study[16], and Rotterdam study[16]), and from 12 East Asian studies identified through the systematic review described above (**Table 1, Supplement** & **eFigure1, eTables 2-3**).

Conventional cardiovascular risk factors For 177,343 participants, we had information on functional variants in *PLA2G7* and conventional cardiovascular risk factors and several other traits, including circulating concentrations of LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, insulin, and C-reactive protein, and values of systolic and diastolic blood pressure, body-mass index, and estimated glomerular filtration rate. Again, we supplemented data from our de-novo genotyping, with information from existing global genetics consortia (**Table 1, eTables 2-4**).

Randomized trials of darapladib

To compare genetic associations with effects of pharmacological Lp-PLA$_2$ inhibition, we conducted a systematic review to identify randomized placebo-controlled trials of darapladib that had reported on Lp-PLA$_2$ activity, conventional risk factors, and/or CHD events (**Supplement**). CHD events in the trials were defined as fatal CHD, MI or urgent revascularisation, as recorded in STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) and in SOLID-TIMI 52 (Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52)[5, 6]. We pooled results across trials by fixed-effect inverse-variance weighted meta-analysis (**eFigures 2&3**; see Supplement for details of the methods used).

Statistical methods

We defined effect alleles as those associated with lower Lp-PLA$_2$ activity and assumed an additive model. For participant-level data, we assessed associations of Lp-PLA$_2$-lowering alleles with CHD using the genome-wide efficient mixed model analysis, an approach that models each genetic variant as a fixed-effect, but includes both fixed-effect and random-effects of genetic inheritance[29] to account for population stratification and relatedness among participants (**Supplement**). The four rare loss-of-function variants were tested jointly within each study

by counting the number of loss-of-function alleles carried by each participant. Log odds ratios and standard errors were meta-analysed across studies using fixed-effect meta-analysis. For studies contributing only study-level data, we performed a similar test by conducting a combined burden test across studies using the R package seqMeta v1.2 (http://cran.r-project.org/web/packages/seqMeta/).

We calculated associations of Lp-PLA_2-lowering alleles with soluble Lp-PLA_2 activity and conventional risk factors using linear regression within each study, and then combined the regression coefficients using fixed-effect meta-analysis. When data were missing, we used information on rs1805018 as a proxy for Val279Phe and information on rs7756935 or rs3799277 as proxies for Val379Ala (**Supplement**). To account for population stratification, we adjusted for the first principal component of ancestry (**Supplement)**. We calculated risk ratios for CHD with decrements in Lp-PLA_2 activity, dividing the log transformed risk ratio and confidence interval (CI) by the effect on Lp-PLA_2 activity of the instrument (ie, the genetic variant)[30]. We investigated heterogeneity using the I^2 statistic. We used Stata 13.1.

RESULTS

Of the 261,950 total participants in this analysis, we studied 195,715 individuals of European ancestry, 34,221 individuals of South Asian ancestry, and 32,014 individuals of East Asian ancestry. In people of European or South Asian ancestry without CHD, the frequency of alleles in *PLA2G7* that lower Lp-PLA_2 activity was 0.005% at c.109+2T>C, 0.04% at Arg82His, 0.04% at Val279Phe, and 0.025% at Gln287Ter (i.e., in aggregate, 0.2% of the European or South Asian participants in the current study carried one of these loss-of-function alleles, although no one carried more than one of these variants), and about 80% at Val379Ala. In people of East Asian ancestry without CHD, the frequency of Val279Phe was about 15% and about 2% of the individuals were homozygous carriers of the 279Phe allele.

Soluble Lp-PLA_2 activity

Compared with non-carriers, homozygote carriers of the 279Phe allele had 94% lower Lp-PLA_2 activity ($p<10^{-300}$). For each 279Phe allele inherited, Lp-PLA_2 activity decreased by 45% (1.59 SD, 95% CI: 1.61-1.57; $p<10^{-300}$). In Europeans who inherited any one of the four rare Lp-PLA_2 loss-of-function alleles, Lp-PLA_2 activity decreased by 64% (2.25 SD, 2.68-1.83; $p=1.6\times10^{-25}$). For each 379Ala allele inherited, Lp-PLA_2 activity decreased by 2.7% (0.096 SD, 0.122-0.069; $p=1.9\times10^{-12}$). By comparison, 160mg once-daily darapladib reduced Lp-PLA_2 activity by 65% (2.26 SD, 2.31-2.21; $p<10^{-300}$). Study-level estimates are provided in **eFigure 2**.

Cardiovascular risk factors

None of the Lp-PLA_2–related variants we studied was significantly associated with values of LDL-cholesterol, HDL-cholesterol, triglycerides, systolic or diastolic blood pressure, body-mass index, estimated glomerular filtration rate, glucose, insulin, and C-reactive protein (**Figure 2**). By comparison, in previous randomized placebo-controlled trials, darapladib did not significantly affect concentrations of LDL-cholesterol or log triglycerides, but could have slightly increased systolic blood pressure and HDL-cholesterol values and slightly decreased C-reactive protein concentration (**Figure 2**).

Clinical CHD outcomes

Compared to non-carriers, the odds ratio for CHD was 0.99 (0.95-1.03) in 279Phe heterozygotes, and 0.93 (0.82–1.05) in 279Phe homozygotes (i.e. nearly complete loss of Lp-PLA_2 function: **Figure 3**). For each loss-of-function (279Phe) allele inherited, the odds ratio for CHD was 0.97 (0.91-1.02; I^2=30%; $P_{Heterogeneity}$=0.2). In Europeans and South Asians who inherited one of the four rare Lp-PLA_2-loss-of-function alleles, the odds ratio for CHD was 0.92 (0.74-1.16; I^2=0%; $P_{Heterogeneity}$=0.8; **Figure 3**). For each 379Ala allele inherited, the odds ratio for CHD was 1.00 (0.98-1.02; I^2=0.0%; $P_{Heterogeneity}$=0.5; **Figure 3**). Study-level results are provided in **eFigure 3**. In sensitivity analyses, odds ratios with each loss-of-function variant were similar to the odds ratio that combined information across the four loss-of-function variants we studied. There was no evidence of heterogeneity in odds ratios between European and South Asian ancestry populations (**eFigure 4**).

Genetic risk ratios for CHD per 65% lower Lp-PLA_2 activity (i.e. the reduction achievable with darapladib treatment) were: 0.95 (0.88-1.03) with Val279Phe in East Asians; and 0.92 (0.74-1.16) with carriage of any one of the four rare variants studied in Europeans and South Asians; and 1.01 (0.68-1.51) with Val379Ala (**Table 2**). By comparison, the risk ratio for CHD with darapladib treatment (i.e. also per 65% lower Lp-PLA_2 activity) was 0.95 (0.89-1.02; **Table 2**).

DISCUSSION

In 2008, GlaxoSmithKline launched a ~$1 billion program of phase 3 trials of darapladib, a compound which did not reduce cardiovascular event rates in two secondary prevention trials. We tested whether Lp-PLA_2 enzyme activity is causally relevant to CHD by studying five functional alleles that produce widely differing degrees of reduction in Lp-PLA_2 activity. We found that none was related to CHD risk. Hence, our large-scale human genetic data, which are concordant with results from phase 3 trials, suggest that Lp-PLA_2 enzyme activity is not causally relevant to CHD. The implication is that darapladib did not reduce CHD risk in recent trials principally because Lp-PLA_2 is not a valid therapeutic target.

Three features of our study merit comment. First, we studied almost 20 times more CHD patients than the previous largest study of loss-of-function *PLA2G7* alleles, thereby providing the first robust genetic evaluation of effect sizes of Lp-PLA_2 inhibition relevant to phase 3 trials such as relative risk reductions for CHD of 20%. For example, for the Val279Phe variant we had >99% power to detect a 20% risk reduction in CHD for a 65% genetic reduction in Lp-PLA2 activity (ie, an effect on Lp-PLA2 activity similar to that achieved by darapladib).

Second, our study has provided the first investigation in CHD of a series of functional alleles that each reduce Lp-PLA_2 function via different molecular mechanisms. Specifically, we studied five different Lp-PLA_2-lowering alleles: three of the alleles were coding variants that produced different amino acid substitutions; two of the alleles produced protein truncations (one due to a nonsense mutation; the other due to a splice-site mutation). Because we observed null and broadly concordant findings for CHD risk across these alleles that each changed the enzyme in a different way, we can more confidently conclude there is no material cause-and-effect relationship. By contrast, when the initial phase 3 trial of darapladib was launched in 2008, only two of the five alleles we studied had yet been identified: data on Val379Ala, a weak effect missense variant, were inconclusive because CHD studies were under-powered[31]; data on Val279Phe, a loss-of-function variant, and CHD risk were sparse and restricted to East Asian populations.

A third feature was our study's analysis of substantial data from three different major ethnic groups: Europeans, South Asians, and East Asians. This ethnic diversity enhanced the generalisability of our results.

Our study had potential limitations. We used the "major coronary events" endpoint from phase 3 darapladib trials for comparison of pharmacological inhibition of Lp-PLA_2 with genetic inhibition, whereas definitions of CHD used in human genetic studies were not strictly uniform (eg, some studies included patients with only

angiographic evidence of CHD). However, about 90% of CHD cases included in our genetic analyses had myocardial infarction or other major acute coronary events.

It could be that cardioprotective benefits of Lp-PLA_2 inhibition were obscured by pleiotropic effects of *PLA2G7* variants; for example, 279Phe is known to produce a misfolded version of Lp-PLA_2 not secreted by cells, prompting suggestions that its carriage could produce "off-target" effects such as increased cell death[32, 33]. However, because we found null associations between four other functional alleles in *PLA2G7* and CHD, each of which operates via a different molecular mechanism, it argues against this explanation.

Lifelong genetic reductions in Lp-PLA_2 could result in compensatory responses that increase CHD risk. However, this explanation seems unlikely because it would require any such compensation to apply similarly across alleles that produce widely differing degrees of reduction in Lp-PLA_2 activity. Furthermore, any such compensation could not operate through known cardiovascular mechanisms because we observed no associations between Lp-PLA_2-lowering alleles and several established and emerging cardiovascular risk factors.

Soluble enzyme activity could be an imperfect indicator of the relevance of Lp-PLA_2 to atherosclerotic plaques. However, for homozygote carriers of 279Phe, Lp-PLA_2 activity should be almost abolished across all tissues. Finally, we studied life-long genetic reductions in Lp-PLA_2 activity in relation to first-onset CHD outcomes rather than recurrent CHD, whereas darapladib trials studied recurrent coronary events in patients with stable or acute coronary disease.

Our findings suggest that, in retrospect, the lack of efficacy of darapladib in phase 3 trials could, in principle, have been anticipated. However, it is important to acknowledge that the methods and data used in the current analysis were not available at the time the darapladib program was launched. Nevertheless, the current data underscore the growing importance of human genetic approaches to enhance the efficiency of development of medicines by validating (or invalidating) novel drug targets[34-37]. Our results also illustrate how human genetic evidence can assist interpretation of observational epidemiological data. We found that functional alleles in *PLA2G7* do not alter levels of pro-atherogenic lipds (eg, LDL-C). This result suggests that such pro-atherogenic lipids do not mediate associations between Lp-PLA_2 activity and CHD, supporting the need to adjust epidemiological associations of Lp-PLA_2 activity with CHD risk for pro-atherogenic lipds (an approach which yields results consistent with non-causality)[2].

In summary, none of a series of Lp-PLA_2–lowering alleles was related to CHD risk, suggesting that Lp-PLA_2 is not a valid therapeutic target.

ACKNOWLEDGEMENTS

The work of the coordinating center was funded by the UK Medical Research Council (G0800270), British Heart Foundation (SP/09/002), British Heart Foundation Cambridge Cardiovascular Centre of Excellence, UK National Institute for Health Research Cambridge Biomedical Research Centre, European Research Council (268834), European Commission Framework Programme 7 (HEALTH-F2-2012-279233). The Supplement includes a list provided by investigators of some of the funders of the component studies in this analysis.

DISCLOSURES

Anders Malarstig and Maria Uria-Nickelsen are full time employees of Pfizer. Since October 2015, Daniel Freitag has been a full time employee of Bayer. 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.

REFERENCES

1. Corson MA. Darapladib: an emerging therapy for atherosclerosis. Ther Adv Cardiovasc Dis 2010;4(4):241-248.

2. Thompson A, Gao P, Orfei L, Watson S, Di AE, Kaptoge S, Ballantyne C, Cannon CP, Criqui M, Cushman M, Hofman A, Packard C, Thompson SG, Collins R, Danesh J. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet* 2010;**375**(9725):1536-1544.

3. Yamada Y, Yoshida H, Ichihara S, Imaizumi T, Satoh K, Yokota M. Correlations between plasma platelet-activating factor acetylhydrolase (PAF-AH) activity and PAF-AH genotype, age, and atherosclerosis in a Japanese population. *Atherosclerosis* 2000;**150**(1):209-216.

4. Jang Y, Waterworth D, Lee JE, Song K, Kim S, Kim HS, Park KW, Cho HJ, Oh IY, Park JE, Lee BS, Ku HJ, Shin DJ, Lee JH, Jee SH, Han BG, Jang HY, Cho EY, Vallance P, Whittaker J, Cardon L, Mooser V. Carriage of the V279F null allele within the gene encoding Lp-PLA(2) is protective from coronary artery disease in South Korean males. *PLoS One* 2011;**6**(4):e18208.

5. O'Donoghue ML, Braunwald E, White HD, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP, Steen DL. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA* 2014;**312**(10):1006-1015.

6. White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF, Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, Lopez-Sendon J, Manolis AJ, Mohler ER, III, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D, Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J, Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med* 2014;**370**(18):1702-1711.

7. UniProt: a hub for protein information. *Nucleic Acids Res* 2014.

8. Tjoelker LW, Eberhardt C, Unger J, Trong HL, Zimmerman GA, McIntyre TM, Stafforini DM, Prescott SM, Gray PW. Plasma platelet-activating factor acetylhydrolase is a secreted phospholipase A2 with a catalytic triad. *J Biol Chem* 1995;**270**(43):25481-25487.

9. Yamada Y, Yokota M. Loss of activity of plasma platelet-activating factor acetylhydrolase due to a novel Gln281-->Arg mutation. *Biochem Biophys Res Commun* 1997;**236**(3):772-775.

10. Kruse S, Mao XQ, Heinzmann A, Blattmann S, Roberts MH, Braun S, Gao PS, Forster J, Kuehr J, Hopkin JM, Shirakawa T, Deichmann KA. The Ile198Thr and Ala379Val variants of plasmatic PAF-acetylhydrolase impair catalytical activities and are associated with atopy and asthma. *Am J Hum Genet* 2000;**66**(5):1522-1530.

11. Song K, Nelson MR, Aponte J, Manas ES, Bacanu SA, Yuan X, Kong X, Cardon L, Mooser VE, Whittaker JC, Waterworth DM. Sequencing of Lp-PLA2-encoding PLA2G7 gene in 2000

Europeans reveals several rare loss-of-function mutations. *Pharmacogenomics J* 2012;**12**(5):425-431.

12. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. An integrated map of genetic variation from 1,092 human genomes. *Nature* 2012;**491**(7422):56-65.

13. Tennessen JA, Bigham AW, O'Connor TD, Fu W, Kenny EE, Gravel S, McGee S, Do R, Liu X, Jun G, Kang HM, Jordan D, Leal SM, Gabriel S, Rieder MJ, Abecasis G, Altshuler D, Nickerson DA, Boerwinkle E, Sunyaev S, Bustamante CD, Bamshad MJ, Akey JM. Evolution and functional impact of rare coding variation from deep sequencing of human exomes. *Science* 2012;**337**(6090):64-69.

14. Stafforini DM, Satoh K, Atkinson DL, Tjoelker LW, Eberhardt C, Yoshida H, Imaizumi T, Takamatsu S, Zimmerman GA, McIntyre TM, Gray PW, Prescott SM. Platelet-activating factor acetylhydrolase deficiency. A missense mutation near the active site of an anti-inflammatory phospholipase. *J Clin Invest* 1996;**97**(12):2784-2791.

15. Grallert H, Dupuis J, Bis JC, Dehghan A, Barbalic M, Baumert J, Lu C, Smith NL, Uitterlinden AG, Roberts R, Khuseyinova N, Schnabel RB, Rice KM, Rivadeneira F, Hoogeveen RC, Fontes JD, Meisinger C, Keaney JF, Jr., Lemaitre R, Aulchenko YS, Vasan RS, Ellis S, Hazen SL, van Duijn CM, Nelson JJ, Marz W, Schunkert H, McPherson RM, Stirnadel-Farrant HA, Psaty BM, Gieger C, Siscovick D, Hofman A, Illig T, Cushman M, Yamamoto JF, Rotter JI, Larson MG, Stewart AF, Boerwinkle E, Witteman JC, Tracy RP, Koenig W, Benjamin EJ, Ballantyne CM. Eight genetic loci associated with variation in lipoprotein-associated phospholipase A2 mass and activity and coronary heart disease: meta-analysis of genome-wide association studies from five community-based studies. *Eur Heart J* 2012;**33**(2):238-251.

16. Polfus LM, Gibbs RA, Boerwinkle E. Coronary heart disease and genetic variants with low phospholipase A2 activity. *N Engl J Med* 2015;**372**(3):295-296.

17. Kulathinal S, Karvanen J, Saarela O, Kuulasmaa K. Case-cohort design in practice - experiences from the MORGAM Project. *Epidemiol Perspect Innov* 2007;**4**:15.

18. Evans A, Salomaa V, Kulathinal S, Asplund K, Cambien F, Ferrario M, Perola M, Peltonen L, Shields D, Tunstall-Pedoe H, Kuulasmaa K. MORGAM (an international pooling of cardiovascular cohorts). *Int J Epidemiol* 2005;**34**(1):21-27.

19. Caslake MJ, Packard CJ, Robertson M, Cooney J, Nelson JJ, Ford I, Gaw A, Jukema JW, Macfarlane PW, Stott DJ, Shepherd J. Lipoprotein-associated phospholipase A(2), inflammatory biomarkers, and risk of cardiovascular disease in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Atherosclerosis* 2010;**210**(1):28-34.

20. Chowdhury R, Alam DS, Fakir II, Adnan SD, Naheed A, Tasmin I, Monower MM, Hossain F, Hossain FM, Rahman MM, Afrin S, Roy AK, Akter M, Sume SA, Biswas AK, Pennells L, Surendran P, Young RD, Spackman SA, Hasan K, Harshfield E, Sheikh N, Houghton R, Saleheen D, Howson JM, Butterworth AS, Raqib R, Majumder AA, Danesh J, Di AE. The Bangladesh Risk of Acute Vascular Events (BRAVE) Study: objectives and design. *Eur J Epidemiol* 2015.

21. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;**301**(22):2331-2339.

22. Danesh J, Saracci R, Berglund G, Feskens E, Overvad K, Panico S, Thompson S, Fournier A, Clavel-Chapelon F, Canonico M, Kaaks R, Linseisen J, Boeing H, Pischon T, Weikert C, Olsen A, Tjonneland A, Johnsen SP, Jensen MK, Quiros JR, Svatetz CA, Perez MJ, Larranaga N, Sanchez CN, Iribas CM, Bingham S, Khaw KT, Wareham N, Key T, Roddam A, Trichopoulou A, Benetou V, Trichopoulos D, Masala G, Sieri S, Tumino R, Sacerdote C, Mattiello A, Verschuren WM, Bueno-de-Mesquita HB, Grobbee DE, van der Schouw YT, Melander O, Hallmans G, Wennberg P, Lund E, Kumle M, Skeie G, Ferrari P, Slimani N, Norat T, Riboli E. EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. *Eur J Epidemiol* 2007;**22**(2):129-141.

23. Saleheen D, Zaidi M, Rasheed A, Ahmad U, Hakeem A, Murtaza M, Kayani W, Faruqui A, Kundi A, Zaman KS, Yaqoob Z, Cheema LA, Samad A, Rasheed SZ, Mallick NH, Azhar M, Jooma R, Gardezi AR, Memon N, Ghaffar A, Fazal uR, Khan N, Shah N, Ali SA, Samuel M, Hanif F, Yameen M, Naz S, Sultana A, Nazir A, Raza S, Shazad M, Nasim S, Javed MA, Ali SS, Jafree M, Nisar MI, Daood MS, Hussain A, Sarwar N, Kamal A, Deloukas P, Ishaq M, Frossard P, Danesh J. The Pakistan Risk of Myocardial Infarction Study: a resource for the study of genetic, lifestyle and other determinants of myocardial infarction in South Asia. *Eur J Epidemiol* 2009;**24**(6):329-338.

24. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;**333**(20):1301-1307.

25. Zhou X, Stephens M. Efficient multivariate linear mixed model algorithms for genome-wide association studies. *Nat Methods* 2014;**11**(4):407-409.

26. Palmer TM, Sterne JA, Harbord RM, Lawlor DA, Sheehan NA, Meng S, Granell R, Smith GD, Didelez V. Instrumental variable estimation of causal risk ratios and causal odds ratios in Mendelian randomization analyses. *Am J Epidemiol* 2011;**173**(12):1392-1403.

27. Casas JP, Ninio E, Panayiotou A, Palmen J, Cooper JA, Ricketts SL, Sofat R, Nicolaides AN, Corsetti JP, Fowkes FG, Tzoulaki I, Kumari M, Brunner EJ, Kivimaki M, Marmot MG, Hoffmann MM, Winkler K, Marz W, Ye S, Stirnadel HA, Boekholdt SM, Khaw KT, Humphries SE, Sandhu MS, Hingorani AD, Talmud PJ. PLA2G7 genotype, lipoprotein-associated phospholipase A2 activity, and coronary heart disease risk in 10 494 cases and 15 624 controls of European Ancestry. *Circulation* 2010;**121**(21):2284-2293.

28. Plenge RM, Scolnick EM, Altshuler D. Validating therapeutic targets through human genetics. *Nat Rev Drug Discov* 2013;**12**(8):581-594.

29. Kamb A, Harper S, Stefansson K. Human genetics as a foundation for innovative drug development. *Nat Biotechnol* 2013;**31**(11):975-978.

30. Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, Fontanillas P, Gupta N, Duga S, Goel A, Farrall M, Saleheen D, Ferrario P, Konig I, Asselta R, Merlini PA, Marziliano N, Notarangelo MF, Schick U, Auer P, Assimes TL, Reilly M, Wilensky R, Rader DJ, Hovingh GK, Meitinger T, Kessler T, Kastrati A, Laugwitz KL, Siscovick D, Rotter JI, Hazen SL, Tracy R, Cresci S, Spertus J, Jackson R, Schwartz SM, Natarajan P, Crosby J, Muzny D, Ballantyne C, Rich SS, O'Donnell CJ, Abecasis G, Sunyaev S, Nickerson DA, Buring JE, Ridker PM, Chasman DI, Austin E, Ye Z, Kullo IJ, Weeke PE, Shaffer CM, Bastarache LA, Denny JC, Roden DM, Palmer C, Deloukas P, Lin DY, Tang ZZ, Erdmann J, Schunkert H, Danesh J, Marrugat J, Elosua R, Ardissino D, McPherson R, Watkins H, Reiner AP, Wilson JG, Altshuler D, Gibbs RA, Lander ES,

Boerwinkle E, Gabriel S, Kathiresan S. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *N Engl J Med* 2014;**371**(22):2072-2082.

31. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, Floratos A, Sham PC, Li MJ, Wang J, Cardon LR, Whittaker JC, Sanseau P. The support of human genetic evidence for approved drug indications. *Nat Genet* 2015;**47**(8):856-860.

32. Schroder M, Kaufman RJ. The mammalian unfolded protein response. *Annu Rev Biochem* 2005;**74**:739-789.

33. Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. *Arterioscler Thromb Vasc Biol* 2005;**25**(5):923-931.

34. Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NE, Ellis SG, Elosua R, Engert JC, Epstein SE, de FU, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJ, Khaw KT, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Muhleisen TW, Muhlestein JB, Munzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nothen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schafer A, Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WH, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE, Wild PS, Willenborg C, Witteman JC, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, Marz W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 2011;**43**(4):333-338.

35. Peden JF, Hopewell JC, Saleheen D, Chambers JC, Hager J, Soranzo N, Collins R, Danesh J, Elliott P, Farrall M, Stirrups K, Zhang W, Hamsten A. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. *Nat Genet* 2011;**43**(4):339-344.

36. Serruys PW, Garcia-Garcia HM, Buszman P, Erne P, Verheye S, Aschermann M, Duckers H, Bleie O, Dudek D, Botker HE, von BC, D'Amico D, Hutchinson T, Zambanini A, Mastik F, van Es GA, van der Steen AF, Vince DG, Ganz P, Hamm CW, Wijns W, Zalewski A. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 2008;**118**(11):1172-1182.

37. Mohler ER, III, Ballantyne CM, Davidson MH, Hanefeld M, Ruilope LM, Johnson JL, Zalewski A. The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart

disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 2008;**51**(17):1632-1641.

38. Daida H, Iwase T, Yagi S, Ando H, Nakajima H. Effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity in Japanese dyslipidemic patients, with exploratory analysis of a PLA2G7 gene polymorphism of Val279Phe. *Circ J* 2013;**77**(6):1518-1525.

39. Randall JC, Winkler TW, Kutalik Z, Berndt SI, Jackson AU, Monda KL, Kilpelainen TO, Esko T, Magi R, Li S, Workalemahu T, Feitosa MF, Croteau-Chonka DC, Day FR, Fall T, Ferreira T, Gustafsson S, Locke AE, Mathieson I, Scherag A, Vedantam S, Wood AR, Liang L, Steinthorsdottir V, Thorleifsson G, Dermitzakis ET, Dimas AS, Karpe F, Min JL, Nicholson G, Clegg DJ, Person T, Krohn JP, Bauer S, Buechler C, Eisinger K, Bonnefond A, Froguel P, Hottenga JJ, Prokopenko I, Waite LL, Harris TB, Smith AV, Shuldiner AR, McArdle WL, Caulfield MJ, Munroe PB, Gronberg H, Chen YD, Li G, Beckmann JS, Johnson T, Thorsteinsdottir U, Teder-Laving M, Khaw KT, Wareham NJ, Zhao JH, Amin N, Oostra BA, Kraja AT, Province MA, Cupples LA, Heard-Costa NL, Kaprio J, Ripatti S, Surakka I, Collins FS, Saramies J, Tuomilehto J, Jula A, Salomaa V, Erdmann J, Hengstenberg C, Loley C, Schunkert H, Lamina C, Wichmann HE, Albrecht E, Gieger C, Hicks AA, Johansson A, Pramstaller PP, Kathiresan S, Speliotes EK, Penninx B, Hartikainen AL, Jarvelin MR, Gyllensten U, Boomsma DI, Campbell H, Wilson JF, Chanock SJ, Farrall M, Goel A, Medina-Gomez C, Rivadeneira F, Estrada K, Uitterlinden AG, Hofman A, Zillikens MC, den HM, Kiemeney LA, Maschio A, Hall P, Tyrer J, Teumer A, Volzke H, Kovacs P, Tonjes A, Mangino M, Spector TD, Hayward C, Rudan I, Hall AS, Samani NJ, Attwood AP, Sambrook JG, Hung J, Palmer LJ, Lokki ML, Sinisalo J, Boucher G, Huikuri H, Lorentzon M, Ohlsson C, Eklund N, Eriksson JG, Barlassina C, Rivolta C, Nolte IM, Snieder H, Van der Klauw MM, Van Vliet-Ostaptchouk JV, Gejman PV, Shi J, Jacobs KB, Wang Z, Bakker SJ, Mateo L, I, Navis G, van der Harst P, Martin NG, Medland SE, Montgomery GW, Yang J, Chasman DI, Ridker PM, Rose LM, Lehtimaki T, Raitakari O, Absher D, Iribarren C, Basart H, Hovingh KG, Hypponen E, Power C, Anderson D, Beilby JP, Hui J, Jolley J, Sager H, Bornstein SR, Schwarz PE, Kristiansson K, Perola M, Lindstrom J, Swift AJ, Uusitupa M, Atalay M, Lakka TA, Rauramaa R, Bolton JL, Fowkes G, Fraser RM, Price JF, Fischer K, Krjuta KK, Metspalu A, Mihailov E, Langenberg C, Luan J, Ong KK, Chines PS, Keinanen-Kiukaanniemi SM, Saaristo TE, Edkins S, Franks PW, Hallmans G, Shungin D, Morris AD, Palmer CN, Erbel R, Moebus S, Nothen MM, Pechlivanis S, Hveem K, Narisu N, Hamsten A, Humphries SE, Strawbridge RJ, Tremoli E, Grallert H, Thorand B, Illig T, Koenig W, Muller-Nurasyid M, Peters A, Boehm BO, Kleber ME, Marz W, Winkelmann BR, Kuusisto J, Laakso M, Arveiler D, Cesana G, Kuulasmaa K, Virtamo J, Yarnell JW, Kuh D, Wong A, Lind L, de FU, Gigante B, Magnusson PK, Pedersen NL, Dedoussis G, Dimitriou M, Kolovou G, Kanoni S, Stirrups K, Bonnycastle LL, Njolstad I, Wilsgaard T, Ganna A, Rehnberg E, Hingorani A, Kivimaki M, Kumari M, Assimes TL, Barroso I, Boehnke M, Borecki IB, Deloukas P, Fox CS, Frayling T, Groop LC, Haritunians T, Hunter D, Ingelsson E, Kaplan R, Mohlke KL, O'Connell JR, Schlessinger D, Strachan DP, Stefansson K. Sex-stratified genome-wide association studies including 270,000 individuals show sexual dimorphism in genetic loci for anthropometric traits. *PLoS Genet* 2013;**9**(6):e1003500.

40. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, Smith AV, Tobin MD, Verwoert GC, Hwang SJ, Pihur V, Vollenweider P, O'Reilly PF, Amin N, Bragg-Gresham JL, Teumer A, Glazer NL, Launer L, Zhao JH, Aulchenko Y, Heath S, Sober S, Parsa A, Luan J, Arora P, Dehghan A, Zhang F, Lucas G, Hicks AA, Jackson AU, Peden JF, Tanaka T, Wild SH, Rudan I, Igl W, Milaneschi Y, Parker AN, Fava C, Chambers JC, Fox ER, Kumari M, Go MJ, van der Harst P, Kao WH, Sjogren M, Vinay DG, Alexander M, Tabara Y, Shaw-Hawkins S, Whincup PH, Liu Y, Shi G, Kuusisto J, Tayo B, Seielstad M, Sim X, Nguyen KD, Lehtimaki T, Matullo G, Wu Y, Gaunt TR, Onland-Moret NC, Cooper MN, Platou CG, Org E, Hardy R, Dahgam S, Palmen J, Vitart V, Braund PS, Kuznetsova T, Uiterwaal CS, Adeyemo A, Palmas W, Campbell H, Ludwig B,

Tomaszewski M, Tzoulaki I, Palmer ND, Aspelund T, Garcia M, Chang YP, O'Connell JR, Steinle NI, Grobbee DE, Arking DE, Kardia SL, Morrison AC, Hernandez D, Najjar S, McArdle WL, Hadley D, Brown MJ, Connell JM, Hingorani AD, Day IN, Lawlor DA, Beilby JP, Lawrence RW, Clarke R, Hopewell JC, Ongen H, Dreisbach AW, Li Y, Young JH, Bis JC, Kahonen M, Viikari J, Adair LS, Lee NR, Chen MH, Olden M, Pattaro C, Bolton JA, Kottgen A, Bergmann S, Mooser V, Chaturvedi N, Frayling TM, Islam M, Jafar TH, Erdmann J, Kulkarni SR, Bornstein SR, Grassler J, Groop L, Voight BF, Kettunen J, Howard P, Taylor A, Guarrera S, Ricceri F, Emilsson V, Plump A, Barroso I, Khaw KT, Weder AB, Hunt SC, Sun YV, Bergman RN, Collins FS, Bonnycastle LL, Scott LJ, Stringham HM, Peltonen L, Perola M, Vartiainen E, Brand SM, Staessen JA, Wang TJ, Burton PR, Soler AM, Dong Y, Snieder H, Wang X, Zhu H, Lohman KK, Rudock ME, Heckbert SR, Smith NL, Wiggins KL, Doumatey A, Shriner D, Veldre G, Viigimaa M, Kinra S, Prabhakaran D, Tripathy V, Langefeld CD, Rosengren A, Thelle DS, Corsi AM, Singleton A, Forrester T, Hilton G, McKenzie CA, Salako T, Iwai N, Kita Y, Ogihara T, Ohkubo T, Okamura T, Ueshima H, Umemura S, Eyheramendy S, Meitinger T, Wichmann HE, Cho YS, Kim HL, Lee JY, Scott J, Sehmi JS, Zhang W, Hedblad B, Nilsson P, Smith GD, Wong A, Narisu N, Stancakova A, Raffel LJ, Yao J, Kathiresan S, O'Donnell CJ, Schwartz SM, Ikram MA, Longstreth WT, Jr., Mosley TH, Seshadri S, Shrine NR, Wain LV, Morken MA, Swift AJ, Laitinen J, Prokopenko I, Zitting P, Cooper JA, Humphries SE, Danesh J, Rasheed A, Goel A, Hamsten A, Watkins H, Bakker SJ, van Gilst WH, Janipalli CS, Mani KR, Yajnik CS, Hofman A, Mattace-Raso FU, Oostra BA, Demirkan A, Isaacs A, Rivadeneira F, Lakatta EG, Orru M, Scuteri A, Ala-Korpela M, Kangas AJ, Lyytikainen LP, Soininen P, Tukiainen T, Wurtz P, Ong RT, Dorr M, Kroemer HK, Volker U, Volzke H, Galan P, Hercberg S, Lathrop M, Zelenika D, Deloukas P, Mangino M, Spector TD, Zhai G. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* 2011;**478**(7367):103-109.

41. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Muller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Doring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Muller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de FU, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R,

578 Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR,
579 Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa
580 M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH,
581 Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW,
582 Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P. Discovery and refinement
583 of loci associated with lipid levels. *Nat Genet* 2013;**45**(11):1274-1283.

584 42. Dehghan A, Dupuis J, Barbalic M, Bis JC, Eiriksdottir G, Lu C, Pellikka N, Wallaschofski H,
585 Kettunen J, Henneman P, Baumert J, Strachan DP, Fuchsberger C, Vitart V, Wilson JF, Pare G,
586 Naitza S, Rudock ME, Surakka I, de Geus EJ, Alizadeh BZ, Guralnik J, Shuldiner A, Tanaka T, Zee
587 RY, Schnabel RB, Nambi V, Kavousi M, Ripatti S, Nauck M, Smith NL, Smith AV, Sundvall J,
588 Scheet P, Liu Y, Ruokonen A, Rose LM, Larson MG, Hoogeveen RC, Freimer NB, Teumer A,
589 Tracy RP, Launer LJ, Buring JE, Yamamoto JF, Folsom AR, Sijbrands EJ, Pankow J, Elliott P,
590 Keaney JF, Sun W, Sarin AP, Fontes JD, Badola S, Astor BC, Hofman A, Pouta A, Werdan K,
591 Greiser KH, Kuss O, Meyer zu Schwabedissen HE, Thiery J, Jamshidi Y, Nolte IM, Soranzo N,
592 Spector TD, Volzke H, Parker AN, Aspelund T, Bates D, Young L, Tsui K, Siscovick DS, Guo X,
593 Rotter JI, Uda M, Schlessinger D, Rudan I, Hicks AA, Penninx BW, Thorand B, Gieger C, Coresh J,
594 Willemsen G, Harris TB, Uitterlinden AG, Jarvelin MR, Rice K, Radke D, Salomaa V, Willems van
595 DK, Boerwinkle E, Vasan RS, Ferrucci L, Gibson QD, Bandinelli S, Snieder H, Boomsma DI, Xiao
596 X, Campbell H, Hayward C, Pramstaller PP, van Duijn CM, Peltonen L, Psaty BM, Gudnason V,
597 Ridker PM, Homuth G, Koenig W, Ballantyne CM, Witteman JC, Benjamin EJ, Perola M,
598 Chasman DI. Meta-analysis of genome-wide association studies in >80 000 subjects identifies
599 multiple loci for C-reactive protein levels. *Circulation* 2011;**123**(7):731-738.

600 43. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL,
601 Bouatia-Naji N, Gloyn AL, Lindgren CM, Magi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin
602 D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin
603 CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparso T, Doney A,
604 Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proenca C, Kumari M, Qi L,
605 Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P, O'Connell J, Luan J, Elliott A,
606 McCarroll SA, Payne F, Roccasecca RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B,
607 Barter P, Beilby JP, Ben-Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M,
608 Boerwinkle E, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Bottcher Y, Brunner E,
609 Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M,
610 Crawford G, Crisponi L, Day IN, de Geus EJ, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-
611 Rosinsky A, Forouhi NG, Fox CS, Frants R, Franzosi MG, Galan P, Goodarzi MO, Graessler J,
612 Groves CJ, Grundy S, Gwilliam R, Gyllensten U, Hadjadj S, Hallmans G, Hammond N, Han X,
613 Hartikainen AL, Hassanali N, Hayward C, Heath SC, Hercberg S, Herder C, Hicks AA, Hillman DR,
614 Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jorgensen T, Jula A, Kaakinen M,
615 Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM,
616 Lawlor DA, Le BO, Lecoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martinez-
617 Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell
618 BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orru M, Pakyz R,
619 Palmer CN, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Perola M, Pfeiffer AF,
620 Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W,
621 Rayner NW, Rice K, Ripatti S, Rivadeneira F, Roden M, Rolandsson O, Sandbaek A, Sandhu M,
622 Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurethsson G, Sijbrands
623 EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvanen AC, Tanaka
624 T, Thorand B, Tichet J, Tonjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van HM, Varma D,
625 Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL,
626 Watkins H, Weedon MN, Wild SH, Willemsen G, Witteman JC, Yarnell JW, Zeggini E, Zelenika D,
627 Zethelius B, Zhai G, Zhao JH, Zillikens MC, Borecki IB, Loos RJ, Meneton P, Magnusson PK,

628 Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR,
629 Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Rios M, Morris
630 AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WH, Pankow JS, Sampson
631 MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP. New genetic loci implicated in
632 fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet*
633 2010;**42**(2):105-116.

634 44. Pattaro C, Kottgen A, Teumer A, Garnaas M, Boger CA, Fuchsberger C, Olden M, Chen MH, Tin
635 A, Taliun D, Li M, Gao X, Gorski M, Yang Q, Hundertmark C, Foster MC, O'Seaghdha CM, Glazer
636 N, Isaacs A, Liu CT, Smith AV, O'Connell JR, Struchalin M, Tanaka T, Li G, Johnson AD, Gierman
637 HJ, Feitosa M, Hwang SJ, Atkinson EJ, Lohman K, Cornelis MC, Johansson A, Tonjes A, Dehghan
638 A, Chouraki V, Holliday EG, Sorice R, Kutalik Z, Lehtimaki T, Esko T, Deshmukh H, Ulivi S, Chu
639 AY, Murgia F, Trompet S, Imboden M, Kollerits B, Pistis G, Harris TB, Launer LJ, Aspelund T,
640 Eiriksdottir G, Mitchell BD, Boerwinkle E, Schmidt H, Cavalieri M, Rao M, Hu FB, Demirkan A,
641 Oostra BA, de AM, Turner ST, Ding J, Andrews JS, Freedman BI, Koenig W, Illig T, Doring A,
642 Wichmann HE, Kolcic I, Zemunik T, Boban M, Minelli C, Wheeler HE, Igl W, Zaboli G, Wild SH,
643 Wright AF, Campbell H, Ellinghaus D, Nothlings U, Jacobs G, Biffar R, Endlich K, Ernst F, Homuth
644 G, Kroemer HK, Nauck M, Stracke S, Volker U, Volzke H, Kovacs P, Stumvoll M, Magi R, Hofman
645 A, Uitterlinden AG, Rivadeneira F, Aulchenko YS, Polasek O, Hastie N, Vitart V, Helmer C, Wang
646 JJ, Ruggiero D, Bergmann S, Kahonen M, Viikari J, Nikopensius T, Province M, Ketkar S, Colhoun
647 H, Doney A, Robino A, Giulianini F, Kramer BK, Portas L, Ford I, Buckley BM, Adam M, Thun GA,
648 Paulweber B, Haun M, Sala C, Metzger M, Mitchell P, Ciullo M, Kim SK, Vollenweider P,
649 Raitakari O, Metspalu A, Palmer C, Gasparini P, Pirastu M, Jukema JW, Probst-Hensch NM,
650 Kronenberg F, Toniolo D, Gudnason V, Shuldiner AR, Coresh J, Schmidt R, Ferrucci L, Siscovick
651 DS, van Duijn CM, Borecki I, Kardia SL, Liu Y, Curhan GC, Rudan I, Gyllensten U, Wilson JF,
652 Franke A, Pramstaller PP, Rettig R, Prokopenko I, Witteman JC, Hayward C, Ridker P, Parsa A,
653 Bochud M, Heid IM, Goessling W, Chasman DI, Kao WH, Fox CS. Genome-wide association and
654 functional follow-up reveals new loci for kidney function. *PLoS Genet* 2012;**8**(3):e1002584.
655
656

AUTHOR CONTRIBUTIONS:

FIGURE LEGENDS

Figure 1: Summary of study design

Figure 2 Mean per allele differences in Lp-PLA_2 activity and cardiovascular risk factor levels by Lp-PLA_2 lowering alleles or with darapladib 160mg daily

Figure 3: Association of Lp-PLA_2 lowering alleles with Lp-PLA_2 activity and CHD risk

APPENDIX

List of authors and affiliations

John M. Gregson* PhD, Daniel F. Freitag* PhD, Praveen Surendran PhD, Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Nathan O. Stitziel MD PhD, Departments of Medicine and Genetics, Washington University School of Medicine, St Louis, Missouri 63110, USA; Rajiv Chowdhury MD, Stephen Burgess PhD, Stephen Kaptoge PhD, Pei Gao PhD, James R. Staley MSc, Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Peter Willeit MD, PhD, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK and Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; Sune F. Nielsen PhD, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark; Muriel Caslake PhD, University of Glasgow, Glasgow, UK; Stella Trompet PhD, Leiden University Medical Center, Leiden, Netherlands; Linda M. Polfus PhD, University of Texas Health Science Center Houston, TX, USA; Kari Kuulasmaa PhD, Jukka Kontto MSSc, THL-National Institute for Health and Welfare, Helsinki, Finland; Markus Perola MD, PhD, Institute of Molecular Medicine FIMM, University of Helsinki and Department of Health, National Institute for Health and Welfare, Helsinki, Finland; Stefan Blankenberg MD, Department of General and Interventional Cardiology, University Heart Center Hamburg, Germany and University Medical Center Hamburg Eppendorf, Hamburg, Germany; Giovanni Veronesi PhD, EPIMED Research Center, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy; Francesco Gianfagna MD, PhD, EPIMED Research Center, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy and Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy; Satu Männistö, THL-National Institute for Health and Welfare, Helsinki, Finland; Akinori Kimura MD, PhD, Department of Molecular Pathogenesis, Medical Research Institute, Tokyo Medical and Dental University (TMDU), Tokyo, Japan; Honghuang Lin PhD, Section of Computational Biomedicine, Department of Medicine, Boston University School of Medicine, Boston, MA, USA and The NHLBI's Framingham Heart Study, Framingham, MA, USA; Dermot F.Reilly PhD, Merck Research Laboratories, Genetics and Pharmacogenomics, Boston, Massachusetts, USA; Mathias Gorski, Department of Genetic Epidemiology, University of Regensburg, Regensburg, Germany and Department of Nephrology, University Hospital Regensburg, Regensburg, Germany; Vladan Mijatovic on behalf of the CKDGen

consortium, Department of Life and Reproduction Sciences, University of Verona, Verona, Italy; Patricia B. Munroe PhD, Clinical Pharmacology and The Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK and NIHR Barts Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, UK; Georg B. Ehret MD on behalf of the International Consortium for Blood Pressure;, Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA and Cardiology, Department of Medicine, Geneva University Hospital, Geneva, Switzerland and Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland Alex Thompson PhD, Strategic Epidemiology NewMedicines, UCB, Brussels, Belgium; Maria Uria-Nickelsen PhD, Clinical Research, Pfizer Worldwide R&D, Cambridge, Massachusetts, USA; Anders Malarstig PhD, Clinical Research, Pfizer Worldwide R&D, Sollentuna, Sweden; Abbas Dehghan MD PhD on behalf of the CHARGE inflammation working group, Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands; Thomas F. Vogt PhD, Merck Research Laboratories, Cardiometabolic Disease, Kenilworth, New Jersey, USA and CHDI Management/CHDI Foundation, Princeton, New Jersey, USA; Taishi Sasaoka MD, PhD, Department of Molecular Pathogenesis, Medical Research Institute, Tokyo Meidcal and Dental University (TMDU), Tokyo, Japan; Fumihiko Takeuchi PhD, Norihiro Kato MD, DPhil, Department of Gene Diagnostics and Therapeutics, Research Institute, National Center for Global Health and Medicine, Japan; Yoshiji Yamada MD, PhD, Department of Human Functional Genomics, Life Science Research Center, Mie University, Japan; Frank Kee MD, Director, UKCRC Centre of Excellence for Public Health, Queens, University, Belfast, Ireland; Martina Müller-Nurasyid PhD, Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany and Institute of Medical Informatics, Biometry and Epidemiology, Chair of Genetic Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany and DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany and Department of Medicine I, Ludwig-Maximilians-University Munich, Munich, Germany; Jean Ferrières MD, Department of Epidemiology, UMR 1027- INSERM, Toulouse University-CHU Toulouse, Toulouse, France; Dominique Arveiler MD, Department of Epidemiology and Public Health, EA 3430, University of Strasbourg and Strasbourg University Hospital, Strasbourg, France; Philippe Amouyel MD, Department of Epidemiology and Public Health,Institut Pasteur de Lille, Lille, France; Veikko Salomaa MD, PhD, THL-National Institute for Health and Welfare, Helsinki,

Finland; Eric Boerwinkle PhD, Human Genetics Center, University of Texas Health Science Center at Houston, TX, USA; Simon G. Thompson FMedSci, Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Ian Ford PhD, University of Glasgow, Glasgow, UK; J. Wouter Jukema MD, Leiden University Medical Center, Leiden, Netherlands; Naveed Sattar MD, Chris J. Packard PhD, University of Glasgow, Glasgow, UK; Abdulla al Shafi Majumder MD, National Institute of Cardiovascular Diseases, Sher-e-Bangla Nagar, Dhaka, Bangladesh; Dewan S Alam MD, PhD, Centre for Global Health Research, St. Michael Hospital, Toronto, ON, Canada; Panos Deloukas PhD, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; Heribert Schunkert MD, Deutsches Herzzentrum München, Technische Universität München, and German Centre for Cardiovascular Research (DZHK), partner site Munich Heart Alliance, all Munich, Germany; Nilesh J. Samani FMedSci, Department of Cardiovascular Sciences, University of Leicester and National Institute for Health Research Leicester Cardiovascular Biomedical Research Unit, Leicester, UK; Sekar Kathiresan MD on behalf of the MICAD Exome consortium, Broad Institute, Cambridge and Massachusetts General Hospital, Boston, MA, USA; Børge G. Nordestgaard MD, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark; Danish Saleheen* MD, University of Pennsylvania, Philadelphia, US and Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Joanna M.M. Howson* PhD, Emanuele Di Angelantonio* MD, Adam S. Butterworth* PhD, Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; John Danesh* FMedSci on behalf of the EPIC-CVD Consortium and the CHD Exome+ Consortium, Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK and Wellcome Trust Sanger Institute, Hinxton, UK

TABLES

Table 1: Definitions and source of contributing data for the main study outcome

Lp-PLA$_2$ assessment tool	**Val279Phe, Loss-of-function variant common in East Asians‡**	**Four loss-of-function variants*, rare in Europeans & South Asians†**		**Val379Ala, modest impact variant**				**Darapladib**
Data sources	Systematic review: Study-level data from up to 12 East Asian studies	De-novo genotyping and participant-level data: up to 8 European or or South Asian ancestry studies from the CHD Exome+ Consortium[18-25]; De-novo genotyping and study-level data: up to 15 European ancestry studies from the MICAD Exome consortium[37] and 3 European ancestry studies from the CHARGE Consortium[16, 28]; Plus publicly available consortium data						Systematic review: Study-level data from up to 5 randomized clinical trials[5, 6, 38-40] from a systematic review
Endpoint	**Number of studies and unique individuals contributing to analyses; n total *or* cases / controls**							
Coronary heart disease^	7 East Asian studies	8 European or South Asian ancestry studies from the CHD Exome+ Consortium[18-25]	15 European ancestry studies from the MICAD Exome consortium[37]	8 European or South Asian ancestry studies from the CHD Exome+ Consortium[18-25]	8 European ancestry studies from the MICAD Exome consortium[37]	14 European ancestry studies from the CARDIoGRAM consortium[26]	4 European or South Asian ancestry studies from the C4D consortium[27]	2 phase III randomized clinical trials of darapladib[5, 6]
	10,088 cases 15,199 controls	35,829 cases 44,948 controls	35,533 cases 64,130 controls	32,196 cases 41,464 controls	14,976 cases 32,084 controls	20,315 cases 58,419 controls	15,420 cases 15,062 controls	3364 cases 25,490 non-cases
Lp-PLA$_2$ activity$	12 East Asian studies	1 European ancestry study from the CHD Exome+ Consortium[24]	1 European ancestry study from the CHARGE Consortium[28]	2 European ancestry studies from the CHD Exome+ Consortium[21, 22, 24]		3 European ancestry studies from the CHARGE consortium[16]		3 phase II randomized clinical trials[38-40]
	8468	1240	8564	2173		11,662		854
Conventional risk factors$	12 East Asian studies	8 European or South Asian ancestry studies from the CHD Exome+ Consortium[18-25]		8 European or South Asian ancestry studies from the CHD Exome+ Consortium[18-25]		Publicly available consortium data		5 randomized clinical trials[5, 6, 38-40]
BMI	17,898	76,584		51,201		126,142 from 46 studies from the GIANT Consortium[41]		NA
Blood pressure	6705	72,450		71,256		69,245 from 29 studies from the ICBP Consortium[42]		323
Lipids	17,643	76,826		55,431		94,311 from 46 studies from the GLGC Consortium[43]		803
C-reactive protein	2914	40,484		41,442		66,185 from 15 studies from the CHARGE Consortium[44]		848
Glycaemic traits	2914	9420		9408		46,186 from 21 studies from the MAGIC Consortium[45]		NA
eGFR	4017	32,929		32,190		74,354 from 26 studies from the CKDGen Consortium[46]		NA

^ In genetic analysis, CHD was defined as myocardial infarction and other major coronary events (~90% of cases) or angiographic stenosis only (~10% of cases) see eTables 2 & 3 for details. In the darapladib analysis CHD was defined as fatal coronary disease, non-fatal MI or urgent revascularization for myocardial ischaemia.

$ See eTables 2 & 3 for details on risk factor measurements

rs142974898 (c.109+2T>C), rs144983904 (Arg82His), rs76863441 (Val279Phe), rs140020965 (Gln287Ter); see also **Figure 1B** for further variant details; BMI = Body-mass index, eGFR = estimated glomerular filtration rate, NA= Data not available. Further detail on the individual studies is provided in **eTables 2-3.**

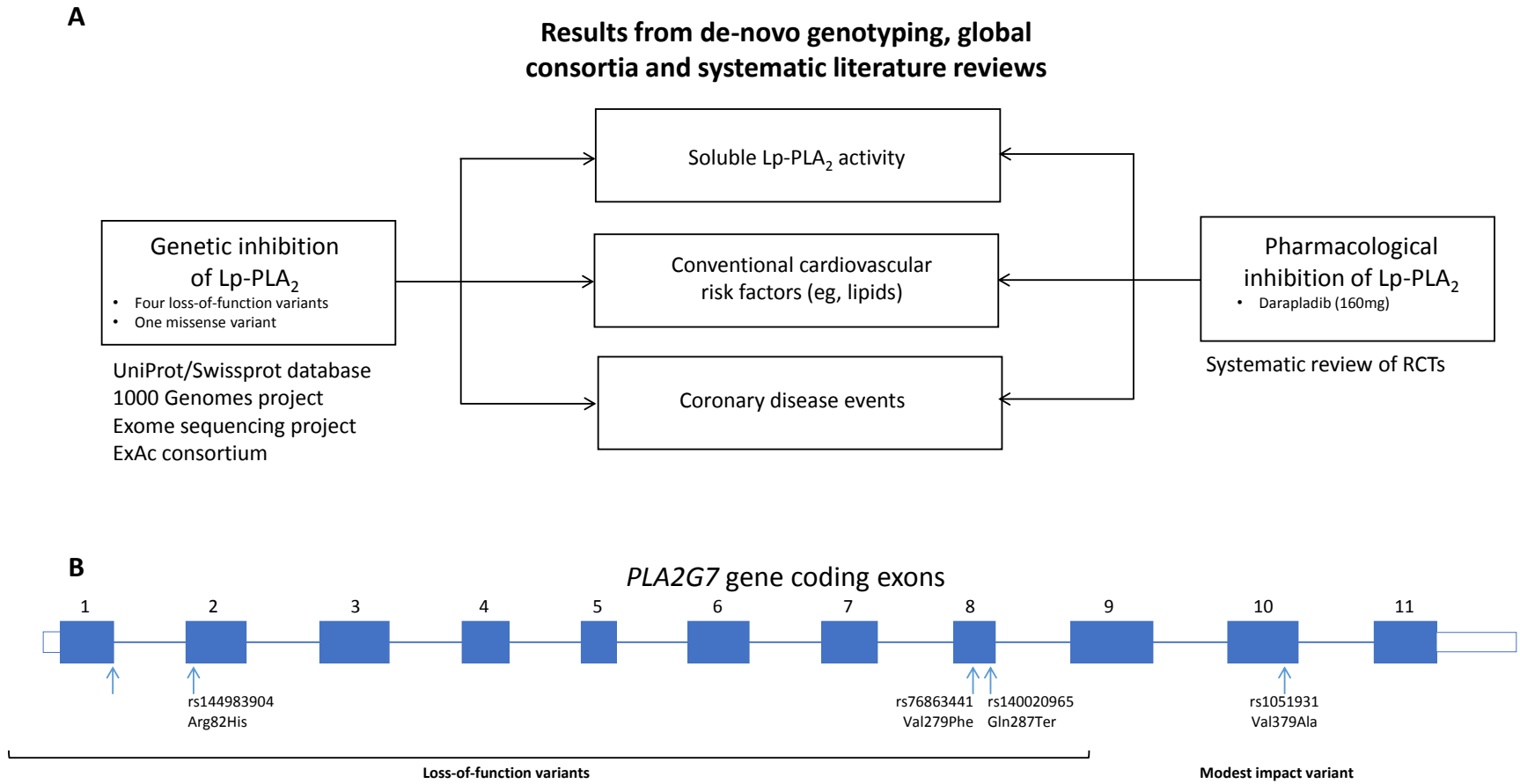
CARDIoGRAM=Coronary ARtery DIsease Genome wide Replication and Meta-analysi; CHARGE=Cohorts for Heart and Aging Research in Genomic Epidemiology; CKDGen=Chronic Kidney Disease GENetics consortium; GIANT=Genetic Investigation of ANthropometric Traits Consortium; GLCC=**Global Lipids Genetics Consortium;** ICBP=International Consortium for Blood Pressure; MAGIC=Meta-Analyses of Glucose and Insulin-related traits **Consortium;**

Table 2: Comparison on a common scale of human genetic and randomized trial evidence for Lp-PLA_2 lowering and CHD

	CHD patients	Controls	Risk ratio for CHD per 65% lower Lp-PLA_2 activity (95% CI)
Genetically lowered Lp-PLA_2			
Val279Phe (East Asian LoF variant)	10,088	15,199	0.95 (0.88 - 1.03)
Four LoF variants*	71,362	109,078	0.92 (0.74 – 1.16)
Val379Ala	82,907	147,029	1.01 (0.68 – 1.51)
Pharmacologically lowered Lp-PLA_2			
Darapladib	3364	25,490	0.95 (0.89 – 1.02)

* Carriage of any of the four loss-of-function variants c.109+2T>C, Arg82His; Val279Phe; Gln287Ter; LoF = Loss-of-function

761 **Figure 1**: Summary of study design

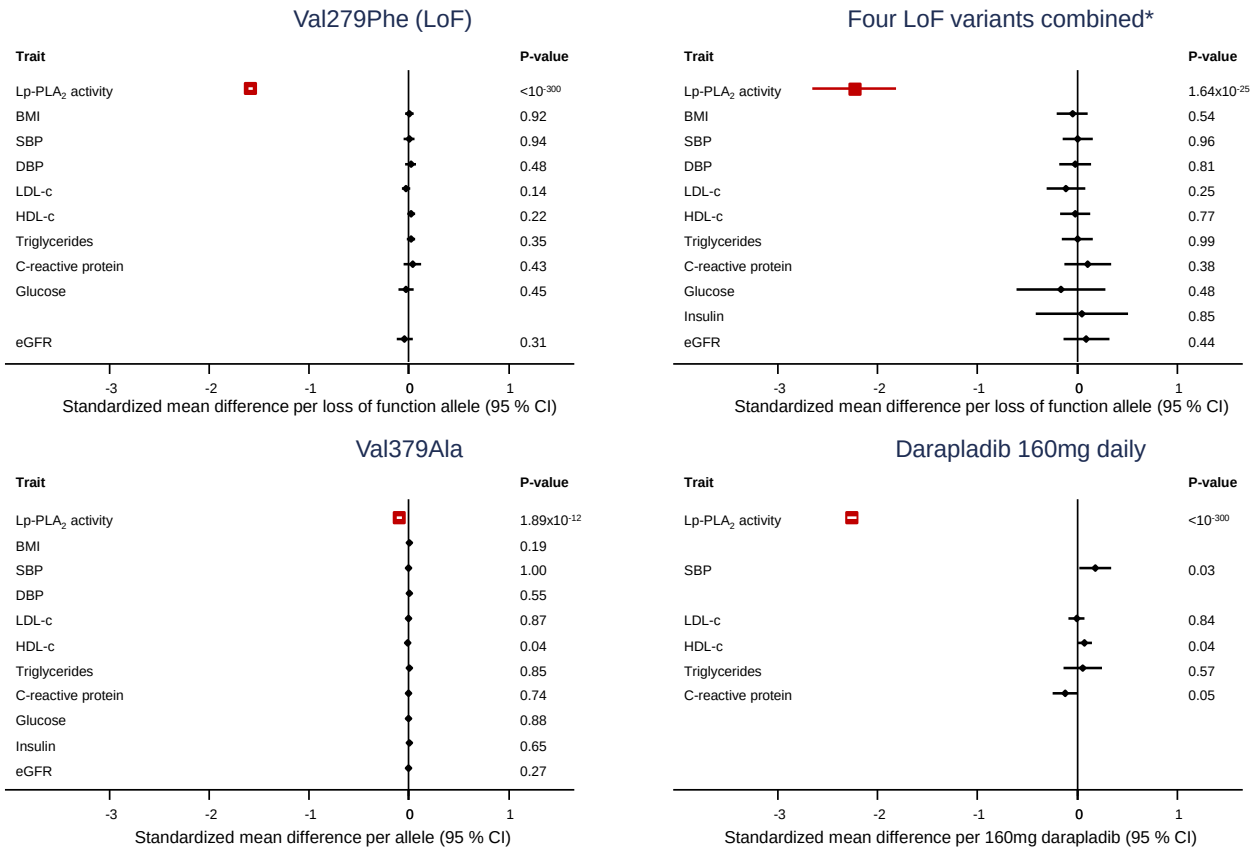


762

763 A) Flow chart of study design B) Exonic structure of the *PLA2G7* gene and location of variants used in this study.; ExAc = Exome Aggregation consortium, Lp-PLA$_2$ = Lipoprotein-associated phospholipase A$_2$, RCT =

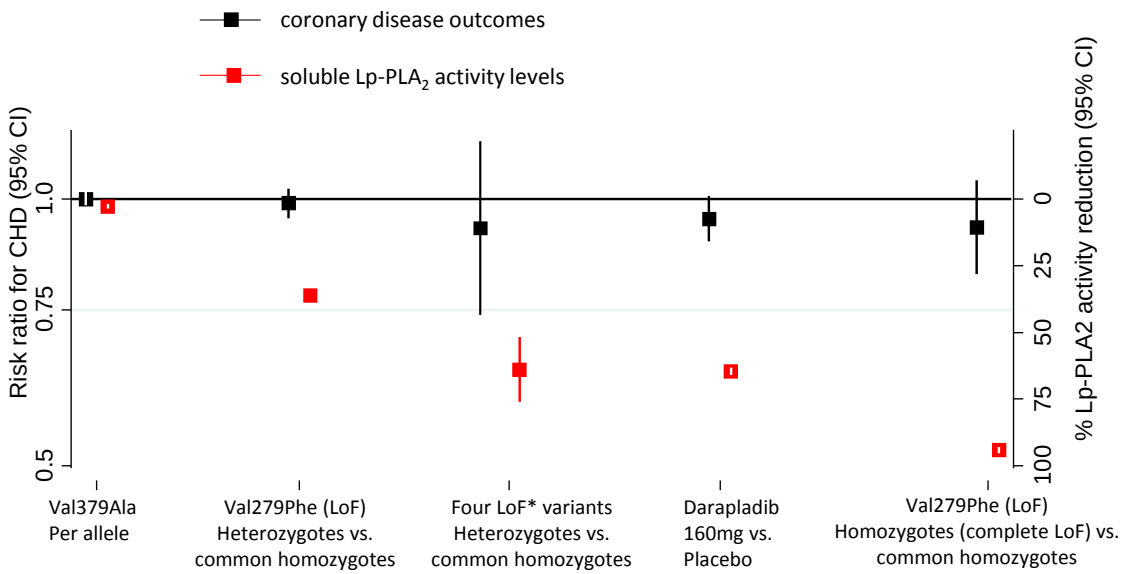
764 Randomized controlled trial, UniProt/Swissprot = Manually annotated and reviewed section of the Universal Protein resource database.

Figure 2



To enable comparison of the magnitude of associations across several different markers, analyses were undertaken with standardized units of measurement for each marker. Associations are presented as per allele change in the biomarker expressed as standard deviations. * Carriage of any of the four loss-of-function variants c.109+2T>C, Arg82His; Val279Phe; Gln287Ter; BMI = Body-mass index, DBP = Diastolic blood pressure, eGFR = estimated glomerular filtration rate, HDL-c = High-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, LoF = Loss-of-function, Lp-PLA_2 = Lipoprotein associated phospholipase A_2, SBP = systolic blood pressure. Numbers of participants are provided in **Table 1**. Details of contributing studies are provided in **eTables 2-3**.

Figure 3



Analysis of coronary heart disease outcomes	Cases	82,907	8789†	71,362	3364	6983†
	Controls	147,029	13,190†	109,078	25,490	10,206†
Analysis of soluble Lp-PLA$_2$ activity	Participants	13,835	8264	9804	854	5997

Spectrum of functional alleles in *PLA2G7* and effects on Lp-PLA2 activity (red estimates) and coronary heart disease risk (black estimates); * Carriage of any of the four loss-of-function variants c.109+2T>C, Arg82His; Val279Phe; Gln287Ter; † One study did not provide tabular data to enable calculation of CHD odds ratios in heterozygotes or homozygotes. Hence, numbers are less than those presented for the per allele analysis in **Table 2**; LoF = Loss-of-function

Reference List

1. Corson MA. Darapladib: an emerging therapy for atherosclerosis. Ther Adv Cardiovasc Dis 2010;**4**(4):241-248.
2. Thompson A, Gao P, Orfei L, Watson S, Di AE, Kaptoge S, Ballantyne C, Cannon CP, Criqui M, Cushman M, Hofman A, Packard C, Thompson SG, Collins R, Danesh J. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet 2010;**375**(9725):1536-1544.
3. Jang Y, Waterworth D, Lee JE, Song K, Kim S, Kim HS, Park KW, Cho HJ, Oh IY, Park JE, Lee BS, Ku HJ, Shin DJ, Lee JH, Jee SH, Han BG, Jang HY, Cho EY, Vallance P, Whittaker J, Cardon L, Mooser V. Carriage of the V279F null allele within the gene encoding Lp-PLA(2) is protective from coronary artery disease in South Korean males. PLoS One 2011;**6**(4):e18208.
4. Yamada Y, Yoshida H, Ichihara S, Imaizumi T, Satoh K, Yokota M. Correlations between plasma platelet-activating factor acetylhydrolase (PAF-AH) activity and PAF-AH genotype, age, and atherosclerosis in a Japanese population. Atherosclerosis 2000;**150**(1):209-216.
5. O'Donoghue ML, Braunwald E, White HD, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP, Steen DL. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. JAMA 2014;**312**(10):1006-1015.
6. White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF, Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, Lopez-Sendon J, Manolis AJ, Mohler ER, III, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D, Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J, Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart disease. N Engl J Med 2014;**370**(18):1702-1711.
7. UniProt: a hub for protein information. Nucleic Acids Res 2014.
8. Lek M, Karczewski K, Minikel E, Samocha K, Banks E, Fennell T, O'Donnell-Luria A, Ware J, Hill A, Cummings B, Tukiainen T, Birnbaum D, Kosmicki J, Duncan L, Estrada K, Zhao F, Zou J, Pierce-Hoffman E, Cooper D, DePristo M, Do R, Flannick J, Fromer M, Gauthier L, Goldstein J, Gupta N, Howrigan D, Kiezun A, Kurki M, Levy Moonshine A, Natarajan P, Orozco L, Peloso G, Poplin R, Rivas M, Ruano-Rubio V, Ruderfer D, Shakir K, Stenson P, Stevens C, Thomas B, Tiao G, Tusie-Luna M, Weisburd B, Won H-H, Yu D, Altshuler D, Ardissino D, Boehnke M, Danesh J, Roberto E, Florez J, Gabriel S, Getz G, Hultman C, Kathiresan S, Laakso M, McCarroll S, McCarthy M, McGovern D, McPherson R, Neale B, Palotie A, Purcell S, Saleheen D, Scharf J, Sklar P, Patrick S, Tuomilehto J, Watkins H, Wilson J, Daly M, MacArthur D. Analysis of protein-coding genetic variation in 60,706 humans. bioRxiv 2015.
9. Kruse S, Mao XQ, Heinzmann A, Blattmann S, Roberts MH, Braun S, Gao PS, Forster J, Kuehr J, Hopkin JM, Shirakawa T, Deichmann KA. The Ile198Thr and Ala379Val variants of plasmatic PAF-acetylhydrolase impair catalytical activities and are associated with atopy and asthma. Am J Hum Genet 2000;**66**(5):1522-1530.
10. Tjoelker LW, Eberhardt C, Unger J, Trong HL, Zimmerman GA, McIntyre TM, Stafforini DM, Prescott SM, Gray PW. Plasma platelet-activating factor acetylhydrolase is a secreted phospholipase A2 with a catalytic triad. J Biol Chem 1995;**270**(43):25481-25487.
11. Yamada Y, Yokota M. Loss of activity of plasma platelet-activating factor acetylhydrolase due to a novel Gln281-->Arg mutation. Biochem Biophys Res Commun 1997;**236**(3):772-775.

12. Song K, Nelson MR, Aponte J, Manas ES, Bacanu SA, Yuan X, Kong X, Cardon L, Mooser VE, Whittaker JC, Waterworth DM. Sequencing of Lp-PLA2-encoding PLA2G7 gene in 2000 Europeans reveals several rare loss-of-function mutations. Pharmacogenomics J 2012;**12**(5):425-431.
13. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;**491**(7422):56-65.
14. Tennessen JA, Bigham AW, O'Connor TD, Fu W, Kenny EE, Gravel S, McGee S, Do R, Liu X, Jun G, Kang HM, Jordan D, Leal SM, Gabriel S, Rieder MJ, Abecasis G, Altshuler D, Nickerson DA, Boerwinkle E, Sunyaev S, Bustamante CD, Bamshad MJ, Akey JM. Evolution and functional impact of rare coding variation from deep sequencing of human exomes. Science 2012;**337**(6090):64-69.
15. Stafforini DM, Satoh K, Atkinson DL, Tjoelker LW, Eberhardt C, Yoshida H, Imaizumi T, Takamatsu S, Zimmerman GA, McIntyre TM, Gray PW, Prescott SM. Platelet-activating factor acetylhydrolase deficiency. A missense mutation near the active site of an anti-inflammatory phospholipase. J Clin Invest 1996;**97**(12):2784-2791.
16. Grallert H, Dupuis J, Bis JC, Dehghan A, Barbalic M, Baumert J, Lu C, Smith NL, Uitterlinden AG, Roberts R, Khuseyinova N, Schnabel RB, Rice KM, Rivadeneira F, Hoogeveen RC, Fontes JD, Meisinger C, Keaney JF, Jr., Lemaitre R, Aulchenko YS, Vasan RS, Ellis S, Hazen SL, van Duijn CM, Nelson JJ, Marz W, Schunkert H, McPherson RM, Stirnadel-Farrant HA, Psaty BM, Gieger C, Siscovick D, Hofman A, Illig T, Cushman M, Yamamoto JF, Rotter JI, Larson MG, Stewart AF, Boerwinkle E, Witteman JC, Tracy RP, Koenig W, Benjamin EJ, Ballantyne CM. Eight genetic loci associated with variation in lipoprotein-associated phospholipase A2 mass and activity and coronary heart disease: meta-analysis of genome-wide association studies from five community-based studies. Eur Heart J 2012;**33**(2):238-251.
17. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjonnes A, Chasman DI, Chen S, Ford I, Franceschini N, Gieger C, Grace C, Gustafsson S, Huang J, Hwang SJ, Kim YK, Kleber ME, Lau KW, Lu X, Lu Y, Lyytikainen LP, Mihailov E, Morrison AC, Pervjakova N, Qu L, Rose LM, Salfati E, Saxena R, Scholz M, Smith AV, Tikkanen E, Uitterlinden A, Yang X, Zhang W, Zhao W, de Andrade M, de Vries PS, van Zuydam NR, Anand SS, Bertram L, Beutner F, Dedoussis G, Frossard P, Gauguier D, Goodall AH, Gottesman O, Haber M, Han BG, Huang J, Jalilzadeh S, Kessler T, Konig IR, Lannfelt L, Lieb W, Lind L, Lindgren CM, Lokki ML, Magnusson PK, Mallick NH, Mehra N, Meitinger T, Memon FU, Morris AP, Nieminen MS, Pedersen NL, Peters A, Rallidis LS, Rasheed A, Samuel M, Shah SH, Sinisalo J, Stirrups KE, Trompet S, Wang L, Zaman KS, Ardissino D, Boerwinkle E, Borecki IB, Bottinger EP, Buring JE, Chambers JC, Collins R, Cupples LA, Danesh J, Demuth I, Elosua R, Epstein SE, Esko T, Feitosa MF, Franco OH, Franzosi MG, Granger CB, Gu D, Gudnason V, Hall AS, Hamsten A, Harris TB, Hazen SL, Hengstenberg C, Hofman A, Ingelsson E, Iribarren C, Jukema JW, Karhunen PJ, Kim BJ, Kooner JS, Kullo IJ, Lehtimaki T, Loos RJ, Melander O, Metspalu A, Marz W, Palmer CN, Perola M, Quertermous T, Rader DJ, Ridker PM, Ripatti S, Roberts R, Salomaa V, Sanghera DK, Schwartz SM, Seedorf U, Stewart AF, Stott DJ, Thiery J, Zalloua PA, O'Donnell CJ, Reilly MP, Assimes TL, Thompson JR, Erdmann J, Clarke R, Watkins H, Kathiresan S, McPherson R, Deloukas P, Schunkert H, Samani NJ, Farrall M, Consortium CAD. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015;**47**(10):1121-30.
18. Chowdhury R, Alam DS, Fakir II, Adnan SD, Naheed A, Tasmin I, Monower MM, Hossain F, Hossain FM, Rahman MM, Afrin S, Roy AK, Akter M, Sume SA, Biswas AK, Pennells L, Surendran P, Young RD, Spackman SA, Hasan K, Harshfield E, Sheikh N, Houghton R, Saleheen D, Howson JM, Butterworth AS, Raqib R, Majumder AA, Danesh J, Di AE. The Bangladesh Risk of Acute Vascular Events (BRAVE) Study: objectives and design. Eur J Epidemiol 2015.
19. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009;**301**(22):2331-2339.
20. Danesh J, Saracci R, Berglund G, Feskens E, Overvad K, Panico S, Thompson S, Fournier A, Clavel-Chapelon F, Canonico M, Kaaks R, Linseisen J, Boeing H, Pischon T, Weikert C, Olsen A, Tjonneland A, Johnsen SP, Jensen MK, Quiros JR, Svatetz CA, Perez MJ, Larranaga N, Sanchez CN, Iribas CM, Bingham S, Khaw KT, Wareham N, Key T, Roddam A, Trichopoulou A, Benetou V, Trichopoulos D, Masala G, Sieri S, Tumino R, Sacerdote C, Mattiello A, Verschuren WM, Bueno-de-Mesquita HB, Grobbee DE, van der Schouw YT, Melander O, Hallmans G, Wennberg P, Lund E, Kumle M, Skeie G, Ferrari P, Slimani N, Norat T, Riboli E. EPIC-Heart: the

876 cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000
877 middle-aged participants from 10 European countries. Eur J Epidemiol 2007;**22**(2):129-141.
878 21. Evans A, Salomaa V, Kulathinal S, Asplund K, Cambien F, Ferrario M, Perola M, Peltonen L, Shields D,
879 Tunstall-Pedoe H, Kuulasmaa K. MORGAM (an international pooling of cardiovascular cohorts). Int J Epidemiol
880 2005;**34**(1):21-27.
881 22. Kulathinal S, Karvanen J, Saarela O, Kuulasmaa K. Case-cohort design in practice - experiences from the
882 MORGAM Project. Epidemiol Perspect Innov 2007;**4**:15.
883 23. Saleheen D, Zaidi M, Rasheed A, Ahmad U, Hakeem A, Murtaza M, Kayani W, Faruqui A, Kundi A, Zaman
884 KS, Yaqoob Z, Cheema LA, Samad A, Rasheed SZ, Mallick NH, Azhar M, Jooma R, Gardezi AR, Memon N, Ghaffar
885 A, Fazal uR, Khan N, Shah N, Ali SA, Samuel M, Hanif F, Yameen M, Naz S, Sultana A, Nazir A, Raza S, Shazad M,
886 Nasim S, Javed MA, Ali SS, Jafree M, Nisar MI, Daood MS, Hussain A, Sarwar N, Kamal A, Deloukas P, Ishaq M,
887 Frossard P, Danesh J. The Pakistan Risk of Myocardial Infarction Study: a resource for the study of genetic,
888 lifestyle and other determinants of myocardial infarction in South Asia. Eur J Epidemiol 2009;**24**(6):329-338.
889 24. Caslake MJ, Packard CJ, Robertson M, Cooney J, Nelson JJ, Ford I, Gaw A, Jukema JW, Macfarlane PW,
890 Stott DJ, Shepherd J. Lipoprotein-associated phospholipase A(2), inflammatory biomarkers, and risk of
891 cardiovascular disease in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Atherosclerosis
892 2010;**210**(1):28-34.
893 25. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ. Prevention
894 of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary
895 Prevention Study Group. N Engl J Med 1995;**333**(20):1301-1307.
896 26. Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M,
897 Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball
898 SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS,
899 Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan
900 A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NE, Ellis SG, Elosua R, Engert JC,
901 Epstein SE, de FU, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR,
902 Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA,
903 Kaplan LM, Kastelein JJ, Khaw KT, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre
904 G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger
905 T, Melander O, Merlini PA, Mooser V, Morgan T, Muhleisen TW, Muhlestein JB, Munzel T, Musunuru K,
906 Nahrstaedt J, Nelson CP, Nothen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA,
907 Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schafer A,
908 Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A,
909 Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WH, Tennstedt S, Thorgeirsson G,
910 Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE,
911 Wild PS, Willenborg C, Witteman JC, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA,
912 Quertermous T, Marz W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR,
913 Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ. Large-scale
914 association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet 2011;**43**(4):333-
915 338.
916 27. Peden JF, Hopewell JC, Saleheen D, Chambers JC, Hager J, Soranzo N, Collins R, Danesh J, Elliott P, Farrall
917 M, Stirrups K, Zhang W, Hamsten A. A genome-wide association study in Europeans and South Asians identifies
918 five new loci for coronary artery disease. Nat Genet 2011;**43**(4):339-344.
919 28. Polfus LM, Gibbs RA, Boerwinkle E. Coronary heart disease and genetic variants with low phospholipase
920 A2 activity. N Engl J Med 2015;**372**(3):295-296.
921 29. Zhou X, Stephens M. Efficient multivariate linear mixed model algorithms for genome-wide association
922 studies. Nat Methods 2014;**11**(4):407-409.
923 30. Palmer TM, Sterne JA, Harbord RM, Lawlor DA, Sheehan NA, Meng S, Granell R, Smith GD, Didelez V.
924 Instrumental variable estimation of causal risk ratios and causal odds ratios in Mendelian randomization
925 analyses. Am J Epidemiol 2011;**173**(12):1392-1403.

31. Casas JP, Ninio E, Panayiotou A, Palmen J, Cooper JA, Ricketts SL, Sofat R, Nicolaides AN, Corsetti JP, Fowkes FG, Tzoulaki I, Kumari M, Brunner EJ, Kivimaki M, Marmot MG, Hoffmann MM, Winkler K, Marz W, Ye S, Stirnadel HA, Boekholdt SM, Khaw KT, Humphries SE, Sandhu MS, Hingorani AD, Talmud PJ. PLA2G7 genotype, lipoprotein-associated phospholipase A2 activity, and coronary heart disease risk in 10 494 cases and 15 624 controls of European Ancestry. Circulation 2010;**121**(21):2284-2293.
32. Schroder M, Kaufman RJ. The mammalian unfolded protein response. Annu Rev Biochem 2005;**74**:739-789.
33. Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. Arterioscler Thromb Vasc Biol 2005;**25**(5):923-931.
34. Kamb A, Harper S, Stefansson K. Human genetics as a foundation for innovative drug development. Nat Biotechnol 2013;**31**(11):975-978.
35. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, Floratos A, Sham PC, Li MJ, Wang J, Cardon LR, Whittaker JC, Sanseau P. The support of human genetic evidence for approved drug indications. Nat Genet 2015;**47**(8):856-860.
36. Plenge RM, Scolnick EM, Altshuler D. Validating therapeutic targets through human genetics. Nat Rev Drug Discov 2013;**12**(8):581-594.
37. Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, Fontanillas P, Gupta N, Duga S, Goel A, Farrall M, Saleheen D, Ferrario P, Konig I, Asselta R, Merlini PA, Marziliano N, Notarangelo MF, Schick U, Auer P, Assimes TL, Reilly M, Wilensky R, Rader DJ, Hovingh GK, Meitinger T, Kessler T, Kastrati A, Laugwitz KL, Siscovick D, Rotter JI, Hazen SL, Tracy R, Cresci S, Spertus J, Jackson R, Schwartz SM, Natarajan P, Crosby J, Muzny D, Ballantyne C, Rich SS, O'Donnell CJ, Abecasis G, Sunyaev S, Nickerson DA, Buring JE, Ridker PM, Chasman DI, Austin E, Ye Z, Kullo IJ, Weeke PE, Shaffer CM, Bastarache LA, Denny JC, Roden DM, Palmer C, Deloukas P, Lin DY, Tang ZZ, Erdmann J, Schunkert H, Danesh J, Marrugat J, Elosua R, Ardissino D, McPherson R, Watkins H, Reiner AP, Wilson JG, Altshuler D, Gibbs RA, Lander ES, Boerwinkle E, Gabriel S, Kathiresan S. Inactivating mutations in NPC1L1 and protection from coronary heart disease. N Engl J Med 2014;**371**(22):2072-2082.
38. Daida H, Iwase T, Yagi S, Ando H, Nakajima H. Effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity in Japanese dyslipidemic patients, with exploratory analysis of a PLA2G7 gene polymorphism of Val279Phe. Circ J 2013;**77**(6):1518-1525.
39. Mohler ER, III, Ballantyne CM, Davidson MH, Hanefeld M, Ruilope LM, Johnson JL, Zalewski A. The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 2008;**51**(17):1632-1641.
40. Serruys PW, Garcia-Garcia HM, Buszman P, Erne P, Verheye S, Aschermann M, Duckers H, Bleie O, Dudek D, Botker HE, von BC, D'Amico D, Hutchinson T, Zambanini A, Mastik F, van Es GA, van der Steen AF, Vince DG, Ganz P, Hamm CW, Wijns W, Zalewski A. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. Circulation 2008;**118**(11):1172-1182.
41. Randall JC, Winkler TW, Kutalik Z, Berndt SI, Jackson AU, Monda KL, Kilpelainen TO, Esko T, Magi R, Li S, Workalemahu T, Feitosa MF, Croteau-Chonka DC, Day FR, Fall T, Ferreira T, Gustafsson S, Locke AE, Mathieson I, Scherag A, Vedantam S, Wood AR, Liang L, Steinthorsdottir V, Thorleifsson G, Dermitzakis ET, Dimas AS, Karpe F, Min JL, Nicholson G, Clegg DJ, Person T, Krohn JP, Bauer S, Buechler C, Eisinger K, Bonnefond A, Froguel P, Hottenga JJ, Prokopenko I, Waite LL, Harris TB, Smith AV, Shuldiner AR, McArdle WL, Caulfield MJ, Munroe PB, Gronberg H, Chen YD, Li G, Beckmann JS, Johnson T, Thorsteinsdottir U, Teder-Laving M, Khaw KT, Wareham NJ, Zhao JH, Amin N, Oostra BA, Kraja AT, Province MA, Cupples LA, Heard-Costa NL, Kaprio J, Ripatti S, Surakka I, Collins FS, Saramies J, Tuomilehto J, Jula A, Salomaa V, Erdmann J, Hengstenberg C, Loley C, Schunkert H, Lamina C, Wichmann HE, Albrecht E, Gieger C, Hicks AA, Johansson A, Pramstaller PP, Kathiresan S, Speliotes EK, Penninx B, Hartikainen AL, Jarvelin MR, Gyllensten U, Boomsma DI, Campbell H, Wilson JF, Chanock SJ, Farrall M, Goel A, Medina-Gomez C, Rivadeneira F, Estrada K, Uitterlinden AG, Hofman A, Zillikens MC, den HM, Kiemeney LA, Maschio A, Hall P, Tyrer J, Teumer A, Volzke H, Kovacs P, Tonjes A, Mangino M, Spector TD, Hayward C, Rudan I, Hall AS, Samani NJ, Attwood AP, Sambrook JG, Hung J, Palmer LJ, Lokki ML, Sinisalo J, Boucher G, Huikuri H, Lorentzon M, Ohlsson C, Eklund N, Eriksson JG, Barlassina C, Rivolta C, Nolte IM, Snieder H, Van der Klauw MM, Van Vliet-Ostaptchouk JV, Gejman PV, Shi J, Jacobs KB, Wang Z, Bakker SJ, Mateo LI, Navis G, van der

977 Harst P, Martin NG, Medland SE, Montgomery GW, Yang J, Chasman DI, Ridker PM, Rose LM, Lehtimaki T,
978 Raitakari O, Absher D, Iribarren C, Basart H, Hovingh KG, Hypponen E, Power C, Anderson D, Beilby JP, Hui J,
979 Jolley J, Sager H, Bornstein SR, Schwarz PE, Kristiansson K, Perola M, Lindstrom J, Swift AJ, Uusitupa M, Atalay M,
980 Lakka TA, Rauramaa R, Bolton JL, Fowkes G, Fraser RM, Price JF, Fischer K, Krjuta KK, Metspalu A, Mihailov E,
981 Langenberg C, Luan J, Ong KK, Chines PS, Keinanen-Kiukaanniemi SM, Saaristo TE, Edkins S, Franks PW, Hallmans
982 G, Shungin D, Morris AD, Palmer CN, Erbel R, Moebus S, Nothen MM, Pechlivanis S, Hveem K, Narisu N, Hamsten
983 A, Humphries SE, Strawbridge RJ, Tremoli E, Grallert H, Thorand B, Illig T, Koenig W, Muller-Nurasyid M, Peters
984 A, Boehm BO, Kleber ME, Marz W, Winkelmann BR, Kuusisto J, Laakso M, Arveiler D, Cesana G, Kuulasmaa K,
985 Virtamo J, Yarnell JW, Kuh D, Wong A, Lind L, de FU, Gigante B, Magnusson PK, Pedersen NL, Dedoussis G,
986 Dimitriou M, Kolovou G, Kanoni S, Stirrups K, Bonnycastle LL, Njolstad I, Wilsgaard T, Ganna A, Rehnberg E,
987 Hingorani A, Kivimaki M, Kumari M, Assimes TL, Barroso I, Boehnke M, Borecki IB, Deloukas P, Fox CS, Frayling T,
988 Groop LC, Haritunians T, Hunter D, Ingelsson E, Kaplan R, Mohlke KL, O'Connell JR, Schlessinger D, Strachan DP,
989 Stefansson K. Sex-stratified genome-wide association studies including 270,000 individuals show sexual
990 dimorphism in genetic loci for anthropometric traits. PLoS Genet 2013;**9**(6):e1003500.
991 42. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, Smith AV, Tobin MD, Verwoert GC,
992 Hwang SJ, Pihur V, Vollenweider P, O'Reilly PF, Amin N, Bragg-Gresham JL, Teumer A, Glazer NL, Launer L, Zhao
993 JH, Aulchenko Y, Heath S, Sober S, Parsa A, Luan J, Arora P, Dehghan A, Zhang F, Lucas G, Hicks AA, Jackson AU,
994 Peden JF, Tanaka T, Wild SH, Rudan I, Igl W, Milaneschi Y, Parker AN, Fava C, Chambers JC, Fox ER, Kumari M, Go
995 MJ, van der Harst P, Kao WH, Sjogren M, Vinay DG, Alexander M, Tabara Y, Shaw-Hawkins S, Whincup PH, Liu Y,
996 Shi G, Kuusisto J, Tayo B, Seielstad M, Sim X, Nguyen KD, Lehtimaki T, Matullo G, Wu Y, Gaunt TR, Onland-Moret
997 NC, Cooper MN, Platou CG, Org E, Hardy R, Dahgam S, Palmen J, Vitart V, Braund PS, Kuznetsova T, Uiterwaal CS,
998 Adeyemo A, Palmas W, Campbell H, Ludwig B, Tomaszewski M, Tzoulaki I, Palmer ND, Aspelund T, Garcia M,
999 Chang YP, O'Connell JR, Steinle NI, Grobbee DE, Arking DE, Kardia SL, Morrison AC, Hernandez D, Najjar S,
1000 McArdle WL, Hadley D, Brown MJ, Connell JM, Hingorani AD, Day IN, Lawlor DA, Beilby JP, Lawrence RW, Clarke
1001 R, Hopewell JC, Ongen H, Dreisbach AW, Li Y, Young JH, Bis JC, Kahonen M, Viikari J, Adair LS, Lee NR, Chen MH,
1002 Olden M, Pattaro C, Bolton JA, Kottgen A, Bergmann S, Mooser V, Chaturvedi N, Frayling TM, Islam M, Jafar TH,
1003 Erdmann J, Kulkarni SR, Bornstein SR, Grassler J, Groop L, Voight BF, Kettunen J, Howard P, Taylor A, Guarrera S,
1004 Ricceri F, Emilsson V, Plump A, Barroso I, Khaw KT, Weder AB, Hunt SC, Sun YV, Bergman RN, Collins FS,
1005 Bonnycastle LL, Scott LJ, Stringham HM, Peltonen L, Perola M, Vartiainen E, Brand SM, Staessen JA, Wang TJ,
1006 Burton PR, Soler AM, Dong Y, Snieder H, Wang X, Zhu H, Lohman KK, Rudock ME, Heckbert SR, Smith NL, Wiggins
1007 KL, Doumatey A, Shriner D, Veldre G, Viigimaa M, Kinra S, Prabhakaran D, Tripathy V, Langefeld CD, Rosengren
1008 A, Thelle DS, Corsi AM, Singleton A, Forrester T, Hilton G, McKenzie CA, Salako T, Iwai N, Kita Y, Ogihara T,
1009 Ohkubo T, Okamura T, Ueshima H, Umemura S, Eyheramendy S, Meitinger T, Wichmann HE, Cho YS, Kim HL, Lee
1010 JY, Scott J, Sehmi JS, Zhang W, Hedblad B, Nilsson P, Smith GD, Wong A, Narisu N, Stancakova A, Raffel LJ, Yao J,
1011 Kathiresan S, O'Donnell CJ, Schwartz SM, Ikram MA, Longstreth WT, Jr., Mosley TH, Seshadri S, Shrine NR, Wain
1012 LV, Morken MA, Swift AJ, Laitinen J, Prokopenko I, Zitting P, Cooper JA, Humphries SE, Danesh J, Rasheed A, Goel
1013 A, Hamsten A, Watkins H, Bakker SJ, van Gilst WH, Janipalli CS, Mani KR, Yajnik CS, Hofman A, Mattace-Raso FU,
1014 Oostra BA, Demirkan A, Isaacs A, Rivadeneira F, Lakatta EG, Orru M, Scuteri A, Ala-Korpela M, Kangas AJ,
1015 Lyytikainen LP, Soininen P, Tukiainen T, Wurtz P, Ong RT, Dorr M, Kroemer HK, Volker U, Volzke H, Galan P,
1016 Hercberg S, Lathrop M, Zelenika D, Deloukas P, Mangino M, Spector TD, Zhai G. Genetic variants in novel
1017 pathways influence blood pressure and cardiovascular disease risk. Nature 2011;**478**(7367):103-109.
1018 43. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML,
1019 Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB,
1020 Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen
1021 E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP,
1022 Magnusson PK, Mangino M, Mihailov E, Montasser ME, Muller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD,
1023 Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ,
1024 Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu
1025 Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G,
1026 Dimitriou M, Doney AS, Doring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito
1027 ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones

MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Muller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de FU, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P. Discovery and refinement of loci associated with lipid levels. Nat Genet 2013;**45**(11):1274-1283.

44. Dehghan A, Dupuis J, Barbalic M, Bis JC, Eiriksdottir G, Lu C, Pellikka N, Wallaschofski H, Kettunen J, Henneman P, Baumert J, Strachan DP, Fuchsberger C, Vitart V, Wilson JF, Pare G, Naitza S, Rudock ME, Surakka I, de Geus EJ, Alizadeh BZ, Guralnik J, Shuldiner A, Tanaka T, Zee RY, Schnabel RB, Nambi V, Kavousi M, Ripatti S, Nauck M, Smith NL, Smith AV, Sundvall J, Scheet P, Liu Y, Ruokonen A, Rose LM, Larson MG, Hoogeveen RC, Freimer NB, Teumer A, Tracy RP, Launer LJ, Buring JE, Yamamoto JF, Folsom AR, Sijbrands EJ, Pankow J, Elliott P, Keaney JF, Sun W, Sarin AP, Fontes JD, Badola S, Astor BC, Hofman A, Pouta A, Werdan K, Greiser KH, Kuss O, Meyer zu Schwabedissen HE, Thiery J, Jamshidi Y, Nolte IM, Soranzo N, Spector TD, Volzke H, Parker AN, Aspelund T, Bates D, Young L, Tsui K, Siscovick DS, Guo X, Rotter JI, Uda M, Schlessinger D, Rudan I, Hicks AA, Penninx BW, Thorand B, Gieger C, Coresh J, Willemsen G, Harris TB, Uitterlinden AG, Jarvelin MR, Rice K, Radke D, Salomaa V, Willems van DK, Boerwinkle E, Vasan RS, Ferrucci L, Gibson QD, Bandinelli S, Snieder H, Boomsma DI, Xiao X, Campbell H, Hayward C, Pramstaller PP, van Duijn CM, Peltonen L, Psaty BM, Gudnason V, Ridker PM, Homuth G, Koenig W, Ballantyne CM, Witteman JC, Benjamin EJ, Perola M, Chasman DI. Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. Circulation 2011;**123**(7):731-738.

45. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Magi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparso T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proenca C, Kumari M, Qi L, Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, McCarroll SA, Payne F, Roccasecca RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B, Barter P, Beilby JP, Ben-Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M, Boerwinkle E, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Bottcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M, Crawford G, Crisponi L, Day IN, de Geus EJ, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Fox CS, Frants R, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Groves CJ, Grundy S, Gwilliam R, Gyllensten U, Hadjadj S, Hallmans G, Hammond N, Han X, Hartikainen AL, Hassanali N, Hayward C, Heath SC, Hercberg S, Herder C, Hicks AA, Hillman DR, Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jorgensen T, Jula A, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le BO, Lecoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martinez-Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orru M, Pakyz R, Palmer CN, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Perola M, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W, Rayner NW, Rice K, Ripatti S, Rivadeneira F, Roden M,

Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurethsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvanen AC, Tanaka T, Thorand B, Tichet J, Tonjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van HM, Varma D, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL, Watkins H, Weedon MN, Wild SH, Willemsen G, Witteman JC, Yarnell JW, Zeggini E, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, Borecki IB, Loos RJ, Meneton P, Magnusson PK, Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Rios M, Morris AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WH, Pankow JS, Sampson MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 2010;**42**(2):105-116.

46. Pattaro C, Kottgen A, Teumer A, Garnaas M, Boger CA, Fuchsberger C, Olden M, Chen MH, Tin A, Taliun D, Li M, Gao X, Gorski M, Yang Q, Hundertmark C, Foster MC, O'Seaghdha CM, Glazer N, Isaacs A, Liu CT, Smith AV, O'Connell JR, Struchalin M, Tanaka T, Li G, Johnson AD, Gierman HJ, Feitosa M, Hwang SJ, Atkinson EJ, Lohman K, Cornelis MC, Johansson A, Tonjes A, Dehghan A, Chouraki V, Holliday EG, Sorice R, Kutalik Z, Lehtimaki T, Esko T, Deshmukh H, Ulivi S, Chu AY, Murgia F, Trompet S, Imboden M, Kollerits B, Pistis G, Harris TB, Launer LJ, Aspelund T, Eiriksdottir G, Mitchell BD, Boerwinkle E, Schmidt H, Cavalieri M, Rao M, Hu FB, Demirkan A, Oostra BA, de AM, Turner ST, Ding J, Andrews JS, Freedman BI, Koenig W, Illig T, Doring A, Wichmann HE, Kolcic I, Zemunik T, Boban M, Minelli C, Wheeler HE, Igl W, Zaboli G, Wild SH, Wright AF, Campbell H, Ellinghaus D, Nothlings U, Jacobs G, Biffar R, Endlich K, Ernst F, Homuth G, Kroemer HK, Nauck M, Stracke S, Volker U, Volzke H, Kovacs P, Stumvoll M, Magi R, Hofman A, Uitterlinden AG, Rivadeneira F, Aulchenko YS, Polasek O, Hastie N, Vitart V, Helmer C, Wang JJ, Ruggiero D, Bergmann S, Kahonen M, Viikari J, Nikopensius T, Province M, Ketkar S, Colhoun H, Doney A, Robino A, Giulianini F, Kramer BK, Portas L, Ford I, Buckley BM, Adam M, Thun GA, Paulweber B, Haun M, Sala C, Metzger M, Mitchell P, Ciullo M, Kim SK, Vollenweider P, Raitakari O, Metspalu A, Palmer C, Gasparini P, Pirastu M, Jukema JW, Probst-Hensch NM, Kronenberg F, Toniolo D, Gudnason V, Shuldiner AR, Coresh J, Schmidt R, Ferrucci L, Siscovick DS, van Duijn CM, Borecki I, Kardia SL, Liu Y, Curhan GC, Rudan I, Gyllensten U, Wilson JF, Franke A, Pramstaller PP, Rettig R, Prokopenko I, Witteman JC, Hayward C, Ridker P, Parsa A, Bochud M, Heid IM, Goessling W, Chasman DI, Kao WH, Fox CS. Genome-wide association and functional follow-up reveals new loci for kidney function. PLoS Genet 2012;**8**(3):e1002584.