Institution:
University of Cambridge

Unit of Assessment:
UoA2

Title of case study:
Optimising the management of cardiovascular disease

1. Summary of the impact (indicative maximum 100 words)

The Cambridge-led Emerging Risk Factors Collaboration (ERFC) is a global consortium involving individual-participant data on 2.5 million participants from 130 cohort studies. The ERFC has helped optimise approaches to cardiovascular disease (CVD) risk assessment by: 1) quantifying the incremental predictive value provided by assessment of risk factors 2) evaluating the independence of associations between risk factors and CVD and 3) addressing uncertainties related to the implementation of screening. ERFC publications on lipids, lipoproteins, and inflammation biomarkers have been cited by 9 guidelines published since 2010, including those of the European Society of Cardiology and the American Heart Association.

2. Underpinning research (indicative maximum 500 words)

To help target scarce preventive resources, promote behavioural change, and monitor risk, CVD risk is assessed in primary prevention settings in most high-income countries. There is, however, substantial debate about what constitutes an optimum approach to risk assessment.

Researchers and outputs The ERFC was conceived and established by Professor John Danesh (Professor since 2001), together with colleagues at the Department of Public Health and Primary Care, including Dr Emanuele Di Angelantonio (UL since 2010) and Dr Stephen Kaptoge (SRA since 2007). Under the direction of Professor Danesh, the Cambridge coordinating centre has since 2003 led all aspects of this consortium, including: choice of hypotheses to study, collation and harmonisation of data, statistical analyses, interpretation of data, reporting and dissemination of findings. The ERFC has also given rise to other closely-related consortia led by the same Cambridge investigators, such as the LpPLA2 Studies Collaboration. Research Refs #1-5 provide examples of substantive findings. Professor Danesh has been the key senior scientific leader in all the substantive reports, exemplified by his role as the senior author and/or corresponding author.

Underpinning data and methods About 130 long-term prospective cohort studies based in 25 different countries have shared extensive individual-level data with the Cambridge coordinating centre of the ERFC. This effort has yielded one of the largest and most detailed central databases in CVD epidemiology worldwide (i.e., up to ~500 covariates for each of 2.5 million participants). More than 100,000 incident CVD outcomes have been recorded during 15 million person-years at risk. More than 300,000 people have provided serial measurements of risk factors.

In addition to its size and detail, several additional features have distinguished this consortium's approach that have enhanced its power, generalisability, and validity. First, cohorts contributing data to the consortium have typically shared more extensive individual-level data (e.g., additional types of disease endpoints and extended follow-up) than have been reported in their own cohort-specific publications, thereby enhancing power and enabling comparison of different types of CVD outcomes. Second, the coordinating centre has iteratively checked, cleaned, re-coded, and harmonised all data shared in this consortium in close liaison with the investigators of contributing studies, thereby enhancing the validity of the underlying data analysed.

Third, analyses have focused on a uniform and appropriate subset of participants (e.g., people without a history of CVD at the baseline examination who have complete information on relevant risk factors), in contrast with inconsistent inclusion/exclusion criteria used in previous studies. Fourth, the ERFC has used methods specifically appropriate for the evaluation of incremental risk prediction, such as measures of discrimination and reclassification that require time-to-event data. Results have also been expressed in a manner to help enhance understanding by clinicians and policy makers, such as the numbers needed to screen to avoid 1 additional CVD outcome over 10 years of preventive treatment.

Fifth, under the leadership of Professor Simon Thompson (MRC Biostatistics Unit Director until

2011 and Professor since 2002) and Dr Angela Wood (University Lecturer in Biostatistics, Department of Public Health and Primary Care since 2006), the coordinating centre has developed methods to optimise such analyses, including measures of discrimination and reclassification for the multi-study situation [Research Ref #6 provides an example].

3. References to the research (indicative maximum of six references)

1. ERFC: (writing committee: **Di Angelantonio E**, Sarwar N, Perry P, **Kaptoge S**, Ray KK, Thompson A, **Wood AM**, Lewington S, Sattar N, Packard CJ, Collins R, **Thompson SG**, **Danesh J**). Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009;302:1993-2000.

2. The Triglyceride Coronary Disease Genetics Consortium and ERFC: (writing committee: Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, **Di Angelantonio E**, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, **Danesh J**). Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet 2010;375:1634-9.

3. ERFC: (writing committee: Erqou S, **Kaptoge S**, Perry PL, **Di Angelantonio E**, Thompson A, White IR, Marcovina SM, Collins R, **Thompson SG**, **Danesh J**). Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009;302:412-423.

4. The Lp-PLA2 Studies Collaboration: (writing committee: Thompson A, Gao P*, Orfei L*, Watson S, **Di Angelantonio E**, Kaptoge S, Ballantyne C, Cannon CP, Criqui M, Cushman M, Hofman A, Packard C, Thompson SG, Collins R, **Danesh J**). Lipoprotein-associated phospholipase A2 and risk of coronary disease, stroke and mortality: collaborative analysis of 32 prospective studies. Lancet 2010;375:1536–44.

5. ERFC: (writing committee: **Kaptoge S**, **Di Angelantonio E**, Lowe G, Pepys MB, **Thompson SG**, Collins R, **Danesh J**). C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132-40.

6. ERFC: (writing committee: **Thompson SG**, Kaptoge S, White IR, **Wood AM**, Perry PL, **Danesh J**) Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. Int J Epidemiol 2010;39:1345-1359.

Grants Professor Danesh is the PI and holder of grants which have supported the ERFC:

Emerging risk factors in CVD	BHF	2003-2008	£780K
Pooled analyses of CRP	BUPA	2005-2007	£160K
Pooled analyses of triglycerides	MRC	2006-2009	£440K
Statistical methods for risk prediction	MRC	2008-2013	£440K
Emerging risk factors in CVD	BHF	2008-2013	£1.9M
Risk factors in coronary heart disease	MRC/BHF	2013-2018	£4M

4. Details of the impact (indicative maximum 750 words)

Nature of impact Publications from the ERFC have been cited by 9 guideline statements:

2010: European Atherosclerosis Society (EAS) Consensus Panel on lipoprotein(a) in cardiovascular disease.
2010: American College of Cardiology Foundation / American Heart Association (ACCF / AHA) guideline for assessment of cardiovascular risk in asymptomatic adults
2011: European Society of Cardiology and European Atherosclerosis Society (ESC / EAS) Guidelines for the management of dyslipidaemias
2011: American Heart Association statement on Triglycerides and cardiovascular disease
2011: American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan
2011: US National Lipid Association expert advice
2012: Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

2012: European Society of Cardiology (ESC) and Other Societies Guidelines on cardiovascular disease prevention in clinical practice
2012: Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline.

Specific impact

1. Major lipids [Research Refs #1 and #2]

Findings: The ERFC reported that lipid assessment can be greatly simplified by measurement of HDL-cholesterol and total cholesterol without the need to fast and without regard to triglyceride (Research Ref #1), with major implications for screening millions of adults. The same report demonstrated that measurement of apolipoproteins A and B provides similar information about CVD risk as does assessment of conventional lipid fractions. The ERFC reported that large-scale human biomarker and genetic evidence is consistent with a causal association of triglyceride-related pathways in CVD (Research Ref #2).
Impact on guidelines: The ERFC paper on major lipids has been cited in the 2011 ESC / EAS Guidelines for the management of dyslipidaemias [Impact Ref #1: footnote number 42], in the 2012 ESC Guidelines [Impact Ref #2: footnote number 52], the 2011 American Association of Clinical Endocrinologists Medical Guidelines [Impact Ref #4: footnote number 359], and the 2011 AHA Statement on triglycerides and CVD [Impact Ref #5: footnote number 17].
The ERFC publication on the causal relevance of triglyceride-related pathways to CVD (Research Ref #2) has been cited in the following guidelines to support diagnosis and treatment of hypertriglyceridaemia: the 2012 Endocrine Society Clinical Practice Guideline [Impact Ref #3: footnote number 9], the 2011 ESC / EAS Guidelines for the management of dyslipidaemias [Impact Ref #1: footnote number 121], and the 2011 AHA Statement on triglycerides and CVD [Impact Ref #5: footnote number 98].

2. Lipoproteins [Research Refs #3 and #4]

Findings: The ERFC reported that lipoprotein(a) is specifically, continuously and independently associated with CVD in a manner consistent with causality (Research Ref #3). The LpPLA2 Studies Collaboration publication has reported that lipoprotein-associated phospholipase A2 is log-linearly associated with risk of CVD (independent of established lipids), with a similar magnitude of association as for LDL-cholesterol (Research Ref #4).
Impact on guidelines: The ERFC paper on lipoprotein(a) has been cited in the following four guidelines to support assessment of Lp(a) in practice: the 2010 EAS Consensus Panel [Impact Ref #6: footnote number 3], the 2011 ESC / EAS Guidelines for the management of dyslipidaemias [Impact Ref #1: footnote number 49], the 2012 Canadian Cardiovascular Society Guidelines [Impact Ref #7: footnote number 71], and the 2012 Endocrine society [Impact Ref #3: footnote number 44], and the 2010 ACCF / AHA Guidelines [Impact Ref #8: footnote number 102].
The Lp-PLA2 Studies Collaboration publication has been cited the 2011 National Lipid Association expert advice [Impact Ref #9: footnote number 78].

3. Inflammation biomarkers [Research Ref #5]

Findings: The ERFC reported that assessment of inflammation biomarkers provides only modest improvement in CVD prediction (Research Ref #5).
Impact on guidelines: The ERFC paper on inflammation biomarkers has been cited in the following 2 guidelines: the 2011 ESC / EAS Guidelines [Impact Ref #2: footnote number 126], the 2012 ESC Guidelines [Impact Ref #2: footnote number 126], and the 2012 Canadian Cardiovascular Society Guidelines [Impact Ref #7: footnote number 72].

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen M-R, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D, ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the

management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur. Heart J. 2011; 32:1769–1818.

2. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte op Reimer WJM, Vrints C, Wood D, Zamorano JL, Zannad F, European Association for Cardiovascular Prevention & Rehabilitation (EACPR), ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur. Heart J. 2012; 33:1635–1701.

3. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AFH, Endocrine society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. 2012; 97:2969–2989.

4. Task Force for Developing Diabetes Comprehensive Care Plan. Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, Dagogo-Jack S, Davidson JA, Einhorn D, Ganda O, Garber AJ, Hirsch IB, Horton ES, Ismail-Beigi F, Jellinger PS, Jones KL, Jovanovič L, Lebovitz H, Levy P, Moghissi ES, Orzeck EA, Vinik AI, Wyne KL, AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract. 2011; 17 Suppl 2:1–53.

5. Triglycerides and cardiovascular disease a scientific statement from the American Heart Association. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S, American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Nursing, Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011; 123:2292–2333.

6. Nordestgaard BG, Chapman MJ, Ray KK, Borén J, Andreotti F, Watts GF, Ginsberg H, Amarenco P, Catapano A, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Reiner Z, Taskinen MR, Tokgözoglu L, Tybjærg-Hansen A, for the European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: Current status. Eur Heart J 2010;31:2844-2853.

7. Anderson TJ, Grégoire J, Hegele RA, Couture P, Mancini GBJ, McPherson R, Francis GA, Poirier P, Lau DC, Grover S, Genest J, Carpentier AC, Dufour R, Gupta M, Ward R, Leiter LA, Lonn E, Ng DS, Pearson GJ, Yates GM, Stone JA, Ur E. 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol 2013;29 :151-167.

8. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith Jr SC, Taylor AJ, Weintraub WS, Wenger NK. ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation 2010;122:e584-e636.
9. Davidson MH, Ballantyne CM, Jacobson TA, Bittner VA, Braun LT, Brown AS, Brown WV, Cromwell WC, Goldberg RB, McKenney JM, Remaley AT, Sniderman AD, Toth PP, Tsimikas S, Ziajka PE, Maki KC, Dicklin MR. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists. J Clin Lipidol. 2011;5:338-67.