Impact case study (REF3)

Institution: University College London

Unit of Assessment: 2 - Public Health, Health Services and Primary Care

Title of case study: Big data to improve care and outcomes for millions of people with cardiovascular disease.

Period when the underpinning research was undertaken: Between 2008 and 2016

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Harry Hemingway FMedSci	Professor of Clinical Epidemiology; Director of Institute of Health Informatics, UCL; Research Director, Health Data Research UK	Between 1993 and 2021

Period when the claimed impact occurred: Between 2014 and present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Research led by Professor Harry Hemingway at UCL has used large-scale patient data to shape national and international clinical guidelines for the prevention, diagnosis, and treatment of a range of cardiovascular diseases. This has benefited care and improved outcomes for millions of patients worldwide. Evidence from the research has informed new blood pressure thresholds for more accurate diagnosis of hypertension, enabling 13% more US adults to be diagnosed and treated. It has provided the evidence for more accurate early diagnosis of stable coronary disease, preventing 1,100 heart attacks and strokes per year. Hemingway's research has additionally led to safer, more targeted use of oral anti-coagulants to prevent stroke in 340,000 female atrial fibrillation patients across Europe and provided real-world evidence for the effectiveness of a new secondary prevention treatment in heart attack with the blood-thinning drug ticagrelor. Finally, UK efforts to improve the care of heart attack patients have been informed by Hemingway's study of the 'mortality gap' between UK and Swedish patients, which revealed there could have been 10,000 fewer UK deaths if the outcomes had mirrored those of heart attack patients in Sweden.

2. Underpinning research

Earlier diagnosis of coronary artery disease: Hemingway co-led (with Timmis, Queen Mary University of London, QMUL) research **[R1]** informing a major change in the earlier diagnosis of suspected coronary disease, from exercise electrocardiography (ECG) to CT angiography. The research, published in 2008, helped to establish an important principle that clinically recorded data (i.e. data not collected under research conditions) could generate robust research findings. At the time this was considered 'big data' in terms of 'volume, variety and veracity': the cohort included 8,176 patients from six centres and was substantially the largest clinical cohort of patients with chest pain and suspected stable coronary disease followed up with electronic health records for clinical outcomes. Hemingway's research provided key new evidence demonstrating that the exercise ECG ('treadmill'), which had been the mainstay of diagnosis up until the 2010s, added little diagnostic or prognostic information beyond a structured history of the chest pain, and conventional cardiovascular risk factors and resting ECG findings.

Largest ever cohort study changes threshold for hypertension diagnosis: UCL-led research published in 2014 **[R2]** informed major changes in the blood pressure threshold at which hypertension is diagnosed. The research involved the largest ever cohort study, involving 1.25 million patients, of blood pressure and cardiovascular diseases. By using electronic health records linked to hospitalisation data (Clinical Practice Research Datalink, CALIBER platform) the UCL research team were able to show for the first time previously undetected disease associations. These associations extended across a wider range of observed blood pressure levels and were in relation to a wider range of cardiovascular diseases (12 in total) than had previously been studied. These findings were relevant to

deciding threshold blood pressure levels at which hypertension is diagnosed. Previous studies had largely focused on cardiovascular death only, or were limited to heart attack and stroke; and these earlier studies had been too small to reliably estimate risks among people with systolic blood pressure of 130mmHg at different ages.

Change to policy on treating atrial fibrillation in women: A major change in policy for the treatment with anticoagulants of women with atrial fibrillation was based directly on research published by the UCL team in 2016 **[R3]**. The research involved 70,000 patients with atrial fibrillation in the linked primary-secondary care electronic health record platform, CALIBER. The UCL team demonstrated how the net clinical benefit of warfarin in people with atrial fibrillation (AF) varies across a measure of risk widely used in clinical practice: the CHA_2DS_2-VASC score. Warfarin has a major side effect of bleeding, so haemorrhagic strokes are a particular concern in this group. The UCL team found that women with a CHA_2DS_2-VASC score of 1 or 0 had net clinical benefit; this means that the benefits of warfarin in preventing ischaemic strokes is nullified by the harms of haemorrhagic stroke. This is one of the first examples of a major clinical guideline development group (the European Society of Cardiology, the AF guidelines have >8,000 citations) working synchronously with an academic group (UCL) to generate new evidence which in turn directly informed a change in clinical recommendation.

Informing regulatory approval of ticagrelor for heart attack survivors: Continuing Hemingway's ground-breaking use of big data, a study of heart attack survivors in England, US, Sweden and France using real-world data from electronic health records was published by UCL in 2016 **[R4]** which informed regulatory approval of ticagrelor in heart attack survivors. Two aspects of this research were novel: first, nearly all previous research on heart attack starts follow-up on the day of the heart attack; by contrast Hemingway and colleagues studied only those people who had already survived for 365 days. Second, this research was, and remains, one of a small number of studies comparing care and outcomes across several countries using clinically collected data on care and outcomes. The research demonstrated the surprisingly high risk of these heart attack survivors (between 25 and 36% of patients had died or had a heart attack or stroke after a further three years) and thus showed the international unmet need for additional secondary prevention in these countries and the real-world effectiveness of ticagrelor as prolonged dual anti-platelet therapy.

Improving UK heart attack care and outcomes: Further research to inform UK efforts to improve heart attack care and outcomes was published by the UCL team in 2014 **[R5]**. Hemingway and colleagues identified a 'mortality gap' between UK and Sweden, based on research on more than 500,000 heart attack patients from nationwide registries. This was the first time that nationwide data (ie. from all hospitals in the country) in two countries had been used to study both the care and outcome of any disease – in this sense, it was pioneering. Hemingway and colleagues compared the quality of healthcare (i.e. the level of adherence to guideline-recommended medications and procedures), and the number of patients who had died within 30 days of having a heart attack. They found that 10,000 fewer deaths would have occurred in the UK if the outcomes had mirrored those of Swedish patients.

The research team, led by Hemingway, comprised UCL Professors Aroon Hingorani (Clinical Pharmacology), Bryan Williams (Medicine); with Professors Spiros Denaxas (Biomedical Informatics) and John Deanfield (Cardiology). The UCL Team collaborated with QMUL (Professor Adam Timmis, Cardiology, and Professor Mark Caulfield Clinical Pharmacology) and LSHTM (Liam Smeeth, General Practice).

3. References to the research

[R1] Sekhri, N., Feder, G.S., Junghans, C., Eldridge, S., Umaipalan, A., Madhu, R., **Hemingway, H.,** Timmis, A.D. (2008). 'Incremental prognostic value of the exercise electrocardiogram in the initial assessment of patients with suspected angina: cohort study'. *BMJ*, **337**, a2240. DOI: 10.1136/bmj.a2240. **Earlier diagnosis of suspected**

coronary disease: replacing exercise electrocardiography with CT angiography.

[R2]   **Rapsomaniki, E.**, Timmis, A., George, J, Pujades-Rodriguez, M., Shah, A.D., **Denaxas, S.**, White, I.R., Caulfield, M.J., **Deanfield, J.E.**, Smeeth, L., **Williams, B.**, **Hingorani, A.**, **Hemingway, H**. (2014). 'Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people'. *Lancet.* **383** (9932), 1899–1911. DOI: 10.1016/S0140-6736(14)60685-1 **Changing the blood pressure threshold at which hypertension is diagnosed.**

[R3]   **Allan, V., Banerjee, A., Shah, A.D., Patel, R., Denaxas, S., Casas, J.P., Hemingway, H.** (2017). 'Net clinical benefit of warfarin in individuals with atrial fibrillation across stroke risk and across primary and secondary care'. *Heart.* **103** (3), 210-218. DOI: 10.1136/heartjnl-2016-309910. **Targeting safer treatment for atrial fibrillation.**

[R4]   **Rapsomaniki, E.**, Thuresson, M., Yang, E., Blin, P., Hunt, P., Chung, S-C., Stogiannis, D., Pujades-Rodriguez, M., Timmis, A., **Denaxas, S.C.**, Danchin, N., Stokes, M., Thomas-Delecourt, F., Emmas, C., Hasvold, P., Jennings, E., Johansson, S., Cohen, D.J., Jernberg, T., Moore, N., Janzon, M., **Hemingway, H**. (2016). 'Using big data from health records from four countries to evaluate chronic disease outcomes: a study in 114,364 survivors of myocardial infarction'. *EurHeartJ: Quality Care Clin Outcomes.* **2**(3),172-83. DOI: 10.1093/ehjqcco/qcw004. **Evidence of unmet need and real-world effectiveness of ticagrelor.**

[R5]   **Chung, S-C.**, Gedeborg, R., Nicholas, O., James, S., Jeppson, A., Wolfe, C., Heuschmann, P., Wallentin, L., **Deanfield, J.**, Timmis, T., Jernberg, T., **Hemingway, H**. (2014). 'Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK'. *The Lancet*. **383**(9925),1305-12. DOI: 10.1016/S0140-6736(13)62070-X. **Nationwide comparisons of UK and Sweden on the care and outcomes of heart attack patients.**

4. Details of the impact

Cardiovascular diseases are the most common cause of death worldwide, responsible for an estimated 31% of all deaths, according to the World Health Organization. UCL research between 2014 and 2020, led by Professor Hemingway, has made novel use of large-scale health records data to gain several important insights into the diagnosis and treatment of the most common cardiovascular diseases: high blood pressure, coronary disease, heart attack and atrial fibrillation. His insights have challenged the status quo, shaped policy, and informed improvements in care for millions of patients worldwide.

The impacts started with a radical change in the standard method for diagnosis of coronary disease, in people with stable (non-emergency) chest pain**.** Research **[R1]** led by Hemingway and colleagues at QMUL was cited 16 times in the NICE Guidelines Committee on Chest pain (CG95) **[S1]**, which recommended that exercise ECG should no longer be the standard diagnostic procedure. Hemingway was a member of this NICE guideline committee. Each year since 2014, approximately 100,000 new patients are seen in the NHS with suspected stable coronary disease. Subsequent near-complete abandonment of exercise ECG has allowed an estimated 15,000 more people per year to be diagnosed with coronary disease - earlier and with greater accuracy - by CT angiography. This, in turn, enables sooner treatment with secondary preventative medication (such as aspirin, statins or beta blockers), which is estimated to have averted 1,100 fatal and non-fatal cardiovascular events per year.

Hemingway's UCL hypertension research was cited as observational evidence informing the decision to make one of the most significant changes in the international clinical guidelines **[S2, S3]**, for blood pressure management in recent years: lowering the blood pressure thresholds at which hypertension is diagnosed from ≥140 systolic or ≥90mmHg diastolic to ≥130 systolic or ≥80mmHg diastolic **[R2]**. As a result, a larger proportion of the general population are now eligible for drug and other interventions to reduce risks of heart attack and

stroke which are caused by high blood pressure. Health care professionals have benefitted from new, clear guidance on how to manage such patients. This major change in clinical guidelines has been estimated to increase by 4,200,000 the number of US adults now diagnosed and recommended for blood pressure-lowering medication, compared with the previous guidelines in 2003 **[S4]**.

Further research from UCL in 2016 has challenged the status quo of 'gender blind' treatment of the most common heart rhythm disorder, atrial fibrillation. This evidence on safe targeting of oral anticoagulants in women with atrial fibrillation **[R3]** was solely responsible for changing major international clinical guidelines **[S5, S6]**. The 2012 guidelines did not offer sex-specific thresholds of risk in the prescribing of anti-coagulants for preventing stroke; but it was known that men are at greater risk of stroke than women. Based on new UCL evidence, the 2016 European guidelines were then changed to explicitly recommend anti-coagulation to women with a score of ≥2. There are an estimated 5 million women with atrial fibrillation in Europe, about 7.4% (370,000) of whom have a CHA2DS2-VASC score of 2, and in whom anti-coagulation confers net clinical benefit. Hemingway and colleagues estimate that - even assuming only 50% of women in this group are anticoagulated - this prevents up to 1,900 fatal and non-fatal strokes each year. Such prevention is particularly important given the high levels of disability and health care use associated with stroke.

Research on unmet need and real-world effectiveness of the blood-thinning drug ticagrelor **[R4]**, published by the UCL team in 2016, was cited in the NICE regulatory approval (TA420) **[S7]** for ticagrelor use for preventing atherothrombotic events after myocardial infarction. This changed clinical practice to address the very high risk of major cardiovascular events in heart attacks survivors, demonstrated by the UCL research. NICE approved the use of prolonged (effectively lifelong) medication with dual anti-platelet therapy (i.e. aspirin and ticagrelor). Previously, only certain sub-groups of patients were prescribed ticagrelor and ticagrelor was stopped within one year after heart attack. This research helps to show how the risk of further heart attacks in such patients can be further reduced. The British Heart Foundation estimates that there are 1,300,000 survivors of acute myocardial infarction, most of whom now are recommended for prolonged dual anti-platelet therapy with ticagrelor. Hemingway and colleagues' research **[R4]** is based on unselected clinical populations, which provides a more real-world estimate of risks of cardiovascular events (compared to the lower risks estimated in healthier populations selected into trials). Using the real-world risks, and assuming only half of eligible patients receive dual anti-platelet treatment, an estimated 6,500 cardiovascular deaths, non-fatal myocardial infarction or strokes are prevented every year in the UK.

The UCL research demonstrating the 'international mortality gap' between the UK and Sweden **[R5]** among heart attack patients has had impacts beyond stimulating cardiologists to provide better care and close the mortality gap; it informed amendments to the Health and Social Care Act. The research was published on 23 January 2014 amidst public concerns that the government may sell NHS data to insurance companies in the 'care.data' programme. The widespread TV and print media coverage of the research (with headlines such as 'Second rate care' - Sky) ensured that the research was used in discussions with the Secretary of State for Health **[S8]** about the value of health data. On 12 February 2014, Secretary of State for Health, Jeremy Hunt, called a meeting with Chair of the UK Academy of Medical Royal Colleges, among others. An email from the Chair about the meeting describes how the UCL findings had shaped the Health and Social Care Act: *"I used your [UCL] examples of linking datasets to improve quality of care now and the Swedish comparison. The latter seemed to make a big impact. The immediate result is Jeremy Hunt made an amendment to the [Heath and Social] Care Act the same day to ensure the public that care.data will not be available to insurance companies, mortgage lenders etc."* **[S8]**

The research rapidly became an influential example of public good arising from public sector access to health record data, with appropriate information governance. The amendments were passed in the Care Act 2014, to allow data release only: *"for the purposes of—the*

provision of health care or adult social care, or the promotion of health." This stimulated professional societies to understand care and outcomes from NHS care **[S9]***.*

5. Sources to corroborate the impact

[S1] National Institute for Health and Care Excellence (NICE) Clinical Guideline. CG95 Chest pain of recent onset. 2010. http://guidance.nice.org.uk/CG95

[S2] Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E. Jr, Collins, K,J., Dennison, Himmelfarb C., DePalma, S.M., Gidding, S., Jamerson, K.A., Jones, D.W., MacLaughlin, E.J., Muntner, P., Ovbiagele, B., Smith, S.C. Jr, Spencer, C.C., Stafford, R.S., Taler, S.J., Thomas, R.J., Williams, K.A. Sr, Williamson, J.D., Wright, J.T. Jr. (2018). 'ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines'. *Hypertension*. **71**, e13– e115. DOI: 10.1161/HYP.0000000000000065

[S3] Williams, B., Mancia, G., Spiering, W., et al. (2018). 'ESC/ESH Guidelines for the management of arterial hypertension'. *Eur. Heart J*. **39**(33), 3021-3104. DOI: 0.1093/eurheartj/ehy339 [published correction appears in *Eur Heart J*. (2019) **40**(5), 475].

[S4] Muntner, P., Carey, R.M., Gidding, S., et al. (2018). 'Potential US population impact of the 2017 ACC/AHA high blood pressure guideline'. *Circulation*. **137**, 109–118. DOI: 10.1161/CIRCULATIONAHA.117.032582

[S5] Kirchhof, P., Benussi S., Kotecha D., Ahlsson A., Atar D., Casadei B., Castella M., Diener H-C., Heidbuchel H., Hendriks J., Hindricks G., Manolis A.S., Oldgren J., Popescu B.A., Schotten U., Van Putte B., Vardas P. (2016). European Society of Cardiology Scientific Document Group: '2016 European Society of Cardiology Guidelines for the management of atrial fibrillation developed in collaboration with European Association of Cardio Thoracic Surgeons'. *Eur. Heart J.* **37** (38), 2893– 2962. DOI: 10.1093/eurheartj/ehw210

[S6] January C.T., Wann L.S., Calkins H., et al. (2019). 'AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society'. *J Am Coll Cardiol*. **74**(1), 104-132. [published correction appears in *J Am Coll Cardiol*. (2019) **74**(4), 599]. DOI: 10.1016/j.jacc.2019.01.011.

[S7] National Institute for Health and Care Excellence (NICE). (2017). 'Ticagrelor for preventing atherothrombotic events after myocardial infarction'. NICE technology appraisal guidance, **420**. London: NICE. https://www.nice.org.uk/guidance/ta420

[S8] Email from Chair, UK Academy of Medical Royal Colleges, 27 February 2014.

[S9] Care Act 2014. Section 122 Health and Social Care Information Centre, Restrictions on dissemination of information (amending Section 261 of Health and Social Care Act 2012) https://www.legislation.gov.uk/ukpga/2014/23/section/122/enacted