Institution: University of Glasgow (UofG)

Unit of Assessment: UoA1 Clinical Medicine

Title of case study: Demonstrating risks and benefits of glucose-lowering drugs in type-2 diabetes leads to new uses of these drugs in treating heart failure.

Period when the underpinning research was undertaken: 2007–present

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

Names(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof. John McMurray	Professor of Medical Cardiology	1999–present
Dr Pardeep Jhund	Clinical lecturer; Senior Clinical Lecturer; Reader	2008–2015; 2015–2019; 2019–present
Prof. Mark Petrie	Professor	2016–present

Period when the impact occurred: 2017–present

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

1. Summary of the impact

Cardiovascular (CV) events are the leading cause of death and disability in patients with type-2 diabetes (T2D). UofG research was instrumental in demonstrating the CV safety of certain drugs for T2D patients through high-quality, regulatory CV outcome trials that provided the data necessary to secure approval for four glucose-lowering drugs to treat T2D patients. To date, these drugs have been used in millions of patients worldwide, with global sales of over USD8 billion. The trials further confirmed the CV benefits of two key families of glucose-lowering agents, now recommended in international guidelines. Building on this research, the glucose-lowering drug dapagliflozin, previously used solely in T2D patients, is now used to treat heart failure (HF) irrespective of T2D.

2. Underpinning research

Since 2008, regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), have required robust CV-outcome data from randomised controlled trials (RCTs) to grant and sustain the approval of drugs for diabetes. CV outcome trials (CVOTs) evaluate the CV safety of a drug compared to a placebo or standard care. CVOTs are a vital component of the regulatory process for approving drugs for T2D. This process arose due to a controversy surrounding the glucose-lowering drug, rosiglitazone (GSK), where a meta-analysis of small studies showed that the drug increased the risk of CV events in patients with T2D. Prof. John McMurray was a member of the steering group of the RECORD trial reported in 2009 (New England Journal of Medicine, 373:2125-35) that ultimately showed that this drug increased the risk of HF, but not of myocardial infarction, in T2D patients, compared with standard glucose-lowering drugs.

Owing to a significant body of trial design and leadership in HF, as well as involvement in the RECORD study and the critical analysis that followed, Prof. McMurray has played a key role in designing and/or leading CVOTs across key families of glucose-lowering agents:

Prof. McMurray led the **VIVIDD** trial (May 2009–August 2012), which tested the effect of Novartis' drug, vildagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, on ventricular function in patients with T2D and HF [3.1]. This trial found that, compared with placebo, vildagliptin had no major effect on left ventricular ejection fraction but increased left ventricular systolic and diastolic volumes (clinical significance unknown) in patients over 52 weeks of follow-up.

Prof. McMurray also designed the pivotal **ELIXA** trial, which was the first completed long-term safety study of a glucagon-like peptide-1 receptor agonist (GLP-1RA) called lixisenatide (Sanofi). Prof. McMurray was the only UK member of the trial's Executive Committee. Between July 2010–August 2013, the study recruited 6068 patients who had T2D and a recent acute coronary syndrome, and who were randomly assigned to either lixisenatide or placebo, in addition to standard care. This trial found, as reported in 2015, that lixisenatide had no major effect on the primary composite outcome of major adverse cardiac events (cardio-vascular death, non-fatal myocardial infarction, or non-fatal stroke) compared to placebo [3.2].

Prof. McMurray joined five other researchers to conduct a prospective **meta-analysis** of CV safety across nine **Harmony** trials that were sponsored by GSK, to support the approval application of the GSK GLP-1RA drug, albiglutide, by fulfilling the requirement for CV safety required by the US FDA. These **Harmony** trials consisted of eight, phase-3 trials and one phase-2b trial. Prof. McMurray was chair of the endpoint adjudication committee for the study.

The study, published in 2015, established that CV events were no more likely to occur with albiglutide than with placebo or any other comparator drugs tested in the Harmony trials [3.3]. The FDA also requested a post-approval CVOT. Between 2015–2018, **Harmony Outcomes** recruited 9,463 patients with T2D and CV disease across 610 sites in 28 countries. Patients were randomised to a once weekly albiglutide injection or placebo, in addition to existing therapy. Prof. McMurray designed the trial and was the only UK member of the Executive Committee. The findings, published in 2018, showed that compared to placebo, albiglutide reduced the risk of major adverse CV events by 22% when used in addition to standard care [3.4]. This outcome established the CV safety profile of albiglutide for use in patients with T2D and is one of the few large-scale trials in T2D to show improved CV outcomes while also improving glycaemic control in this high-risk population.

Identifying wider CV benefits of anti-diabetic drugs

Traditionally, surrogate measures of CV risk, such as lowering of glycated haemoglobin (HbA_{1c}), have been used in CV safety trials. In a 2014 review McMurray et al proposed that HF should be systematically evaluated in CVOTs of all new glucose-lowering drugs and, in particular, with hospitalisation for HF as an outcome measure [3.5]. Hospital admission for HF is a common and prognostically important CV complication of T2D and is the one CV outcome that is increased by some glucose-lowering drugs.

In light of this, and given his significant contribution to the evaluation of drug safety for T2D and HF patients, AstraZeneca invited Prof. McMurray to design and lead an international study to evaluate their drug dapagliflozin, which belongs to the sodium-glucose co-transporter-2 (SGLT-2) family of glucose-lowering drugs [3.6]. This study, called **DAPA-HF**, unlike a standard CVOT, aimed to assess the CV benefits of an anti-diabetic drug in HF patients, both with and without T2D. It was the first trial to explore SLGLT2 inhibitors for use outside of T2D. Between 2017–18, the phase-3 DAPA-HF study assigned 4,744 patients with a diagnosis of HF with reduced ejection fraction (HFrEF) to dapagliflozin or placebo, in addition to recommended therapy. HFrEF is where insufficient blood is pumped from the heart's left side and comprises ~50% of HF cases. The UofG's Dr Jhund was the independent statistician and Prof. Petrie was the UK lead for this trial. The findings, published in 2019, showed that dapagliflozin reduced the first episode of worsening HF (e.g. hospitalisation for HFrEF) or death from CV causes by 26%, compared to placebo [3.6]. These benefits, seen across all age groups, were in addition to those provided by other guideline-directed therapy, which over 95% of participants were on. Furthermore, dapagliflozin was as effective in patients without T2D (~55% of participants) as in those with T2D. 58% of patients (n=1,383) also had a clinically meaningful increase in their quality of life score after 8 months of treatment, compared with 51% (n=1,207) of the placebo group—one of the largest differences recorded in any trials of drugs or devices for the treatment of HF. This is all the more remarkable given that the placebo group are already on the current recommended therapies.

3. References to the research

1. **McMurray JJV**, et al. (2018). Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure: A Randomized Placebo-Controlled Trial. *JACC Heart Fail*. 6(1):8-17. (doi: 10.1016/j.jchf.2017.08.004)
2. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, **McMurray JJ**, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. (2015) Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 373(23):2247-57. (doi: 10.1056/NEJMoa1509225)

3. Fisher M, **Petrie MC**, Ambery PD, Donaldson J, Ye J, **McMurray JJ**. (2015) Cardiovascular safety of albiglutide in the Harmony programme: a meta-analysis. *Lancet Diabetes Endocrinol*. 3(9):697-703. (doi: 10.1016/S2213-8587(15)00233-8)
4. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, Thorpe KM, **McMurray JJV**, Del Prato S; Harmony Outcomes committees and investigators. (2018) Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 392:1519-1529. (doi: 10.1016/S0140-6736(18)32261-X)
5. **McMurray JVV**, et al. (2014) Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol*. 2:843-51 (doi: 10.1016/S2213-8587(14)70031-2)
6. **McMurray JJV**, et al. (2019) Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 381(21):1995-2008. (doi: 10.1056/NEJMoa1911303)

Grants: All sponsored by the respective pharmaceutical companies.

4. Details of the impact

Patients with T2D make up 30–40% of the ~20 million HF patients in Europe and the USA, with CV events the leading cause of death and disability in this group. CV mortality rates, including death caused by worsening HF, are 50–90% greater in patients with T2D and HF. FDA guidance in 2008 stated the importance of determining the CV safety of T2D medicines. In response, UofG researchers have provided vitally important data for regulatory and healthcare provider approval through randomised controlled trials to determine the safety of diabetic medications in treatment populations. These studies also provided key data on the complex interactions between T2D and HF, helping to demonstrate the value of different classes of new glucose-lowering drugs and the wider populations who might benefit from them.

Regulatory approval

UofG has provided the pre- and post-marketing CVOTs necessary to secure the approval of four glucose-lowering drugs (vildagliptin, lixisenatide, albiglutide and dapagliflozin), ensuring their safe use in T2D patients at high CV risk. These drugs are used in over 130 countries worldwide with over 17 million patients and have earned over USD8 billion in sales.

- **Vildagliptin:** was conditionally approved by the EMA in February 2008 (under the brand name Galvus, Novartis), but required a post-approval CVOT. **VIVIDD** [3.1], demonstrated CV safety to the EMA in 2013, as described within the summary of product characteristics [5.A]. As a result of the VIVIDD trial, within the current REF2021 period, the drug has continued to be marketed in over 130 countries (20 more since 2013), prescribed to 17 million patients since launch and earning USD7.5 billion between 2014–2019 [5.B].
- **Lixisenatide: ELIXA** [3.2] was the pivotal trial that confirmed, for FDA approval in 2016, the CV safety of lixisenatide (brand name Adlyxin, Sanofi). Following discussions with the FDA in 2013, Sanofi had withdrawn their previous regulatory submission pending completion of ELIXA to address the FDA's request to demonstrate CV safety [5.C1]. The **ELIXA** results are described in the FDA drug label [5.C2&3], and the drug launched in the USA in January 2017. A combination drug comprising Adlyxin together with insulin glargine was approved by the FDA (Soliqua, 2016) and EMA (Suliqua, 2017) with **ELIXA** data establishing the CV safety of the Adlyxin component [5.D1–3]. Launched in 2018, these products are available for use in 20 countries and have earned EUR39 million and EUR122 million, respectively [5.D4]
- **Albiglutide**: **The Harmony meta-analysis** findings [3.3] provided to regulators led to the approval for use in the USA in April 2014 (brand name Tanzeum, GlaxoSmithKline) [5.E1] and in the EU (brand name Eperzan) [5.E2]. Between 2014–2018 the drug earned GBP286 million [5.E3] (GSK withdrew the drug from the market in July 2018 solely on commercial grounds, owing to over-competition in a crowded market) [5.E4].
- **Dapagliflozin**: as a result of the **DAPA-HF** findings [5.F1], in January 2020 the FDA granted priority review of dapagliflozin for adults diagnosed with HFrEF, irrespective of T2D status. The FDA approved dapagliflozin (Farxiga) in the USA for this new indication on 6 May 2020

[5.F2], the first T2D medication to be approved in HF. Subsequent approvals followed in Canada, Switzerland and India by July and the European Union (including UK) in November 2020 [5.F3].

Changes in use: glucose-lowering drug classes
UofG research has added to the weight of evidence demonstrating that certain classes of glucose-lowering drugs can reduce HF and offer CV benefits, in particular the SGLT-2 inhibitors (which are preferred for patients with HF) and GLP-1RAs (preferred for patients at risk of major adverse cardiac events, such as heart attack and stroke).

SGLT-2 inhibitors
Dapagliflozin (brand name Farxiga, AstraZeneca) was already approved worldwide for use in patients with T2D to lower blood glucose and reduce *the risk* of HF in T2D patients with multiple CV risk factors. However, the **DAPA-HF** trial allowed changes in clinical practice by showing that SGLT2 inhibitors can also be used as *a new treatment for patients with a diagnosis of HFrEF*, rather than just to prevent HF. The November 2019 trial findings led initially to dapagliflozin being used to treat HFrEF in T2D patients, as it was already approved for use in T2D.

- The 2019 update to the 2018 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines, citing DAPA-HF [3.5], state that '**SGLT2 inhibitors are recommended in patients with type-2 diabetes and HF, particularly those with HFrEF, to reduce hHF** [hospitalisation for HF]**, MACE** [major adverse CV events]**, and CV death**' [5.G]. This can be considered in patients irrespective of their baseline HbA_{1c} target, recognising the benefit the drug offers beyond lowering blood sugar.
- A 2020 European Society of Cardiology (ESC) and Heart Failure Association position paper highlighted the positive role and safety of new glucose-lowering drugs in patients with HF, stating that **dapagliflozin can be considered in patients with T2D and HFrEF**, citing DAPA-HF as a key trial throughout [5.H].
- The 2020 Canadian Cardiovascular Society HF practice guidelines recommend **use of dapagliflozin in HFrEF in patients *both with and without a T2D diagnosis*** [5.I].

DAPA-HF data *led directly* to both FDA and European Union approval of dapagliflozin to treat HFrEF independent of T2D status—transforming an anti-diabetes drug into a HF drug. The new indication **extends this drug's application to treat an additional 2.1 million non-diabetic HFrEF patients in the USA** that are projected to be candidates for SGLT2 inhibitor therapy (69% of the 3.1 million HFrEF patients). Empirical estimates indicate that its **new use in this group will prevent up to 34,125 deaths per year in the USA** [5.J]. Meanwhile, a July 2020 UK health economic paper estimated dapagliflozin is cost-effective at £5822 per quality adjusted life year (QALY). This estimated an increase in per patient life-years and QALYs from 5.62 to 6.20 (+0.58) and 4.13 to 4.61 (+0.48), respectively, and 14 fewer deaths after 1 year (and 57 fewer after 5 years) per 1000 treated patients [5.K]. In August 2020, the **American College of Cardiology and the ADA issued a joint endorsement for dapagliflozin to reduce the risk of CV death and hospitalisation for HF in adults with HFrEF** [5.L].

GLP1-Receptor Agonists
While albiglutide was only marketed for four years, in 2018 the **Harmony Outcomes** findings provided critical insights into the significant CV benefits of the drug in patients with T2D, assuaging any remaining doubts about the CV effects of the GLP-1RA class of drugs as a whole. This trial's findings support other evidence that the drugs in the GLP-1RA class can be used as part of a strategy to reduce the risk of CV events. The **Harmony Outcomes** trial is one of five trials cited as directly supporting ESC diabetes guidelines that **recommend that GLP1-RAs be considered for T2D patients with prevalent, or high risk of, CV disease** [5.M].

5. Sources to corroborate the impact [PDFs provided unless otherwise indicated]

A. Galvus vildagliptin, annex 1, Guideline on Summary of Product Characteristics [Direct link] (SmPC), European Medicines Agency (Section on clinical efficacy and safety, p.13, para 3)

B. Vildagliptin: (1) Patient numbers: Mathieu *et al*. (2017) *Eur Endocrinol*.13:68–72. (doi: 10.17925/EE.2017.13.02.68); (2) Earnings calculated from Novartis Annual Reports (2014–19); and (3) Number of approvals: SEC Form F20, p.49.

C. Lixisenatide: (1) FDA Approves Adlyxin, 28 July 2016; (2) Adlyxin label, FDA (Section 14.6 – section on ELIXA outcomes); and (3) Adlyxin NDA submission review, FDA (see Clinical Inspection Summary, p.59 of PDF)

D. (1) Soliqua (North America): Frias *et al*. (2019). A Review of the Safety and Adverse Event Profile of the Fixed-Ratio Combination of Insulin Glargine and Lixisenatide. *Diabetes Ther.10:* 21–33. (doi: 10.1007/s13300-018-0547-5) (see p.29); (2) Suliqua (Europe): EMA Summary of Product Characteristics [direct link, see p.19]; and (3) Sanofi press release, February 2020 (p.67).

E. Albiglutide: (1) Center for Drug Evaluation & Research, FDA, 15 April 2015: Summary review, Cardiovascular Risk Assessment (p.14–15) and Statistical Reviews; (2) EMA CHMP Assessment Report, 23 January 2014 (refers to meta-analysis throughout); (3) Albiglutide earnings data calculated from GSK annual reports 2014–18; (4) EMA notice of Eperzan/Tanzeum withdrawal from market, November, 2018.

F. Dapagliflozin approvals in heart failure: (1) FDA Farxiga label (5 May 2020), new indication listed p.1, description of DAPA-HF on p.38, Section 14.3; (2) FDA approval of dapagliflozin for heart failure (4 May 2020); (3) European Union approval (5 November 2020)

G. Buse *et al*. (2019) 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*, 43(2):487-493. doi: 10.2337/dci19-0066 (ref.8, p.488)

H. Seferović *et al*. (2020) European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. *Eur J Heart Fail*. 22(2):196-213 (Section beginning p.8, see p.9 and final paras of p.12)

I. O'Meara *et al*. (2020) CCS/CHFS Heart Failure Guidelines. *Can J Cardiol*. 36: 159–169, doi: 10.1016/j.cjca.2019.11.036. (See page 165 'Established HF due to reduced LVEF' and recommendations 8 & 9, p. 166)

J. Bassi *et al*. (2020) Association of Optimal Implementation of Sodium-Glucose Cotransporter 2 Inhibitor Therapy with Outcome for Patients with Heart Failure. *JAMA Cardiol*. doi:10.1001/jamacardio.2020.0898

K. McEwan *et al*. (2020) Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. *Eur. J. Heart Fail*., doi: 10.1002/ejhf.1978

L. 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes. *JACA*, 76:1117–1145, doi: 10.1016/j.jacc.2020.05.037 (Section 5.3, Table 5, p.1131; and Figure 2, p.1133)

M. Cosentino *et al*. (2019) 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J*, 41 (2): 255–323 doi: 10.1093/eurheartj/ehz486. (Table 4 [level 2b], section 7.1.2.3 and Fig.3)