Institution: University of Dundee		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: Use of population-based health informatics research to improve care for patients with cardio-metabolic diseases		
Period when the underpinning research was undertaken: 2000-2020		
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:**
Chim C. Lang Alastair Emslie-Smith Andrew Morris	Professor of Cardiology Clinical Research Fellow Reader/Professor	2004 to date July 2000 – Aug 2003 April 2000 – Aug 2014
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

The University of Dundee has pioneered the use of population-based integrated electronic health records for drug safety studies. The availability of such records creates affordable and efficient research opportunities, benefitting from large sample size and generalisable patient populations. Professor **Lang** has exploited this, demonstrating how enhanced linkage to vital records can support regulatory decision-making and guideline development, thus widening treatment options to improve health outcomes. His research has evidenced treatment targets and safe use of drugs in cardiovascular settings in which they would previously have been avoided.

2. Underpinning research

Electronic health records (EHRs) can be used to support evidence-based clinical decision-making where no randomised controlled trials exist, randomisation would be unethical or the diversity of the patient population means that informative trials would have to be unaffordably large.

This case study exemplifies the use of EHRs to address key knowledge gaps in Type II diabetes and chronic heart disease. It addresses two common and important clinical scenarios in which the absence of randomised trial data makes it difficult to outline an evidence-based treatment strategy.

Through its Tayside Medicine Monitoring Unit (MEMO) and Health Informatics Centre (HIC), which maintains a clinical data repository of eHealth data covering approximately 20% of the Scottish population and extending back 30 years, the University of Dundee pioneered the use of EHRs for drug safety studies. Working with MEMO and HIC, **Lang** linked EHRs with key cardiac investigations including echocardiograms to generate population data which was used to demonstrate the safe use of drugs that had previously been avoided because of perceived contraindications.

One such scenario is renin-angiotensin system (RAS) blockade in aortic stenosis, the commonest form of valvular heart disease in North America and Western Europe, affecting 2-4% of adults >65 years of age. Hypertension is a common comorbidity in patients with asymptomatic aortic stenosis; it is associated with a 56% higher incidence of cardiovascular events and a doubling in mortality. There was, until recently, uncertainty about the best drug treatment for this condition, but the role of the RAS in adverse left ventricular remodelling in aortic stenosis

suggested the possibility of using RAS blockers. Population-based EHR research on 2117 aortic stenosis patients demonstrated a 23% reduction in cardiovascular events and 24% fewer deaths with RAS blockade **[R1]**. **Lang**'s team was the first to provide this key observational evidence that angiotensin-converting enzyme inhibitors or angiotensin II receptor 1 blockers are safe to use and associated with improved outcome in both aortic stenosis **[R1]** and aortic regurgitation **[R2]**.

A second scenario is Type II diabetes and heart failure, a common, lethal disease combination. The prevalence of this combination in heart failure cohorts is 10-47% while in Type II diabetes it is 9-22%. **Lang**'s team investigated the use of metformin, which was previously listed as contraindicated in heart failure in both the British National Formulary (BNF) and Physicians' Desk Reference because of concerns regarding lactic acidosis, in these patients. Analysis (published in 2001 and 2010) of the EHRs of 1847 Type II diabetics who had redeemed prescriptions for metformin between January 1993 and June 1995 showed that metformin was not only safe to use **[R3**; **Emslie-Smith, Morris** and colleagues**]** but possibly associated with improved survival in patients with concomitant Type II diabetes mellitus and heart failure **[R4]**.

Lang's team also demonstrated the existence of a U-shaped relationship between HbA_{1c} in both incident heart failure and mortality in patients with Type II diabetes and heart failure, the lowest risk being observed in patients with moderate glycaemic control (HbA_{1c} 7.1-8.0%) **[R5, R6]**. This was important because, when combined with evidence that metformin could safely be used in patients with heart failure, it opened up the possibility of using this cheap, convenient oral treatment to maintain moderate glycaemic control in heart failure patients.

3. References to the research

[R1] Nadir, M. A., Wei, L., Elder, D. H., Libianto, R., Lim, T. K., Pauriah, M., Pringle, S. D., Doney, A. D., Choy, A. M., Struthers, A. D. & **Lang**, C. C. (2011) Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. *Journal of the American College of Cardiology,* 58 (6)**,** pp. 570-576; DOI: 10.1016/j.jacc.2011.01.063.

[R2] Elder, D. H., Wei, L., Szwejkowski, B. R., Libianto, R., Nadir, A., Pauriah, M., Rekhraj, S., Lim, T. K., George, J., Doney, A., Pringle, S. D., Choy, A. M., Struthers, A. D. & **Lang**, C. C. (2011) The impact of renin-angiotensin-aldosterone system blockade on heart failure outcomes and mortality in patients identified to have aortic regurgitation: A large population cohort study. *Journal of the American College of Cardiology,* 58 (20)**,** pp. 2084-2091; DOI: 10.1016/j.jacc.2011.07.043.

[R3] Emslie-Smith, A. M., Boyle, D. I., Evans, J. M., Sullivan, F. & **Morris, A. D**. (2001) Contraindications to metformin therapy in patients with Type 2 diabetes - A population-based study of adherence to prescribing guidelines. *Diabetic Medicine,* 18 (6)**,** pp.483-488; DOI: 10.1046/j.1464-5491.2001.00509.x.

[R4] Evans, J. M., Doney, A. S., Alzadjali, M. A., Ogston, S. A., Petrie, J. R., Morris, A. D., Struthers, A. D., Wong, A. K. & **Lang**, C. C. (2010) Effect of metformin on mortality in patients with heart failure and Type 2 diabetes mellitus. *American Journal of Cardiology,* 106 (7)**,** pp. 1006-1010; DOI: 10.1016/j.amjcard.2010.05.031.

[R5] Elder, D. H., Singh, J. S., Levin, D., Donnelly, L. A., Choy, A. M., George, J., Struthers, A. D., Doney, A. S. & **Lang**, C. C. (2016) Mean HbA_{1c} and mortality in diabetic individuals with heart failure: a population cohort study. *European Journal of Heart Failure,* 18 (1)**,** pp. 94-102; DOI: 10.1002/ejhf.455.

[R6] Parry, H. M., Deshmukh, H., Levin, D., Van Zuydam, N., Elder, D. H., Morris, A. D., Struthers, A. D., Palmer, C. N., Doney, A. S. & **Lang**, C. C. (2015) Both high and low HbA_{1c} predict incident heart failure in Type 2 diabetes mellitus. *Circulation: Heart Failure,* 8 (2)**,** pp. 236-242; DOI: 10.1161/circheartfailure.113.000920.

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British Heart Foundation: PG/06/143/21897 £175,467 Chim **Lang**

British Heart Foundation (2019-2022): "Immunometabolic Remodelling of Monocyte and Macrophage Responses by Metformin in Non-diabetic CVD", PG/18/79/34106, £205,642, Chim **Lang** and Graham Rena

4. Details of the impact

Lang's work has influenced guideline development and changed prescribing practice in both aortic stenosis and Type II diabetics with heart failure. His analysis of EHRs has been cited in professional body guidelines and scientific statements, leading to changes in prescribing practice. It also provided support for post-hoc analysis of clinical trials which identified potential benefits of RAS inhibitors in reducing hospital readmissions (thus benefitting patients and relieving pressure on health services) and mortality following transcatheter aortic valve implantation (TAVI) for aortic stenosis; this contributed to the design of the first study to prospectively explore the impact of RAS modulation in ventricular remodelling following TAVI.

Changing guidelines and practice and widening treatment options in Aortic Stenosis

By demonstrating that the use of RAS blockers in aortic stenosis is both safe and effective **[R1], Lang** influenced the development of American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the management of valvular heart disease; **R1** is one of three studies cited in the 2014 Guidelines **[E1]** as underpinning evidence for the use of RAS blockers as anti-hypertensives in patients with aortic stenosis (Class 1, Level of Evidence: B). It also contributed to the development of advice on target blood pressure in aortic stenosis patients **[E2]**. The Guidelines Writing Committee Co-Chair writes **[E3]**:

> … the evidence provided by Professor **Lang**'s research was used to support the recommendations for management of adults with aortic stenosis in both the 2014 and 2020 American College of Cardiology/American Heart Association Valvular Heart Disease Clinical Practice Guidelines.

R1 has also been cited in support of post-hoc analyses of large randomised controlled trials (e.g. PARTNER-2) **[E4]** and nationwide registry data **[E5]** investigating the benefit of RAS blockade in aortic stenosis patients undergoing TAVI. In both scenarios, treatment with RAS blockers was associated with reduced mortality 1-3 years post-procedure. In the case of treatment at discharge there was also a reduction in readmission to hospital due to heart failure **[E5]**. This secondary analysis contributed to the latest ACC/AHA guidelines on the use of RAS in TAVI, which state that "In patients who have undergone TAVI, RAS blockers may be considered to reduce the long-term risk of all-cause mortality" **[E2]**. **R1** also helped to underpin the RASTAVI trial (NCT03201185) **[E6]**, a randomised open label study examining the impact of RAS blockers on clinical outcomes and ventricular remodelling after TAVI. This work has directly influenced clinical practice guidelines on the treatment of hypertension in patients with aortic stenosis and indirectly contributed to the provision of additional medication options for aortic stenosis patients undergoing TAVI.

Changing guidelines and practice and widening treatment options in Type II diabetes with concomitant heart failure

In 2016, the FDA lifted its warning on the use of metformin in certain patients with reduced kidney function, acknowledging **Lang**'s evidence **[R3]** that metformin could safely be used in clinical practice outwith the then-current labelling indications **[E7]**. Prescribing practice has also changed in the UK: the BNF now advocates 'caution' when using metformin in patients with chronic stable heart failure rather than listing heart failure as a contraindication for metformin.

At around the same time the AHA issued a Scientific Consensus Statement **[E8]** which recognised **Lang's** work demonstrating the safe use of metformin to achieve glycaemic control in patients suffering from Type II diabetes with concomitant heart failure. In 2019 the AHA and the Heart Failure Society of America (HFSA) issued a joint Scientific Statement **[E9]** identifying metformin as a treatment option in this group. This noted **Lang**'s evidence that metformin has a more acceptable safety profile than sulphonylureas and meant that patients with Type II diabetes and heart failure could be given metformin, which had previously been contraindicated in this group, thus changing clinical practice guidelines and widening treatment options.

Metformin can therefore be used to help achieve glycaemic control and HbA_{1c} targets as recommended by contemporary clinical practice guidelines. The underpinning evidence of **Lang**'s team **[R5]** and others has influenced the development of advice on glycaemic control in patients with Type II diabetes and heart failure **[E9]**; the Co-Chair of Authors of the 2019 AHA/HFSA Scientific Statement writes **[E10]**:

> … the Dundee group's research on metformin use has also been impactful… showing that metformin is safe and may be beneficial in patients with HF. In the 2019 Scientific Statement, we considered use of metformin in patients with DM at risk of or with established HF to be *reasonable*.
>
> Based on the above, I recognize the influence of Professor **Lang**'s group in guiding doctors on how to treat patients with DM and HF and wholeheartedly support his research agenda.

The Co-Chairs of Authors of the AHA/HFSA Scientific Statement **[E9]** and the ACC/AHA Valve Disease Guidelines **[E2]** both confirm **Lang**'s work influence on approaches to treatment across the world; indeed, the latter states **[E3]**:

> Professor **Lang**'s research on RAS blockers in aortic valvular heart disease is a major therapeutic advance that has significant clinical impact and provides the foundation for evidence-based guidelines.

5. Sources to corroborate the impact

[E1] Nishimura, R. A., Otto, C. M., Bonow, R. O., Carabello, B. A., Erwin, J. P., III, Guyton, R. A., O'Gara, P. T., Ruiz, C. E., Skubas, N. J., Sorajja, P., Sundt, T. M., III & Thomas, J. D. (2014) 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: Executive Summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation,* 129 (23)**,** pp. 2440-2492; DOI: 10.1161/cir.0000000000000029. **R1** is cited in Section 3.3 (Reference 53); **R2** is cited in Section 4.3 (Reference 90).

[E2] Otto, C. M., Nishimura, R. A., Bonow, R. O., Carabello, B. A., Erwin, J. P., III, Gentile, F., Jneid, H., Krieger, E. V., Mack, M., McLeod, C., O'Gara, P. T., Rigolin, V. H., Sundt, T. M., III, Thompson, A. & Toly, C. (2020) 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation***,** 143 (5), pp. e72-e227; DOI: 10.1161/cir.0000000000000923. **R1** is cited in Section 3.2.2 (Reference 11); **R2** is cited in Section 4.3.2 (Reference 5).

[E3] Co-Chair 2020, 2017 and 2014 ACC/AHA Valve Disease Guidelines Writing Committees. Re: REF2021. Letter of Support, 18th January 2021.

[E4] Chen, S., Redfors, B., Nazif, T., Kirtane, A., Crowley, A., Ben-Yehuda, O., Kapadia, S., Finn, M. T., Goel, S., Lindman, B. R., Alu, M. C., Chau, K. H., Thourani, V. H., Vahl, T. P., Douglas, P. S., Kodali, S. K. & Leon, M. B. (2020) Impact of renin-angiotensin system inhibitors on clinical outcomes in patients with severe aortic stenosis undergoing transcatheter aortic valve

replacement: An analysis of from the PARTNER 2 trial and registries. *European Heart Journal,* 41 (8)**,** pp. 943-954; DOI: 10.1093/eurheartj/ehz769. **R1** is cited in the first paragraph on page 949 (Reference 20).

[E5] Inohara, T., Manandhar, P., Kosinski, A. S., Matsouaka, R. A., Kohsaka, S., Mentz, R. J., Thourani, V. H., Carroll, J. D., Kirtane, A. J., Bavaria, J. E., Cohen, D. J., Kiefer, T. L., Gaca, J. G., Kapadia, S. R., Peterson, E. D. & Vemulapalli, S. 2018. Association of renin-angiotensin inhibitor treatment with mortality and heart failure readmission in patients with transcatheter aortic valve replacement. JAMA*,* 320 (21)**,** pp. 2231-2241; DOI: 10.1001/jama.2018.18077. **R1** is cited in paragraph 2 on page 2232 (Reference 6).

[E6] Amat-Santos, I. J., Catalá, P., Diez Del Hoyo, F., Fernandez-Diaz, J. A., Alonso-Briales, J. H., Del Trigo, M., Regueiro, A., Juan-Salvadores, P., Serra, V., Gutierrez-Ibanes, E., Muñoz-García, A. J., Nombela-Franco, L., Sabate, M., Jimenez-Diaz, V. A., García Del Blanco, B., López, J., Varela-Falcón, L. H., Sevilla, T., Arnold, R., Revilla, A. & San Roman, J. A. (2018) Impact of renin-angiotensin system inhibitors on clinical outcomes and ventricular remodelling after transcatheter aortic valve implantation: Rationale and design of the RASTAVI randomised multicentre study. *BMJ Open,* 8**,** e020255; DOI: 10.1136/bmjopen-2017-020255. **R1** is cited under Statistical Analysis on page 3 (Reference 22).

[E7] US Food and Drug Administration. (2016) *FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function* [Online]. Available: https://www.fda.gov/media/96771/download [Accessed 30th December 2020]. **R3** is cited in the Data Summary (Reference 7).

[E8] Bozkurt, B., Aguilar, D., Deswal, A., Dunbar, S. B., Francis, G. S., Horwich, T., Jessup, M., Kosiborod, M., Pritchett, A. M., Ramasubbu, K., Rosendorff, C. & Yancy, C. (2016) Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: A Scientific Statement from the American Heart Association. *Circulation,* 134 (23)**,** pp. e535-e578; DOI: 10.1161/cir.0000000000000450. **R4** is cited near the top of e456 (Reference 144).

[E9] Dunlay, S. M., Givertz, M. M., Aguilar, D., Allen, L. A., Chan, M., Desai, A. S., Deswal, A., Dickson, V. V., Kosiborod, M. N., Lekavich, C. L., McCoy, R. G., Mentz, R. J. & Piña, I. L. (2019) Type 2 diabetes mellitus and heart failure: A Scientific Statement from the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA Heart Failure Guideline Update. *Circulation,* 140 (7)**,** pp. e294-e324; DOI: 10.1161/cir.0000000000000691. **R4** is cited in the last paragraph of e301 (Reference 127); **R5** is cited in paragraph 2 of e298 (Reference 105); **R6** is cited in paragraph 2 of e298 (Reference 104)

[E10] Co-Chair Scientific Statement from the American Heart Association and the Heart Failure Society of America 2021. Re: REF2021 Application Entitled, “Use of population-based health informatics research to improve care for patients with cardio-metabolic diseases”. Letter of Support, 15th January 2021.