Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Global implementation of Instantaneous wave-free ratio (iFR) to diagnose coronary stenosis.

Period when the underpinning research was undertaken: 2006 - present

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:
Justin Davies	Senior Clinical Research Fellow	2003 - 2018
Jamil Mayet	Professor of Cardiology (Honorary)	2000 - present
Darrel Francis	Professor of Cardiology	2005 - present
Alun Hughes	Professor of Clinical Pharmacology	2001 - 2013
Kim Parker	Emeritus Professor of Physiological Fluid Mechanics & Senior Research Investigator	1988 - present

Period when the claimed impact occurred: 2013 - present

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

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

Instantaneous wave-free ratio (iFR) is a diagnostic tool that was invented and developed by Imperial College to assess whether a narrowing in a coronary artery is limiting blood flow to the myocardium. It is used to stratify selection of patients for surgery, stenting or medical management. It has been shown to reduce procedural time and costs by 10% compared to the leading alternative (Fractional Flow Reserve) in two large randomised clinical trials. iFR received FDA approval in 2014, is licensed to Volcano-Philips and used in over 5,000 clinical cardiac catheter labs in more than 30 countries.

2. Underpinning research (indicative maximum 500 words)

Coronary artery blockages or stenoses limit blood flow to the heart muscle and can cause angina. Relief of a stenosis by stenting aims to restore vessel patency, improve blood flow and reduce angina symptoms. However, unless stenoses are flow limiting, they can be safely left alone without stenting or surgery, reducing patient exposure to unnecessary procedures and potential complications.

Fractional Flow Reserve (FFR) was the main technique to determine the need for clinical intervention by measuring the pressure drop across a stenosis. This assesses systolic pressure under the condition of maximal vessel dilation, which is dependent on administration of adenosine. The latter adds time to the procedure and often causes significant chest pain. Instantaneous wave-free ratio (iFR) was developed at Imperial College as alternative technique.

The idea emerged from a cardiology-bioengineer collaboration and is based on a technique called wave intensity analysis used in peripheral arterial physiology. Translating it to the coronary arteries was challenging because of the complex relationship between pressure and

flow in arteries supplying the myocardium. From 2006 these technical challenges were overcome (1) and Davies and colleagues at Imperial College conducted a series of studies to understand the factors influencing coronary flow in human physiology and pathology (2, 3).

During these studies they recognised that there was a period in diastole when there are no reflected arterial waves influencing flow and realised that if pressure was monitored at this time point, it would provide a surrogate for flow measurement without needing vasodilation (negating the need for adenosine). This led to the invention of iFR in 2010 and its development and validation as a clinical tool in the clinical cardiac catheter labs at Imperial College Healthcare NHS Trust (ICHT) against the then gold standard FFR (4). The iFR technology was patented by Imperial Innovations and licenced to Volcano-Philips in 2014.

Davies and colleagues then led an international multicentre randomised controlled trial (DEFINE-FLAIR; recruiting 2,492 patients) to compare iFR with FFR (5). Patients were recruited if they had coronary artery disease causing a stenosis of questionable physiological severity in at least one native artery (typically, an artery with 40 to 70% stenosis of the diameter on visual assessment). The study randomly assigned patients to undergo iFR or FFR, and either inserted a stent or not, depending on the measurements. Patients were followed up for 12 months after the procedure. There were no significant differences between the two techniques in subsequent heart attack or mortality, but procedural time was 10% quicker with iFR and it was associated with a 90% reduction in adverse procedure events compared to FFR. These findings were confirmed in an independent study of 2,037 patients by a Swedish group (iFR-SWEDEHEART).

A subsequent study has shown that iFR can assess serial stenoses in coronary arteries, which is an important limitation of FFR (6).

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

(1) Davies, J.E., Whinnett, Z.I., Francis, D.P., Willson, K., Foale, R.A., Malik, I.S., Hughes, A.D., Parker, K.H., Mayet, J. (2006). Use of simultaneous pressure and velocity measurements to estimate arterial wave speed at a single site in humans. *Am J Physiol Heart Circ Physiol*; 290:878-885. DOI.

(2) Davies, J.E., Whinnett, Z.I., Francis, D.P., Willson, K., Foale, R.A., Malik, I.S., Hughes, A.D., Parker, K.H., Mayet, J. (2006). Evidence of a dominant backward-propagating "suction" wave, responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*; 113:1768-78. DOI.

(3) Davies, J.E., Sen, S., Broyd, C., Hadjiloizou, N., Baksi, J., Francis, D.P., Foale, R.A., Parker, K.H., Hughes, A.D., Chukwuemeka, A., Casula, R., Malik, I.S., Mikhail, G.W., Mayet, J. (2011). Arterial pulse wave dynamics after percutaneous aortic valve replacement: fall in coronary diastolic suction with increasing heart rate as a basis for angina symptoms in aortic stenosis. *Circulation*; 124:1565-72. DOI.

(4) Sen, S., Escaned, J., Malik, I.S., Mikhail, G.W., Foale, R.A., Mila, R., Tarkin, J., Petraco, R., Broyd, C., Jabbour, R., Sethi, A., Baker, C.S., Bellamy, M., Al-Bustami, M., Hackett, D., Khan, M., Lefroy, D., Parker, K.H., Hughes, A.D., Francis, D.P., Di Marlo, C., Mayet, J., & Davies, J.E. (2012). Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *Journal of the American College of Cardiology*; 59 (15): 1392-402. DOI.

(5) Davies, J.E., Sen, S., Dehbi, H.-M., Al-Lamee, R., Petraco, R., Nijjer, S.S., Bhindi, R., Lehman, S.J., Walters, D., Sapontis, J., Janssens, L., Vrints, C.J., Khashaba, A., Laine, M., Van Belle, E., Krackhardt, F., W., et al. (2017). Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med*; 376: 1824-34. DOI.

(6) Kikuta, Y., Cook, C.M., Sharp, A.S.P., Salinas, P., Kawase,Y., Shiono, Y., Giavarini, A., Nakayama, M., De Rosa, S., Sen, S., Nijjer, S.S., Al-Lamee, R., Petraco, R., Malik, I.S., Mikhail, G.W., Kaprielian, R.R., … Davies, J.E. (2018). Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Predicts Hemodynamic Outcome in Humans with Coronary Artery Disease: Primary Results of the International Multicenter iFR GRADIENT Registry. *Jacc Cardiovasc Interv*; 11(8): 757-767. DOI.

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

Coronary heart disease (CHD) is now the leading cause of death worldwide. An estimated 3,800,000 men and 3,400,000 women die each year from CHD. The primary cause of this is atherosclerosis that reduces blood flow through the coronary arteries to the heart muscle and can result in angina, heart attack and lead to heart failure and arrhythmias.

The diagnostic workup of patients with angina includes a coronary angiogram to view and measure blood flow in the major coronary vessels. Flow through coronary artery stenoses is measured to assess whether patients might benefit from coronary artery bypass grafting or percutaneous coronary intervention (PCI), usually with coronary stenting. More than 5,000,000 PCIs are performed annually worldwide.

It is difficult to differentiate between functionally significant coronary stenosis and a narrowing that is not substantially affecting blood supply using visual assessment of 2D images from coronary angiograms. Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) provide a functional assessment of the stenosis by more accurately measuring if there is a pressure drop across the site of blockage.

Unlike FFR, iFR does not require the use of hyperemic agents such as adenosine. Use of adenosine can cause severe chest pain and is contraindicated in asthmatics as it can cause bronchospasm. Eliminating the need for adenosine means that iFR can be performed more quickly than FFR, since a pressure wire can be advanced instantly during the procedure without waiting for the drug to be injected, and it is more comfortable for patients, as there is no flushing. The iFR SWEDEHEART trial reported that with no hyperemic agent, a 95.7% reduction in patient discomfort could be achieved using an iFR guided strategy [**A**]. iFR is also more a cost-effective treatment, with a 10% cost reduction and 25% reduction in hospital readmissions [**A**]. The 10% reduction in cost compared to FFR is a saving of approximately $900 per patient [**B**].

The iFR technology created by Dr Davies and colleagues at Imperial was patented in 2010 and subsequently licensed to Volcano (a developer and manufacturer of precision guided therapy tools). It was CE marked and received FDA clearance in 2014 [**C**]. It is now used in over 5,000 catheter labs around the world [**D**].

iFR is recommended in all the major cardiology guidelines, including the 2018 European Society of Cardiology (ESC) and European Association of Cardio-Thoracic Surgery (EACTS) guidelines [**E**] in which it is included as a Class IA recommendation "… *iwFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis*" [**E**]. In the worldwide 2017 ACC/AHA/SCAI guidelines (which include the Appropriate Use Criteria) iFR is included as a measurement tool (described as physiological pressure measurement not requiring hyperemia) [**F**].

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

[**A**] Götberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Öhagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Tödt T, Venetsanos D, James SK, Kåregren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Fröbert O; iFR-SWEDEHEART Investigators. Instantaneous

Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med*. 2017 May 11;376(19):1813-1823. DOI.

[**B**] https://www.philips.com/c-dam/b2bhc/master/education-resources/technologies/igt/images/ifr-class-of-its-own-flyer.pdf?_ga=2.11020532.130870662.1599822809-1614149729.1599822809 (Archived here)

[**C**] https://www.nsmedicaldevices.com/news/volcano-obtains-fda-clearance-of-its-instant-wave-free-ratio-modality-200314-4200181/ http://www.ptca.org/news/2014/0319_VOLCANO_IFR.html. Archived here.

[**D**] https://www.philips.sa/en/healthcare/education-resources/ifr-outcome-data. Archived here.

[**E**] 2018 ESC/EACTS Guidelines on myocardial revascularization: The task force on myocardial revascularization of the European society of cardiology (ESC) and European association for cardio-thoracic surgery (EACTS). *Eur Heart J*. 2018;00:1-96. https://doi.org/10.1093/eurheartj/ehy394 (see recommendation table on page 98 for corroboration).

[**F**] Patel M, et al., ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients with Stable Ischemic Heart Disease. *J Am Coll Cardiol*. 2017 May 2;69(17):2212-2241. https://doi.org/10.1016/j.jacc.2017.02.001 (pages 2218, section 3, point 6).