Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Eliminating Death from Heart Failure in Thalassaemia Major Using T2* Cardiovascular Magnetic Resonance

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

The development of a cardiac magnetic resonance technique at Imperial College and Royal Brompton Hospital to quantify myocardial iron concentration has resulted in the early identification of thalassaemia major patients at risk of heart failure and targeted cardiac treatment with a hitherto little used iron chelator, deferiprone, following randomised controlled trials of efficacy. Since 2008 these advances have resulted in a 71% reduction in cardiac death from myocardial siderosis in thalassemia major in the UK.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Dudley Pennell, Professor of Cardiology (1992-present)
Professor David Firmin, Professor of Biomedical Imaging (1990-present)

Thalassaemia major (TM) is a condition causing profound anaemia that is fatal in childhood unless regular blood transfusions are given. Each unit of blood contains approximately 200mg of iron that cannot be excreted. Unless effective iron chelation treatments are taken throughout life, the iron accumulates causing organ damage and death. Prior to 1998, most TM patients died from heart failure (~75% of patients), and standard monitoring of TM patients consisted of measuring serum ferritin and liver iron concentration. Attempts were made to find empiric thresholds that indicated myocardial siderosis (iron overload). However, the very high death rate from heart failure clearly demonstrated the futility of this approach. The Royal Brompton Hospital and Imperial College Cardiovascular Magnetic Resonance (CMR) Unit therefore launched a research program to directly measure myocardial iron non-invasively.

In 1998, we began assessing cardiac iron from the magnetic disturbance caused by haemosiderin deposited in tissues as a consequence of breakdown of excess ferritin. We wrote CMR pulse sequences to assess T1, T2 and T2* in the heart, which are magnetic relaxation parameters that are affected by the local biochemical environment and T2* was found to be the most robust and sensitive technique in TM patients to identify iron. The new T2* sequence was applied systematically, and we demonstrated the revolutionary finding that liver iron and ferritin did not correlate with cardiac iron. This implied that it was not possible to manage patients in the conventional way, and expect to prevent heart failure and cardiac death. Patients would require direct cardiac iron assessment and treatment directed at cardiac iron (1).

The second major finding was that cardiac iron was unequivocally high in patients with heart failure, and could be reversed with prolonged intensive intravenous chelation with deferoxamine - a difficult and hazardous treatment, but a treatment that saved 6 of 7 lives of the first patients managed in intensive care, a huge improvement on the mortality of historical cohorts with heart failure.

The third major finding was that a little used oral iron chelator, deferiprone, was associated with substantially lower levels of cardiac iron, and higher ejection fractions than matched patients treated with conventional subcutaneous deferoxamine infusions given over 8 hours each night (2).

In 2004, we attracted National Institute of Health funding to validate the T2* technique. Using an international consortium of collaborators, we led the collection of post-mortem hearts from TM patients who died of heart failure and achieved human calibration of myocardial T2* (3). We demonstrated that lethal levels of cardiac iron were very low compared to dangerous levels in the

liver. We also scanned nearly all the UK TM patients and follow them up for clinical events in relation to their baseline T2*. This work proved that a T2* level of 10ms was the threshold for increased heart failure risk, and this is now used internationally to treat TM patients with aggressive chelation (4).

In order to determine best treatment for cardiac iron overload, we ran two randomised controlled trials (2004-2006) to identify how best to remove iron from the heart. Working with ApoPharma, we proved that deferiprone removed cardiac iron better than conventional deferoxamine (5). We also showed in a further trial, that deferiprone could be combined with deferoxamine, especially in severe myocardial siderosis, for synergistic chelation (6).

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

(1) Anderson, L.J., Holden, S., Davies, B., Prescott, E., Charrier, C., Bunce, N.H., Firmin, D.N., Porter, J.B., Wonke, B., Walker, J.M., Pennell, D.J. (2001). Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J*, 22, 2171-2179. DOI. Times cited: 531 (as at 22nd October 2013 on ISI Web of Science). Journal Impact Factor: 14.09.

(2) Anderson, L.J., Wonke, B., Prescott, E., Holden, S., Walker, J.M., Pennell, D.J. (2002). Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. *Lancet*, 360, 516-520. DOI. Times cited: 272 (as at 22nd October 2013 on ISI Web of Science). Journal Impact Factor: 39.06.

(3) Carpenter, J.P., He, T., Kirk, P., Roughton, M., Anderson, L.J., de Noronha, S.V., Sheppard, M.N., Porter, J.B., Walker, J.M., Wood, J.C., Galanello, R., Forni, G., Catani, G., Matta, G., Fucharoen, S., Fleming, A., House, M.J., Black, G., Firmin, D.N., St. Pierre, T.G., Pennell, D.J. (2011). On T2* magnetic resonance and cardiac iron. *Circulation*, 123, 1519-1528. DOI. Times cited: 42 (as at 22nd October 2013 on ISI Web of Science). Journal Impact Factor: 15.20.

(4) Kirk, P., Roughton, M., Porter, J.B., Walker, J.M., Tanner, M.A., Patel, J., Wu, D., Taylor, J., Westwood, M.A., Anderson, L.J., Pennell, D.J. (2009). Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation*, 120, 1961-1968. DOI. Times cited: 103 (as at 22nd October 2013 on ISI Web of Science). Journal Impact Factor: 15.20.

(5) Pennell, D.J., Berdoukas, V., Karagiorga, M., Ladis, V., Piga, A., Aessopos, A., Gotsis, E.D., Tanner, M.A., Smith, G.C., Westwood, M.A., Wonke, B., Galanello, R. (2006). Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. *Blood*, 107, 3738-3744. DOI. Times cited: 199 (as at 22nd October 2013 on ISI Web of Science). Journal Impact Factor: 9.06.

(6) Tanner, M.A., Galanello, R., Dessi, C., Smith, G.C., Westwood, M.A., Agus, A., Roughton, M., Assomull, R., Nair, S.V., Walker, J.M., Pennell, D.J. (2007). A randomized, placebo controlled, double blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation*, 115, 1876-1884. DOI. Times cited: 177 (as at 22nd October 2013 on ISI Web of Science). Journal Impact Factor: 15.20.

Key funding:

- British Heart Foundation (BHF; 1998-2000; £83,637), Principal Investigator (PI), D. Pennell and J. Walker, Assessment of myocardial iron using magnetic resonance T2-relaxometry: Optimisation of chelation therapy in thalassemia for prevention of cardiac mortality (Junior Fellowship)
- BHF (2000-2001; £44,191), PI D. Pennell, Junior fellowship extension
- National Institutes of Health, USA (2004-2009; $1million), PI D. Pennell, MR of Heart Iron: T2*/T2 Calibration and Application
- Novartis (2007-2010; £300,000), PI D. Pennell, Randomised controlled trial comparing oral deferasirox with deferoxamine in patients with transfusion dependent iron overload.

- BHF (2009-2012; £191,140), Co-Principal Investigators (Co-PIs) D. Pennell, J. Carpenter, S. Cook, T. Aitman, E. Petretto, Genetic modifiers of cardiac iron loading in thalassaemia major
- Novartis (2010-2012; £86,269), PI D. Pennell, Evaluation of deferoxamine combined with deferasirox for treatment of cardiac siderosis

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

Impacts include: health and welfare, practitioners and services, public policy and services, commerce
Main beneficiaries include: patients, health professionals, industry

Before the introduction of T2* MR measures, patients at high risk of cardiac complications went undetected. The Imperial research described has allowed early detection of cardiac iron overload in TM major patients which has been incorporated into national and international guidelines.

Follow-up of the UK cohort of TM patients (which represents 97% of the TM population in the UK) has shown a 71% reduction in mortality since the introduction of T2* CMR operating in concert with targeted cardiac iron chelation. This is related to earlier detection of cardiac iron overload and improved treatment, which prevents the onset of heart failure that is associated with a very high mortality rate [1]. A significant reduction in mortality associated with the use of cardiac T2* CMR has been published that is independent of Imperial College in Greece, Cyprus, Italy and Hong Kong. Large studies internationally have demonstrated that the use of deferiprone is associated with lower rates of cardiac death and complications. This confirms the population effect of the cardioprotective nature of deferiprone first demonstrated in our randomised controlled trial [2-3].

Consequently, cardiac T2* is cited as pivotal to the management of TM patients in four international sets of guidelines. The guidelines published by the Thalassemia International Federation describe T2* as the standard method for effectively and rapidly assessing cardiac iron levels [4; see page 40] to determine the course and intensity of treatment [4; see page 49). The UK specific guidelines also state that all patients should have access to T2* MR imaging modalities for monitoring myocardial and liver iron [5; see page 3]. Children with cardiac complications should have the myocardial iron monitored by cardiac T2* from the age of eight, with cardiac T2* maintained at >20 milliseconds by the appropriate adjustment of chelation therapy [5; see page 5]. The Italian guidelines also state that cardiac T2* should be monitored in patients with a poor chelation history [6; see page 747]. US guidelines are currently in press which will also incorporate the use of cardiac T2* [7]. All the guidelines above reference the research of Professor Pennell and colleagues.

Cardiac T2* has been installed in >100 centres worldwide, with calculations suggesting that there is potential for 30,000 lives per year to be saved if universal access to T2* and appropriate treatment can be achieved. Worldwide survey of cardiac T2* at these centres shows that 42% of TM patients have cardiac iron overload [8].

Furthermore, the Summary of Product Characteristics for deferiprone was amended by the European Medicines Agency (EMA) in 2011 to indicate that deferiprone use was associated with a lower mortality [9]. The mortality and cardiac data for deferiprone were used to gain approval for deferiprone from the US Food and Drugs Administration (FDA) in 2011 [10]. The FDA is requiring new chelators (such as deferasirox) to show cardiac efficacy through T2* as part of their assessment program (Novartis, ApoPharma, AMAG, Shire).

Commercial benefits:
An Imperial spin out company named CVIS has been created to commercialise cardiac T2* analysis software.

Magnetic resonance T2* sequences and analysis software have been developed by Siemens, Philips and GE. Siemens state that the availability of T2* MR has been instrumental to the sale of scanners in some regions. ApoPharma's drug Deferiprone has had a significant increase in sales

and has become profitable (letters available upon request from Siemens and Apopharma).

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

[1] Modell, B., Khan, M., Darlison, M., Westwood, M.A., Ingram, D.A., & Pennell, D.J. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*, 2008, 10, 42. DOI.

[2] Maggio, A., Vitrano, A., Capra, M., Cuccia, L., Gagliardotto, F., et al. Improving survival with deferiprone treatment in patients with thalassemia major: a prospective multicenter randomised clinical trial under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies. *Blood Cells Mol Dis*, 2009, 42, 247–251. DOI.

[3] Telfer, P.T., Warburton, F., Christou, S., Hadjigavriel, M., et al. Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone. *Haematologica*, 2009, 94, 1777-1778. DOI.

[4] Cappellini MD, et al. Guidelines for the Clinical Management of Thalassaemia. 2nd Edition Revised. Thalassemia International Federation 2008 (see page 40 and 49). PDF. Archived on 22nd October 2013.

[5] Yardumian A, et al. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. United Kingdom Thalassaemia Society 2008 (see page 3 and 5).

[6] Angelucci E, et al. Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. *Haematologica,* 2008, 93, 741-752 (see page 747). DOI.

[7] Pennell, D.J., Udelson, J., Arai, A., Bozkurt, B., Cohen, A., Galanello, R., Hoffman, T., Kiernan, M., Lerakis, S., Piga, A., Porter, J.B., Walker, J.M., Wood, J. on behalf of the American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology and Council on Cardiovascular Radiology and Imaging. (2013). Cardiovascular function and treatment in beta-thalassemia major: a consensus statement from the American Heart Association. *Circulation*, 128, 281-308. DOI

[8] Carpenter, J.P., Roughton, M., & Pennell, D.J. (2013). International survey of T2* cardiovascular magnetic resonance in beta thalassemia major. *Haematologica*, 98, see page 248. DOI.

[9] EMA amendment of the Summary of Product Characteristics for deferiprone 2011. PDF (see page 7). Archived on 22nd October 2013.

[10] FDA approval of deferiprone (2011). Archived on 22nd October 2013.

Factual statements available from the Director MR Collaborative Management (Siemens) and the Vice President of Medical Affairs (ApoPharma).