Institution: University of Sheffield

Unit of Assessment: 1 - Clinical Medicine

Title of case study: New drug for heart attack victims

1. Summary of the impact

This case study describes the healthcare impact arising from the trial and introduction of a new clinical treatment used in patients with acute coronary syndromes. Research at Sheffield provided robust evidence as to the effectiveness of the anti-thrombotic drug ticagrelor, which directly contributed to its approval by global regulatory authorities and its recommendation by the European Society of Cardiology and the National Institute for Health and Care Excellence as a first-line treatment in the management of acute coronary syndromes. South Yorkshire hospitals were early adopters in February 2012 and ticagrelor has been progressively adopted across other parts of the United Kingdom, with over half of UK hospitals now having adopted it. It has also been adopted in over 80 other countries.

2. Underpinning research

Platelets play a critical role in most heart attacks. Aspirin is commonly used to prevent heart attack but has a weak antiplatelet effect so clopidogrel, an inhibitor of the platelet $P2Y_{12}$ receptor, was developed for additional efficacy in patients with acute coronary syndromes (heart attack or unstable angina). Professor Robert Storey (University of Sheffield, since 2002) and his platelet research group focussed on the limitations of clopidogrel and options for improved therapy. In order to address these limitations, ticagrelor was developed by AstraZeneca as a novel reversibly-binding $P2Y_{12}$ receptor inhibitor. Having previously published research on $P2Y_{12}$ receptor biology and pharmacology, Storey and his group made the following contributions to the development of ticagrelor:

DISPERSE-2 study (October 2004 to May 2005): Storey was one of four members of the Executive Committee and the Chief Investigator of the pharmacodynamic substudy for this phase IIb study, comparing ticagrelor (formerly AZD6140) with clopidogrel in patients with acute coronary syndromes. The study established the safety and tolerability of ticagrelor in this population and demonstrated its superior antiplatelet efficacy, providing a foundation for the design of the subsequent phase III PLATO study. Storey led the analyses of and presented the substudy data and was first author on the substudy publication as well as senior author on the main study publication (R1, R2).

PLATO study (October 2006 to February 2009): Storey was a member of the executive committee for the 18,624-patient phase III PLATO study and contributed to the study design. He was a co-author on the publication of the main study results that demonstrated that ticagrelor reduces recurrent ischaemic events (relative risk reduction 16%) and all-cause mortality (relative risk reduction 22%) compared to the standard treatment with clopidogrel (R3). He was also the Chief Investigator for the PLATO PLATELET substudy that provided valuable additional information about the pharmacodynamic effects of ticagrelor compared to clopidogrel in the PLATO study (R4) and has also led other publications related to analyses of the PLATO database that guide the use of ticagrelor in acute coronary syndromes. In particular, the extent of the mortality reduction with ticagrelor compared to clopidogrel surpassed expectations since other similar studies, such as clopidogrel compared to placebo or prasugrel compared to clopidogrel in acute coronary syndromes, had not achieved significant mortality reduction. Storey led an analysis providing important characterisation of ticagrelor-related dyspnoea and its benign nature, which is essential information for prescribing clinicians (R5). 72% of the patients in PLATO PLATELET were recruited in Sheffield and Storey conducted the analyses, presented and published the data for this substudy.

ONSET/OFFSET study (October 2007 to May 2009): Storey was a senior investigator and UK Chief Investigator for this study, which demonstrated more clearly the pharmacokinetic and pharmacodynamic advantages of ticagrelor compared to clopidogrel in patients with ischaemic heart disease (R6). 30% of the patients were recruited in Sheffield. Storey led the analyses of the cardiopulmonary substudy data, presenting this data and acting as first author on the publication which has provided essential information on ticagrelor-related dyspnoea (European Heart Journal 2010).

3. References to the research (University of Sheffield staff in **bold**)

R1. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, **Storey RF**. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-st-segment elevation acute coronary syndrome: Primary results of the disperse-2 trial. J Am Coll Cardiol. 2007;50:1844-1851 doi: 10.1016/j.jacc.2007.07.053

R2. **Storey RF**, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, Wickens M, Emanuelsson H, Gurbel P, Grande P, Cannon CP. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol. 2007;50:1852-1856. doi: 10.1016/j.jacc.2007.07.058

R3. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, **Storey RF**, Harrington RA, for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-1057 doi: 10.1056/NEJMoa0904327

R4. **Storey RF**, Angiolillo D, **Patil S**, Desai B, **Ecob R**, Husted S, Emanuelsson H, Cannon C, Becker R, Wallentin L. Inhibitory effects of ticagrelor compared to clopidogrel on platelet function in patients with acute coronary syndromes: The PLATO PLATELET substudy J Am Coll Cardiol. 2010;56:1456-1462 doi: 10.1016/j.jacc.2010.03.100

R5. **Storey RF**, Becker RC, Harrington RA, Husted S, James SK, Cools F, Steg PG, Khurmi NS, Emanuelsson H, Cooper A, Cairns R, Cannon CP, Wallentin L. Characterisation of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. Eur Heart J 2011;32:2945-2953 doi: 10.1093/eurheartj/ehr231

R6. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, **Patil SB, Karunakaran A,** Kereiakes DJ, Paris C, Purdy D, Wilson V, Ledley GS, **Storey RF**. Randomized double-blind assessment of the onset and offset of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: The ONSET/OFFSET study. Circulation. 2009;120:2577-2585 doi: 10.1161/CIRCULATIONAHA.109.912550

4. Details of the impact

Research at the University of Sheffield into ticagrelor has had impact on health and welfare through improved treatment for patients with acute coronary syndromes.

In the UK, the National Institute for Health and Care Excellence (NICE) recommended in October 2011 that ticagrelor is a cost-effective and superior alternative to generic clopidogrel in patients with myocardial infarction or moderate-to-high risk unstable angina (S1). The work has supported

the introduction of life-saving therapy in these patients since ticagrelor prevents one in five deaths in a broad spectrum of acute coronary syndrome patients compared to standard therapy with clopidogrel.

Regulatory approval of ticagrelor has now been achieved in more than 80 countries worldwide, including approval by the European Medicines Agency in Europe (2010) (S2) and the Federal Drug Administration in the USA (2011) (S3).

Based on the PLATO study results, two European Society of Cardiology guidelines entitled 'ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation' (published in 2011) (S4) and 'ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation' (published in 2012) (S5) have recommended ticagrelor as first-line treatment in preference to clopidogrel.

The recommendations by the ESC and the approval by NICE then led to use of ticagrelor for acute coronary syndrome patients in the UK. Reflecting the leading role that Sheffield played in the development of ticagrelor, the South Yorkshire region, representing a population of over 1.5 million, was the first to adopt ticagrelor as first-line treatment of acute coronary syndromes in preference to generic clopidogrel in February 2012 (S6) and other regions of the UK have progressively followed suit, with 50% of NHS Trusts in the UK that manage acute coronary syndrome now having adopted ticagrelor (S7).

5. Sources to corroborate the impact

S1. NICE technology appraisal guidance TA236: Ticagrelor for the treatment of acute coronary syndromes (http://tinyurl.com/muuqx9f).

S2. European Medicines Agency assessment report for ticagrelor (http://tinyurl.com/m9x9vvu).

S3. US Federal Drug Administration approved drug products: Ticagrelor (http://tinyurl.com/3hhaw).

S4. Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2011; 32:2999-3054 doi: 10.1093/eurheartj/ehr236

S5. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J 2012;33:2569-2619 doi: 10.1093/eurheartj/ehs215

S6. Sheffield Teaching Hospitals NHS Foundation Trust guidelines for the management of non-ST-elevation myocardial infarction and ST-elevation myocardial infarction (on Sheffield Teaching Hospitals intranet; copy on file).

S7. AstraZeneca. Email on file about number of UK NHS Trusts that have adopted ticagrelor, dated 22 May 2013.