

Institution: University of Sheffield		
Unit of Assessment: A-01 Clinical Medicine		
Title of case study: Long-term ticagrelor improves survival after heart attacks		
Period when the underpinning research was undertaken: 2005–2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Rob Storey	Role(s) (e.g. job title): Professor of Clinical Cardiology	Period(s) employed by submitting HEI: 2005–present
Period when the claimed impact occurred: 2015–2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Unwanted blood clots are a major cause of heart attacks. Ticagrelor is a drug that prevents blood clot formation. Clinical studies pioneered by Professor Rob Storey validated the use of a novel twice-daily 60-mg dosing regimen of ticagrelor for long-term use beyond the first year of heart attack treatment in large international cohorts. This dosing regimen, approved in 2016 by the EU and NICE has been incorporated into international guidelines. It is cost-effective, and through clinical uptake, has improved the prognosis of heart attack patients at risk of a second heart attack or stroke.</p>		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Every day in the UK, approximately 515 people go to the hospital with a heart attack. Most heart attacks, and strokes, are caused by blood clots and can be treated and prevented by antiplatelet drugs. Even when patients have been treated for heart attack, they are at increased risk of a subsequent heart attack, stroke or death. For this reason, dual antiplatelet therapy (aspirin plus another specific antiplatelet agent) is recommended for one year after the initial event.</p> <p>Professor Storey led UK investigations of the antiplatelet drug, ticagrelor, in patients treated for heart attack that led to its approval and first-line use for heart attack. Subsequent research in 10,793 patients compared ticagrelor-versus-clopidogrel-treatment, demonstrated a 50% reduction in stent thrombosis, a potentially fatal complication of heart artery stenting, and an 18% reduction in mortality during the first year with ticagrelor treatment [R1]. However, 20% of heart attack patients go on to have a subsequent heart attack or a stroke or die from cardiovascular causes in the 3 years after completing their first year of treatment.</p> <p>Given this long-term risk in heart attack survivors, Professor Storey led investigations of long-term treatment with ticagrelor in patients who were more than 1 year after their heart attack and had higher risk of further cardiovascular events in a study known as PEGASUS-TIMI 54. This study showed a significant reduction in cardiovascular events with each of two doses of ticagrelor (the usual heart attack dose of 90 mg twice-daily and a new dose of 60 mg twice-daily) compared to placebo [R2], with a marked benefit in those continuing on or with only a short break in dual antiplatelet therapy before entering the study [R3] and evidence of mortality reduction in the highest-risk patients, such as those with peripheral arterial disease [R4].</p>		

Professor Storey also designed and led a platelet function substudy which explained the efficacy of the 60 mg twice-daily ticagrelor dose. This regime achieved high levels of peak and trough platelet inhibition in nearly all patients, similar to that observed with the standard 90 mg twice-daily dose during long-term therapy after heart attack [R5]. Also ticagrelor 60 mg twice-daily was better tolerated by patients due to lower rates of bleeding and other adverse effects [R6]. This evidence underpinned the selection and approval of the ticagrelor 60 mg dose for long-term treatment after the first year of heart attack treatment.

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

- R1.** Gosling, R., Yazdani, M., Parviz, Y., Hall, I. R., Grech, E. D., **Gunn, J. P., Storey, R. F.**, & Iqbal, J. (2017). Comparison of P2Y12 inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: Single center study of 10 793 consecutive 'real-world' patients. *Platelets*, 28(8), 767–773. <https://doi.org/10.1080/09537104.2017.1280601>
- R2.** Bonaca, M. P., Bhatt, D. L., Cohen, M., Steg, P. G., **Storey, R. F.**, Jensen, E. C., Magnani, G., Bansilal, S., Fish, M. P., Im, K., Bengtsson, O., Ophuis, T. O., Budaj, A., Theroux, P., Ruda, M., Hamm, C., Goto, S., Spinar, J., Nicolau, J. C., ... Sabatine, M. S. (2015). Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. *New England Journal of Medicine*, 372(19), 1791–1800. <https://doi.org/10.1056/nejmoa1500857>
- R3.** Bonaca, M. P., Bhatt, D. L., Steg, P. G., **Storey, R. F.**, Cohen, M., Im, K., Oude Ophuis, T., Budaj, A., Goto, S., López-Sendón, J., Diaz, R., Dalby, A., Van de Werf, F., Ardissino, D., Montalescot, G., Aylward, P., Magnani, G., Jensen, E. C., Held, P., ... Sabatine, M. S. (2016). Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54. *European Heart Journal*, 37(14), 1133–1142. <https://doi.org/10.1093/eurheartj/ehv531>
- R4.** Bonaca, M. P., Bhatt, D. L., **Storey, R. F.**, Steg, P. G., Cohen, M., Kuder, J., Goodrich, E., Nicolau, J. C., Parkhomenko, A., López-Sendón, J., Dellborg, M., Dalby, A., Špinar, J. ř., Aylward, P., Corbalán, R., Abola, M. T. B., Jensen, E. C., Held, P., Braunwald, E., & Sabatine, M. S. (2016). Ticagrelor for Prevention of Ischemic Events After Myocardial Infarction in Patients With Peripheral Artery Disease. *Journal of the American College of Cardiology*, 67(23), 2719–2728. <https://doi.org/10.1016/j.jacc.2016.03.524>
- R5.** **Storey, R. F.**, Angiolillo, D. J., Bonaca, M. P., Thomas, M. R., Judge, H. M., Rollini, F., Franchi, F., Ahsan, A. J., Bhatt, D. L., Kuder, J. F., Steg, P. G., Cohen, M., Muthusamy, R., Braunwald, E., & Sabatine, M. S. (2016). Platelet Inhibition With Ticagrelor 60 mg Versus 90 mg Twice Daily in the PEGASUS-TIMI 54 Trial. *Journal of the American College of Cardiology*, 67(10), 1145–1154. <https://doi.org/10.1016/j.jacc.2015.12.062>
- R6.** Bonaca, M. P., Bhatt, D. L., Oude Ophuis, T., Steg, P. G., **Storey, R.**, Cohen, M., Kuder, J., Im, K., Magnani, G., Budaj, A., Theroux, P., Hamm, C., Špinar, J., Kiss, R. G., Dalby, A. J., Medina, F. A., Kontny, F., Aylward, P. E., Jensen, E. C., ... Sabatine, M. S. (2016). Long-term Tolerability of Ticagrelor for the Secondary Prevention of Major Adverse Cardiovascular Events. *JAMA Cardiology*, 1(4), 425. <https://doi.org/10.1001/jamacardio.2016.1017>

4. Details of the impact (indicative maximum 750 words)**Regulatory approval for ticagrelor 60 mg for long-term treatment after a heart attack**

Following the results of the PEGASUS-TIMI 54 study [R2, R5, R6], European, US and more than 110 global regulatory bodies have approved the 60 mg twice-daily dose so that this can now be used as extended therapy in patients from 1 year after their heart attack [S1, S2]. The change to ticagrelor's EU labelling to incorporate ticagrelor 60 mg came into effect from November 2016 [S1].

Endorsement of ticagrelor 60 mg in international guidelines

Following guideline recommendations in 2015 supporting the first-line use of ticagrelor 90 mg in the first year after a heart attack [R1, S3], extended treatment with ticagrelor 60 mg beyond the first year has now been supported by the European Society of Cardiology 2019 guidelines on the diagnosis and management of chronic coronary syndromes [S4]; Professor Storey was a member of this task force. Consequently, ticagrelor 60 mg twice-daily has increasingly been adopted for reducing risk in patients with a previous heart attack. These patients now benefit from lower risks of a subsequent heart attack, stroke and death during long-term treatment while avoiding the adverse effect of long-term anti-platelet agent use.

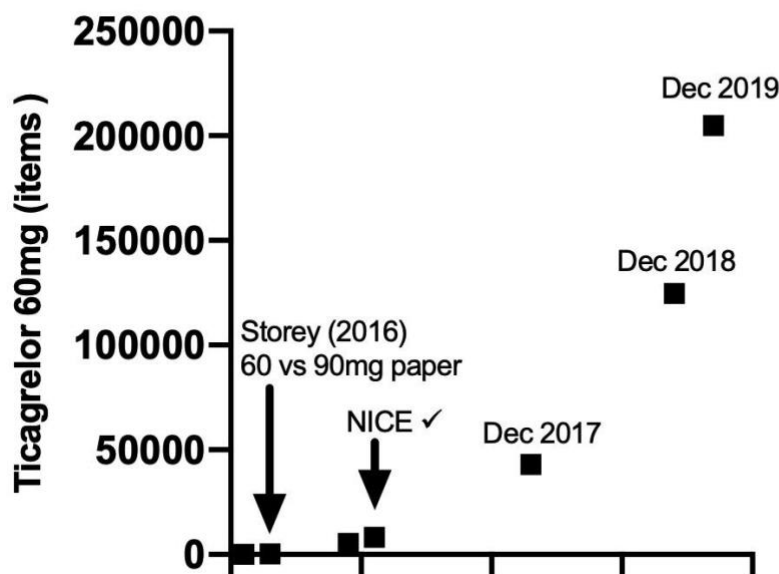
Cost-effectiveness of ticagrelor 60 mg after heart attacks

The National Institute of Clinical Excellence (NICE) were advised by Professor Storey as an external expert on use of antiplatelet agents to reduce risk of secondary heart attacks. They subsequently approved ticagrelor 60 mg twice-daily as a cost-effective option for extended therapy in patients with prior heart attack [S5]. The incremental cost-effectiveness ratio (ICER), determined with a worse-case scenario (probabilistic modelling), is £24,711, which falls within the acceptable quality-adjusted life year (QALY) threshold range set by NICE of £20- 30K, and therefore, a willingness-to-pay was established.

Commercial impact

Ticagrelor was reformulated as a 60 mg tablet in 2016, and prescriptions for ticagrelor 60 mg increased 20-fold per month in the 6 months following Professor Storey's PEGASUS-TIMI 54 platelet substudy publication and a further 20-fold following approval by NICE with 204,991 items prescribed in the month of December 2019, as shown in the figure below (NHS Business Authority English Prescribing dataset). Overall global sales of ticagrelor reached \$400M in Q1 of 2019, an increase of 19% from all sales of 2018 [S6]. AstraZeneca successfully secured a patent series to describe the results of the PEGASUS-TIMI 54 study and its platelet function substudy; Professor Storey is designated as an inventor on this series [S7].

Ticagrelor Dispensed by Pharmacies in England



In 2019, Professor Storey was the winner of the British Cardiovascular Intervention Society Research of the Year Prize following a presentation that included the beneficial impact of Ticagrelor on stent thrombosis risk in heart attack patients.

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

- S1.** The European Medicines Agency approval of ticagrelor 60 mg (<https://www.ema.europa.eu/en/medicines/human/EPAR/brilique>).
- S2.** The Food and Drug Administration (FDA) approval of ticagrelor 60 mg (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf).
- S3.** Roffi, M. ... Storey, R. F., & Windecker, S. (2015). 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal*, 37(3), 267–315. <https://doi.org/10.1093/eurheartj/ehv320>
- S4.** Knuuti J, ... , Storey RF, ... , Bax JJ, and the ESC Scientific Document Group. (2019). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European Heart Journal*, 41(3), 407–477. <https://doi.org/10.1093/eurheartj/ehz425>. The guidelines of the European Society of Cardiology recommended that long-term treatment with aspirin and a P2Y12 inhibitor such as ticagrelor 60 mg twice-daily should be considered beyond the first year after heart attack in patients at higher risk of further cardiovascular events, citing [R2].
- S5.** The guidance from NICE approved the use of ticagrelor 60 mg twice-daily as being cost-effective when used for 3 years after the initial first year of dual antiplatelet therapy in patients at high cardiovascular risk after myocardial infarction. National Institute for Health and Clinical Excellence. Ticagrelor for preventing atherothrombotic events after myocardial infarction: Technology appraisal guidance [TA420]. 2016 (<https://www.nice.org.uk/guidance/ta420>).
- S6.** AstraZeneca annual report 2019 (p.2 for sales from Brilinta and p.15 for sales from Brilique, both of which are brand names for Ticagrelor

Impact case study (REF3)

(https://www.astrazeneca.com/content/dam/az/PDF/2019/Q1-2019/Q1_2019_Results_announcement.pdf).

- S7.** A worldwide patent from AstraZeneca with Storey as an inventor followed the publication of the guidelines cited above. Method of treating or prevention of atherothrombotic events in patients with history of myocardial infarction, WO2016120729A1 (<https://patents.google.com/patent/WO2016120729A1/en>).