Research to Understand Stroke due to Haemorrhage

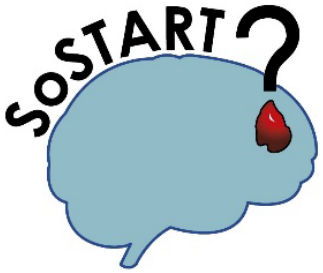
2021 Newsletter

Research during recovery from COVID-19

As the world began to manage the COVID-19 pandemic in 2021, we were fortunate to be able to restart, complete and continue our research studies. In this newsletter, you will find updates about these activities in 2021:

SoSTART results

We began the Start or STop Anticoagulants Randomised Trial (SoSTART) in 2017, with funding from the Medical Research Council and Chest Heart & Stroke Scotland. The British Heart Foundation funded the trial 2018-2021.



Start
or
STop
Anticoagulants
Randomised
Trial

We wanted to find out whether starting or not starting an anticoagulant drug is better for people who have had a bleed within the skull (known as a “brain haemorrhage”) as well as an irregular heartbeat (known as “atrial fibrillation” or “AF”). People with AF take blood-thinning drugs known as “anticoagulants” to prevent blood clots forming. Anticoagulants reduce the risk of clots a lot despite increasing the risk of bleeding a little.

We presented the results at the European Stroke Organisation

Conference in 2021 and *The Lancet Neurology* published them at the same time.

THE LANCET Neurology

The results were promising. You can read a plain English summary of the results on www.SoSTART.ed.ac.uk, and watch a 3-minute video summary

Now, we need to perform a much larger, definitive study to confirm the benefit of anticoagulant drugs for AF after brain haemorrhage.

RESTART results

We began the REstart or STop Antiplatelets Randomised Trial (RESTART) in 2013, with funding from the British Heart Foundation. We wanted to find out whether people with brain haemorrhage who had had a clotting problem like a heart attack benefit from starting an 'antiplatelet' drug (like aspirin) to thin the blood.

REstart or STop Antithrombotics Randomised Trial

RESTART recruited 537 participants 2013-2018. We published the main results in 2019, which showed that antiplatelet drugs were likely to be safe.

We presented the final results after two years of extended follow-up at the European Stroke Organisation Conference in 2021. *JAMA Neurology* published them at the same time.

JAMA Neurology

The next step after RESTART is to confirm the benefit of antiplatelet drugs after brain haemorrhage…

ASPIRING starts

The Antiplatelet Secondary Prevention International Randomised trial after INtracerebral haemorrhaGe (ASPIRING) is for any survivor of brain haemorrhage. Building on the results of RESTART, we aim to produce reliable information about whether antiplatelet drugs like aspirin, which thin the blood, benefit any brain haemorrhage survivor, not just people like the ones in RESTART. This will affect how brain haemorrhage survivors are treated worldwide.

ASPIRING

Antiplatelet Secondary Prevention International Randomised trial after INtracerebral haemorrhaGe

We need to recruit 4,148 participants to answer the question. This is a big ask, so we started a 'pilot phase' in around 20 hospitals in China and Australia in September 2021, with funding from our collaborators' fellowships funded by the Australian government, the Shanghai Shenkang Hospital Development Centre, and the Shenyang First People's Hospital in China. This pilot phase aims to recruit 120 participants, and we're up to 31 already (see https://aspiringtrial.org/). Meantime, with input from our Patient Reference Group, we have applied to multiple funders for the main phase of the trial.

CARE starts

CareTrial

CAVERNOMAS: A RANDOMISED EFFECTIVENESS TRIAL

After working with Cavernoma Alliance UK (CAUK) for a long time, we identified the top uncertainty for people with cavernomas in a Priority Setting

Partnership. This uncertainty was, “Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with brain or spine cavernoma?” With CAUK, we obtained funding from the National Institute for Health Research Health Technology Assessment programme to do a pilot phase study to see if this uncertainty could be resolved. We were delighted to begin recruitment in Edinburgh in September 2021. Currently, 15 hospitals are active in the trial, where six participants have taken part. You can follow our progress via the website: www.ed.ac.uk/care-study.

Staff news

Our dynamic research nurse team continued to support COVID-19 research, whilst starting and reactivating stroke research. Seona Burgess (far right) left the team, which is led by Allan Macraild (second from

the right), Jess Teasdale (left), Rachel Penman (middle), and Michelle Coakley (now on maternity leave).

Dr Nesh Samarasekera (above) continues to work on the NICHE project to understand how swelling changes over time after brain haemorrhage. Changes in swelling over time are likely to affect how well patients recover after a bleed on the brain, even though swelling on the first scan may not. We are close to completing recruitment to the

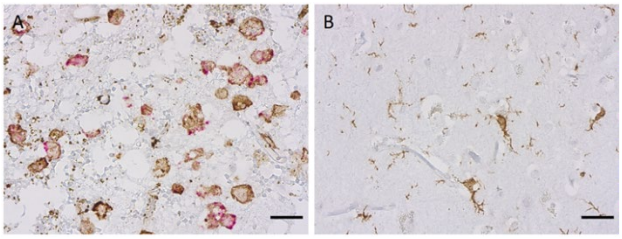
study despite the pandemic, which is a great effort from the team. We look forward to planning which direction the research may take after this project over the next year.

After another three years working with the RUSH team, **Chris Lerpiniere** (above) has now hung up her cape and retired from nursing. However, she continues to contribute part time by perfecting the data about all adults with brain haemorrhage in NHS Lothian who we identified in the second 3-year epoch of our audit. Chris is also completing the Flutemetamol MR PET study for identifying cerebral amyloid angiopathy associated with brain haemorrhage, as part of a consultancy with GE Healthcare.

We will be very sorry to see Chris go in April 2022…

Congratulations to **Jamie Loan** for writing up his PhD, which will be examined in 2022! During the past year Jamie has worked with the RUSH, neuropathology, and brain bank teams in Edinburgh to study the brains of patients who died after stroke due to haemorrhage. These extremely generous donations have allowed him to study how the brain protects itself from toxins produced by bleeding and repairs damaged tissue. Using cells grown in a dish, and mice, Jamie has studied how these protective processes could be boosted using drugs and what happens if they are under active. With other members of RUSH, and collaborators from Radboud University in the Netherlands, he also recently published a study

summarising all previously conducted studies of brain tissue from patients after stroke due to haemorrhage, which will appear in the 2022 publication list.

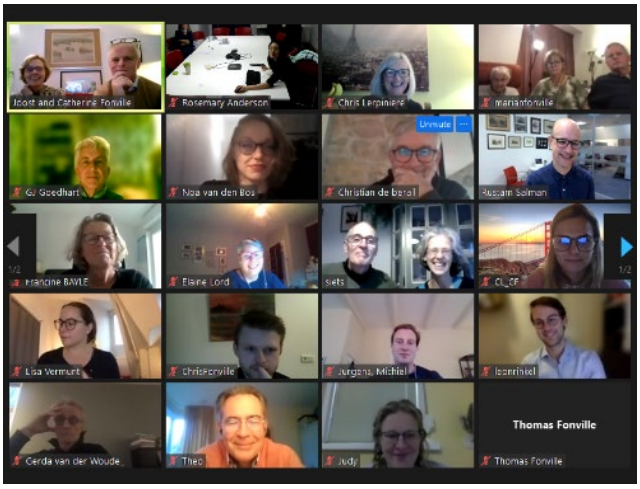


Microscope image of brain tissue from a patient who died after haemorrhagic stroke. Close to the stroke (A) immune cells (brown) accumulate, start to clear up debris and change shape. In doing so, some of these cells produce a protective enzyme to break down toxins released from red blood cells in the clot (pink). On the opposite side of the brain (B), this enzyme is not produced, and the immune cells have a very different appearance.

Jamie has now returned to the wards where he is training to be a neurosurgeon, but retains a clinical lecturer post with the University, so he continues to do research in his 'spare time'!

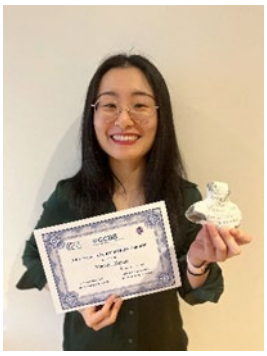
Arthur Fonville Awards for Stroke Research

We had hoped that the seventh annual award ceremony would be in-person, but we felt it more prudent and environmentally friendly to meet virtually (below).



Nonetheless, the meeting was better attended than it would have been in person. The Fonville family and many friends attended from The Netherlands and France. The award attracted its greatest number of applications to date this year, with 10 applications: 5 from Amsterdam and 5 from

Edinburgh. After the usual independent scoring by multiple reviewers, the awards went to:



Noa van den Bos, University of Amsterdam (left) for her essay, "*Patient and proxies' attitudes towards deferred consent in randomised trials of acute treatment for stroke: a qualitative survey"* and Yawen Xiang, The University of Edinburgh (right) for her essay, "*Which pathologies contribute to pre-existing dementia in adults with spontaneous (non-traumatic) intracerebral haemorrhage?"* Congratulations to both of them! Joost & Catherine Fonville presented the awards of the Arthur Stone, £100 prize, and the opportunity to receive a further £750 towards presenting their research at a stroke conference.

Patient Reference Group

Our patient reference group have been invaluable again this year. They advise us about the design of our research. They contribute to grant applications. They oversee the progress of our research. They sit on the committees that supervise our research. They occasionally attend research ethics meetings. They often give us great ideas.

The RUSH team sends quarterly updates to the patient reference group by email. Although we didn't manage a face-to-face meeting (you know why!), we did manage a Zoom meeting in November (see below).

The team give us valuable advice and input on a range of issues. We were also joined by

Professor Nikola Sprigg from the Stroke Trials Unit in Nottingham (bottom row, above), who sought our advice about approaching patients with brain haemorrhage, or their relatives, in the forthcoming TICH-3 trial.

We are looking for more members of the Patient Reference Group

In particular, we are looking for women and people with some disability after brain haemorrhage. You can find out more via our website www.RUSH.ed.ac.uk. If you are interested, please contact us (see details below).

Raising money for RUSH

We are extremely grateful to our donors this year, whose funding has contributed to the studies about swelling of the brain after brain haemorrhage, described by Nesh and Jamie above and in the publications authored by them overleaf.

If you would like to fundraise for us, please click on one of the donations links below, or contact Kerry MacKay (0131 650 9221).

Contact us

We are always happy to hear from the participants in our studies, or their relatives or carers.

Feel free to contact us using any of the methods described below:

RUSH
c/o Ms. Rosemary Anderson, CCBS,
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Crescent, Edinburgh. EH16 4SB
Tel 0131 537 2944
Web www.RUSH.ed.ac.uk
Twitter @BleedingStroke
Facebook www.facebook.com/bleedingstroke

Donations to our research programme:
Single donation http://edin.ac/1iNmqj0,
regular donation http://edin.ac/1iNmwqV

Publications in 2021 that involved the RUSH team:

1. **Al-Shahi Salman R**, Dennis MS, Sandercock PAG, Sudlow CLM, Wardlaw JM, Whiteley WN, Murray GD, Stephen J, Rodriguez A, Lewis S, Werring DJ, White PM, for the RESTART Collaboration. Effects of Antiplatelet Therapy after Stroke due to Intracerebral Hemorrhage. Extended follow-up of the RESTART Randomized Clinical Trial. *JAMA Neurol* 2021;78:1179-86

2. **Al-Shahi Salman R**, Keerie C, Stephen J, Lewis S, Dennis MS, Newby DE, Wardlaw JM, Lip GYH, Parry-Jones A, White PM for the SoSTART Collaboration. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage: a randomised, open-label, assessor-blinded, pilot phase, non-inferiority trial. *Lancet Neurol* 2021;20:842-53

3. Ross Russell AL, Hardwick M, Jeyanantham A, White LM, Deb S, Burnside G, Joy HM, Smith CJ, Pollak TA, Nicholson TR, Davies NWS, Manji H, Easton A, Ray S, Zandi MS, Coles JP, Menon DK, Varatharaj A, McCausland B, Ellul MA, Thomas N, Breen G, Keddie S, Lunn MP, Burn JPS, Quattrocchi G, Dixon L, Rice C, Pengas G, **Al-Shahi Salman R**, Carson A, Joyce E, Turner MR, Benjamin LA, Solomon T, Kneen R, Pett S, Thomas RH, Michael BD, Galea I, on behalf of the CoroNerve Studies Group. Spectrum, risk factors, and outcomes of neurological and psychiatric complications of COVID-19: a UK-wide cross-sectional surveillance study. *Brain Communications* 2021;3(3):fcab168

4. Chung J, Hamilton G, Kim M, Marini S, Montgomery B, Henry JQA, Cho AE, Brown DL, Worrall BB, Meschia JF, Silliman SL, Selim M, Tirschwell DL, Kidwell CS, Kissela S, Greenberg SM, Viswanathan A, Goldstein JN, Langefeld CD, Rannikmae K, Sudlow CLM, **Samarasekera N**, **Rodrigues M**, **Al-Shahi Salman R**, Prendergast JGD, Harris SE, Deary I, Woo D, Rosand J, Van Agtmael T, Anderson CD. Rare Missense Functional Variants at COL4A1 and COL4A2 in Sporadic Intracerebral Hemorrhage. *Neurology* 2021;97(3):e236-e247

5. Wiegertjes K, Dinsmore L, Drever J, **Hutchison A**, Stephen J, Valdés Hernandez MC, Bhatnagar P, Minks DP, **Rodrigues MA**, Werring DJ, de Leeuw F-E, Klijn CJM, **Al-Shahi Salman R**, White PM, Wardlaw JM. Diffusion-weighted imaging lesions and risk of recurrent stroke after intracerebral haemorrhage. *JNNP* 2021;92(9):950-955

6. Hald SM, Möller S, García Rodríguez LA, **Al-Shahi Salman R**, Sharma M, Christensen H, Hellfritzsch M, Pottegård A, Hallas J, Gaist D. Trends in incidence of intracerebral haemorrhage and association with antithrombotic drug use in Denmark, 2005-2018. *JAMA Network Open* 2021;4(5):e218380

7. Hostettler ICC, Schwarz G, Ambler G, Wilson D, Banerjee G, Seiffge DJ, Shakeshaft C, Lunawat S, Cohen H, Yousry TA, **Al-Shahi Salman R**, Lip GYH, Brown MM, Muir KW, Houlden H, Jäger HR, Werring DJ. Cerebral Small Vessel Disease and Functional

Outcome Prediction after Intracerebral Haemorrhage. Neurology 2021;96(15):e1954-e1965

8. Bonello K, Nelson APK, **Moullaali TJ**, **Al-Shahi Salman R** for the Lothian Audit of the Treatment of Cerebral Haemorrhage Collaborators. Prescription of blood pressure lowering treatment after intracerebral haemorrhage: prospective, population-based cohort study. *Eur Stroke J* 2021;6(1):44-52

9. **Rodrigues MA**, **Samarasekera N**, **Lerpiniere C**, Perry LA, **Moullaali TJ**, **Loan JJM**, Wardlaw JM, **Al-Shahi Salman R** for the Lothian Audit of the Treatment of Cerebral Haemorrhage Collaborators. Association between CT biomarkers of small vessel diseases and outcome after intracerebral haemorrhage. *Ann Neurol* 2021;89(2):266-279

10. Li L,* Poon MTC,* **Samarasekera NE**, Perry LA, **Moullaali TJ**, **Rodrigues MA**, **Loan JJM**, Stephen J, **Lerpiniere C**, Tuna MA, Gutnikov SA, Kuker W, Silver LE, **Al-Shahi Salman R**,# Rothwell PM.# Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *The Lancet Neurology* 2021;20:437-47 *# contributed equally

11. Law ZK, Desborough M, Roberts I, **Al-Shahi Salman R**, England TJ, Werring DJ, Robinson T, Krishnan K, Dineen R, Laska AC, Peters N, Egea-Guerrero JJ, Karlinski M, Christensen H, Roffe C, Bereczki D, Ozturk S, Thanabalan J, Collins R, Beridze M, Bath PM, Sprigg N. Outcomes in Antiplatelet-Associated Intracerebral Hemorrhage in the TICH-2 Randomized Controlled Trial. *JAHA* 2021;10:e019130

12. Best JG … 41 authors … **Al-Shahi Salman R** … 70 authors … Werrijng DJ. Development of imaging-based risk scores for prediction of intracranial haemorrhage and ischaemic stroke in patients taking antithrombotic therapy after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *The Lancet Neurology* 2021;20:294-303

13. Papanastasiou G, **Rodrigues MA**, Wang C, Heurling K, Lucatelli C, **Al-Shahi Salman R**, Wardlaw JM, van Beek EJR, Thompson G. Pharmacokinetic modelling for the simultaneous assessment of perfusion and 18F-flutemetamol uptake in cerebral amyloid angiopathy using a reduced PET-MR acquisition time: proof of concept. *NeuroImage* 2021;225:117482

14. Du H, Wilson D, Ambler G, Banerjee G, Shakeshaft C, Cohen H, Yousry T, **Al-Shahi Salman R**, Lip G, Houlden H, Brown M, Muir K, Jäger HR, Werring D. Small vessel disease and ischemic stroke risk during anticoagulation for atrial fibrillation after cerebral ischemia. *Stroke* 2021;52:91-99