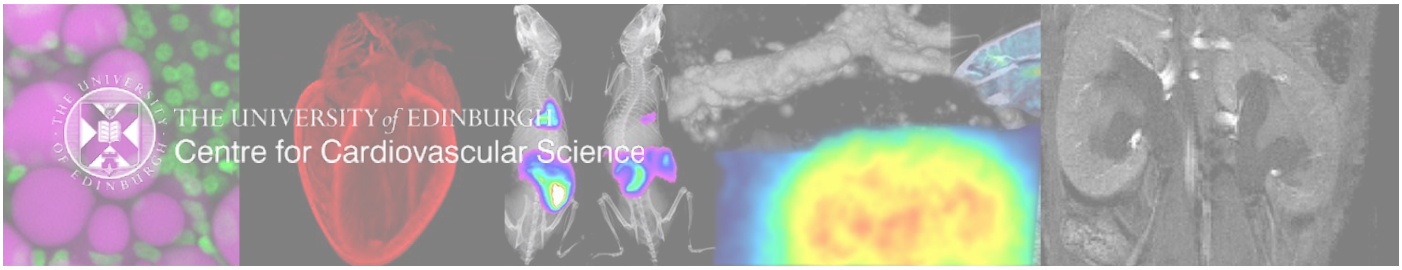
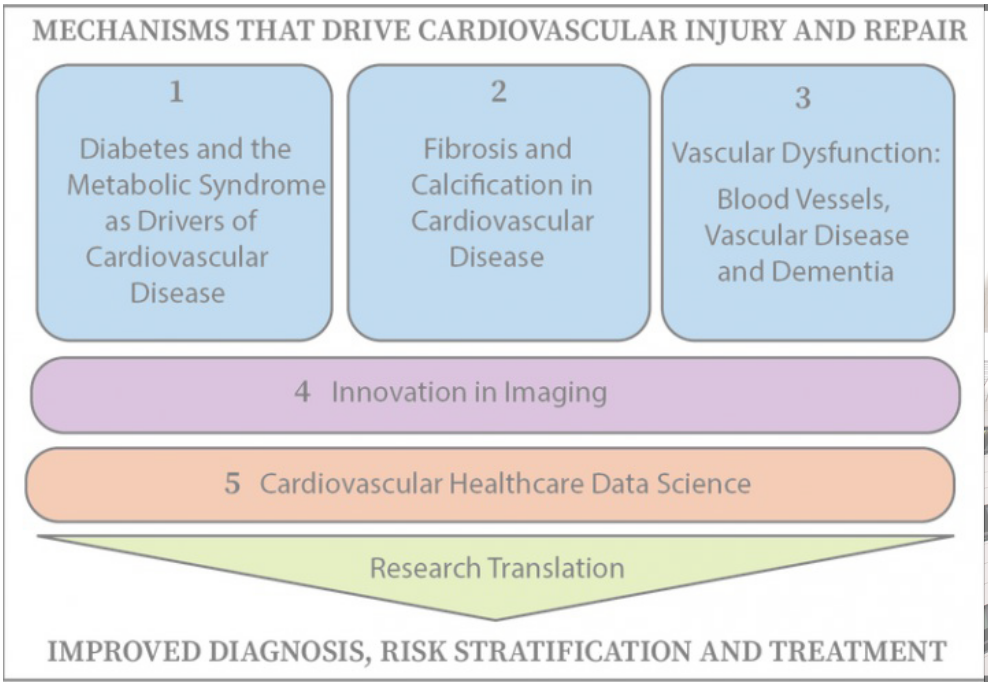
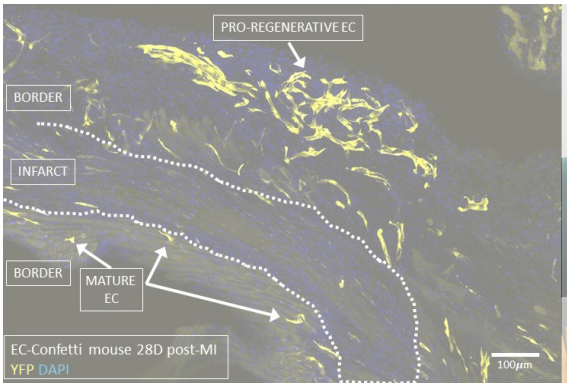


REA3 BIMONTHLY NEWSLETTER

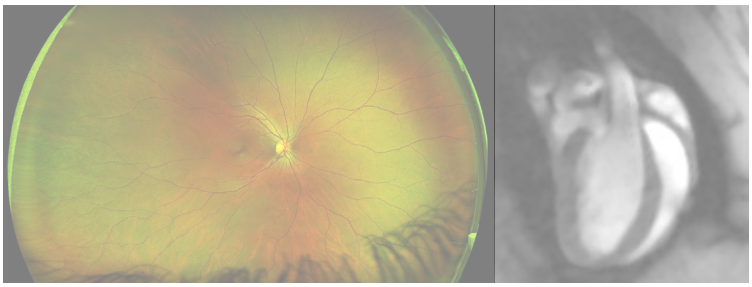
July 2020

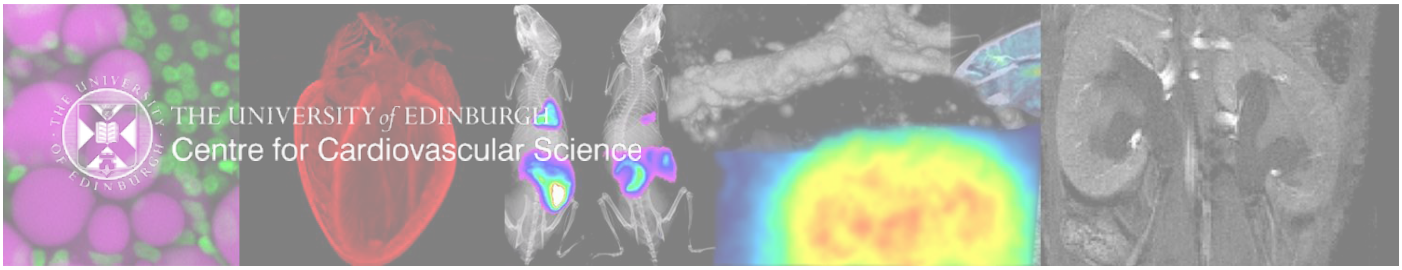




THE UNIVERSITY of EDINBURGH

British Heart Foundation





INTRODUCTION

Welcome to our fourth edition of the bimonthly REA3 Newsletter.

There is optimism that we are slowly returning to some kind of "normality" during these times for REA3 research. Access to QMRI and other research facilities across the unversity, UK and beyond are starting to re-open. Restrictions are still in place for many of the labarotories, which is still impacting on research timelines, productivity and output. Many of our research community continue to work from home while ensuring that the aims of their projects are still met.

In response to the current climate, the REA3 Executive met on 30 June 2020, to review and consider pump priming projects that requested extensions. Out of the 10 that applied, we were able to honour 9 of those studies. This illustrates the impact that COVID-19 has had on our REA3 research and how important it is to provide a degree of flexibility, where the funding allows. Supporting Principal Investigators (PI), Early Career Researchers (ECR), post-doctoral reasearchers, technicians and everyone involved in the research community is crucial to continuing the great work and science produced by REA3.

Within this newsletter there is a summary of the Spring 2020 Pump Priming awards. In this particular round we welcomed applications from Early Career PIs (within 5 years of their first position as PI), and all stages of translational research. In the end 5 proposals were successful with 3 of them from ECRs. Find out more on page 2.

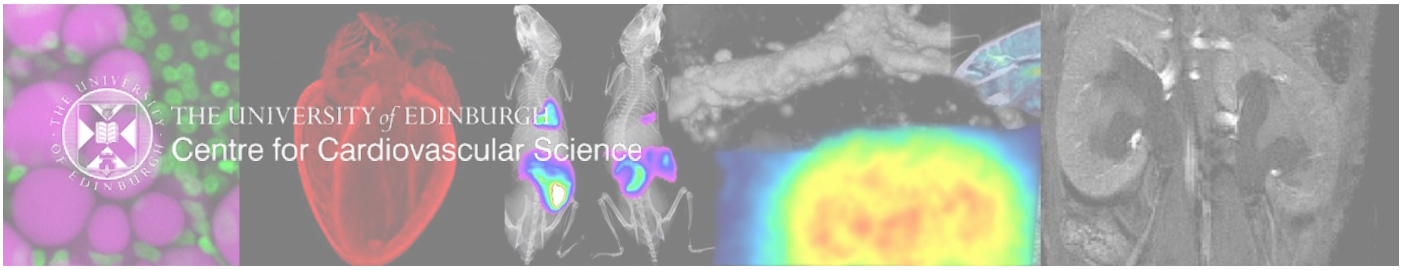
Dr Matthew Brook, one of the ECR awardees has also contributed to this edition . He provides us with a general overview of his funded project, which commences later this year, and what the award means to him.: "***In vivo, genome-wide identification of the post-transcriptional regulation in heart and skeletal muscle that underpins the life-course of obesity-induced diabetes and cardiovascular disease".***

Finally, Dr Anda Bularga, a Clinical Fellow who is undertaking a PhD in Cardiovascular Data Science, provides us with some insight into her current work. Dr Bularga was a co-applicant to REA3 for funds for COVID-19 research. Due to the pandemic the direction of her current research has changed, with the focus being on new studies that summarise the effects of COVID-19 on the heart.

Just a reminder if you are wishing to contribute to any future editions, Research Project Co-ordinator, Gillian Joyce, would be happy to hear from you. If you have any imaginative ideas or would like your REA3 project or event highlighted, please contact her: Gillian.Joyce@ed.ac.uk

Hopefully everyone is managing to take a break over the summer period and if not, we encourage you to do so. We extend our thanks to everyone associated with the REA3 centre and hopefully by the September issue there will be some progression again towards, "normality".

Professor Andrew H Baker, Director REA3
Professor David Newby, Deputy Director REA3



Pump Priming Awards Spring 2020

On 24 April 2020, 11 applications were received for REA3's third and final round of funding for pump priming projects. Applications were considered using the criteria outlined below.

Early Career Prinicpal Investigators (within 5 years of their first position as principal investigator):

- clearly aligned to the REA3 pillars and cross-cutting themes.
- sought to link research between one or more research pillars or themes.
- contained an element of healthcare data science.
- showed a clear and tangible route to further funding

Translational Applications:

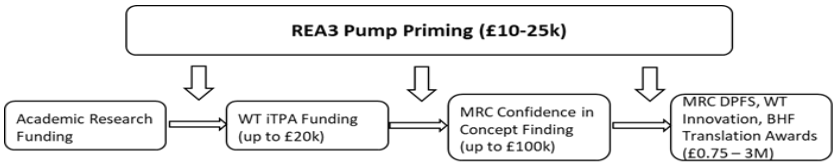
Early stage projects

- Priority given to those proposals that established 'reason to believe' to conduct specific experiments that provided evidence of a new approach to a specific problem. Projects were expected to be in a position to seek follow-on funding for a more substantive programme of translational research.

More established projects

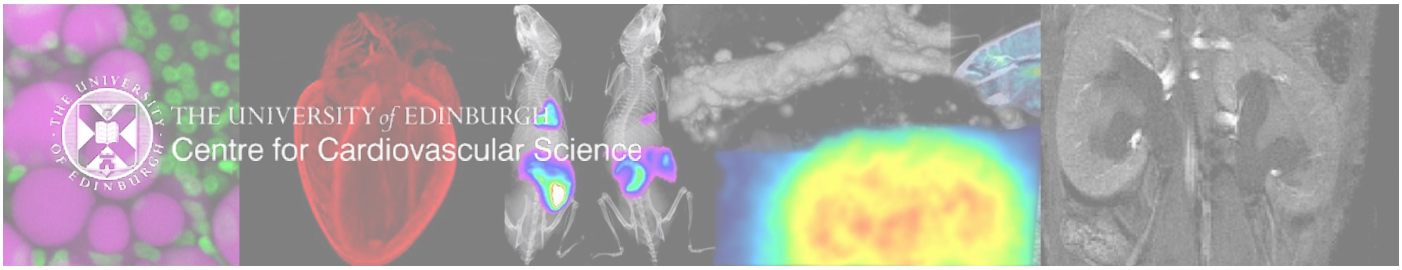
- 'Proof of concept' was required to leverage larger follow-on funding investment. Funding was also considered for projects that required specific datasets to bridge the funding gap.

The typical translational funding pathway.



After careful assessment and setting the ECR scoring threshold as 14 out of 20 (normally 16), the following were successful:

Applicants	ECR or Translational	Title	Funding Amount
Dr Neshika Samarasekera (co-applicants Dr Grant Mair, Dr Adrian Parry-Jones, Dr Tom Moullaali, Dr Xia Wang & Prof Christopher Weir)	ECR	Individual patient data meta-analysis of the association between perihaematomal oedema and outcome after spontaneous intracerebral haemorrhage	£46,740.65
Dr Matthew Brook (co-applicants Dr Etienne Dubiez, Dr Gillian Gray, Prof Nik Morton, Dr Sande Granneman & Dr Alex von Kriegsheim)	ECR	In vivo, genome-wide identification of the post-transcriptional regulation in heart and skeletal muscle that underpins the life-course of obesity-induced diabetes and cardiovascular disease	£28,632.85
Dr Mihaela Crisan (co-applicants Dr Bruno Péault, Dr Adriana Tavares, Prof Carmel Moran, Prof Clare Isacke, Prof David Newby, David Craig, Dr Gillian Gray & Dr Mairi Brittan)	ECR	CD248, a novel pericyte-expressed regulator of cardiac vascular remodelling and fibrosis post-injury?	£30,000.00
Prof Andrew Baker (co-applicants Dr Dónal O'Carroll & Francesca Vacante)	Translational	A gene therapy CRISPR/Cas9 approach to prevent loss of smooth muscle cell identity in pathological blood vessel remodelling	£27,895
Dr Vicky MacRae (co-applicants Prof Scott Webster & Dr Patrick Hadoke)	Translational	Profiling of selective Autotaxin inhibitors in calcific aortic disease	£27,671



Dr Matt Brook - *In vivo*, genome-wide identification of the post-transcriptional regulation in heart and skeletal muscle that underpins the life-course of obesity-induced diabetes and cardiovascular disease

Amount awarded: £28,632.85

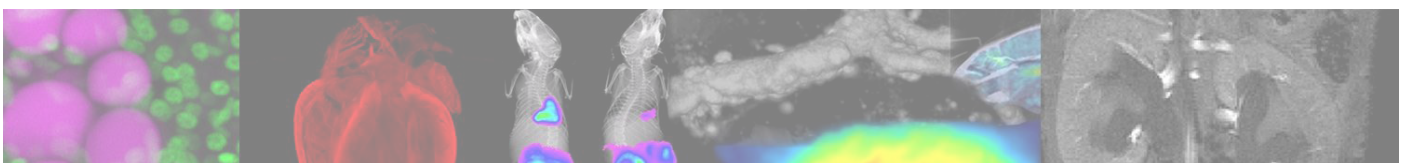
Co-applicants: Prof. Gillian Gray, Prof. Nik Morton, Dr. Sander Granneman, Dr. Alex von Kriegsheim

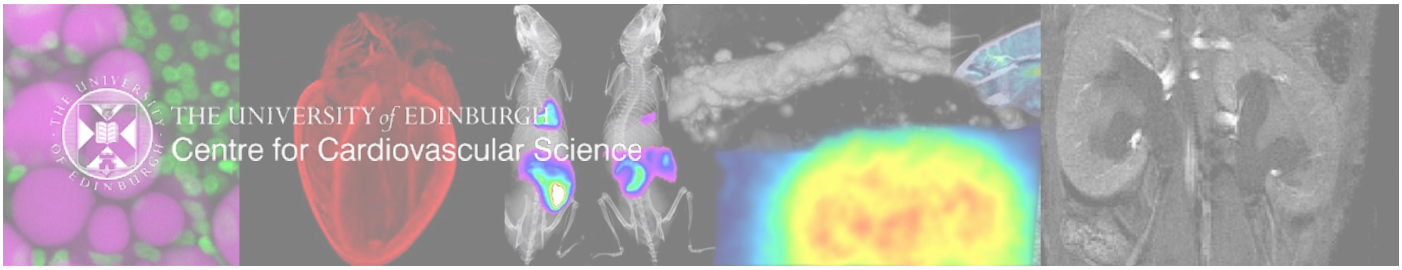
As a recently appointed group leader/lecturer transitioning from Co-Investigator funding and with VERY limited start-up funds, the award of this REA3 pump-prime grant is a vital step towards establishing my lab in CVS. More importantly though, it gives me the opportunity to formally enter the world of cardiometabolic health and disease and, with an exciting interdisciplinary team that spans UoE (CVS, SynthSys, IGMM), to open new research avenues that will (hopefully) be major components of my research for years to come. I am extremely grateful to the BHF and the REA3 committee.

We are all aware of the obesity epidemic and how it is a driver for cardiometabolic comorbidities. What is less well appreciated however, is that the duration for which a person is obese is a key contributor to their risk of cardiovascular disease (CVD) and CVD-induced death. Indeed, CVD mortality risk increases by ~3.5% for every year lived obese and an obese child will already have significantly elevated CVD risk by the time it reaches adulthood. However, obesity also impacts cardiometabolic health long before overt symptoms are detectable and, in the context of increasing childhood obesity (~9% UK increase in last 10 years), it is clear that we urgently need to understand the full life-course of obesity.

My research interests centre around post-transcriptional regulation of gene expression and, in particular, the RNA-binding proteins (RBPs) that coordinate when, where and how frequently an mRNA is translated. My aim is to understand how RBPs are regulated (signalling pathways, PTMs etc.) in response to cues such as nutrient availability, inflammation etc. to determine the utilisation and/or fate of specific mRNAs and, ultimately, to determine correct proteomic composition. The relevance of this to obesity lies in the fact that skeletal muscle protein synthesis is highly sensitive to nutrient status, and muscle-specific modulation of mRNA translation rates dramatically affects whole-body sensitivity to the effects of an obesogenic diet. However, despite 60-90% of mRNAs being subject to one or more forms of post-transcriptional regulation, and clear and long-standing evidence for translational regulation of many key skeletal muscle 'metabolic' genes, the RBPs required have been identified in very few cases. In the meantime, new technologies have revealed that mammalian cells contain >3000 RBPs, with the majority of these being unstudied in terms of their mRNA targets and regulatory functions. Importantly, unlike skeletal muscle, cardiac muscle protein synthesis rates are normally low, including translation of the recently identified cardiac micropeptide-ome, but increase significantly under hypertrophy-promoting conditions (e.g. obesity) via unknown RBP-mediated regulation.

So, this REA3 pump-prime award will enable us to employ agnostic, genome-wide approaches (RBP-interactome capture, quantitative Mass Spec, RNAseq etc) to map the 'RBP-omes' of skeletal muscle and heart in a mouse model of the obesity life-course. Further, we will map the post-translational modification status of the RBP-omes and correlate this with RNA binding to generate the first in vivo insights into the molecular circuitry underpinning the development life-course of obesity/T2D.





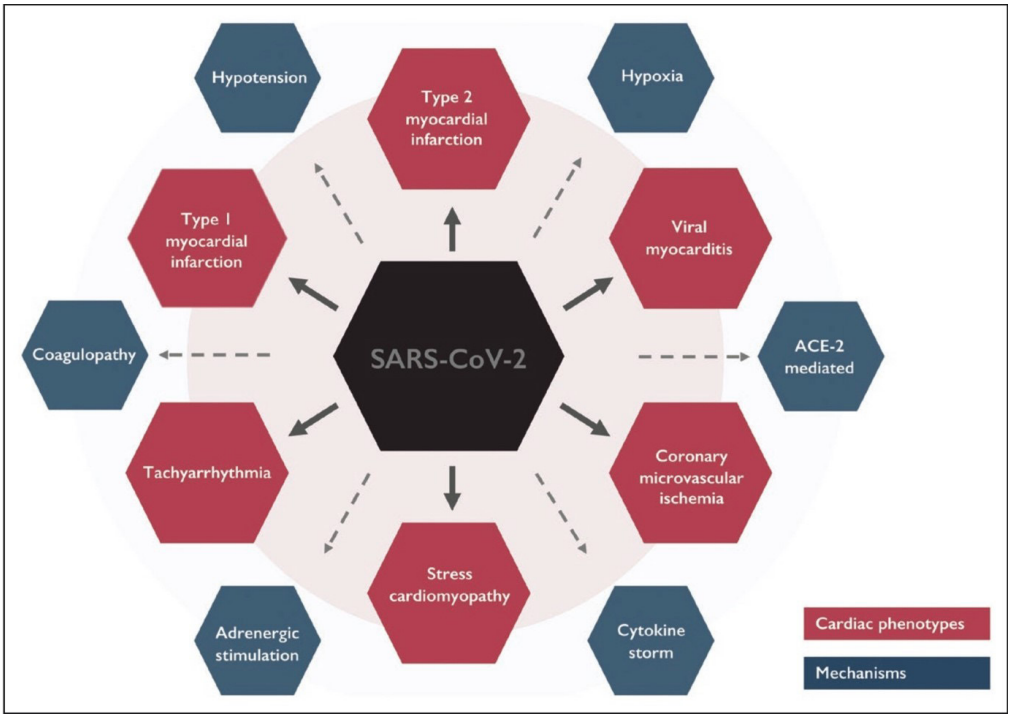
Dr Anda Bularga - Clinical Research Fellow

Anda joined the Centre for Cardiovascular Science in August 2019 through a British Heart Foundation funded scholarship and is now currently funded by REA3. She completed her core medical training in the South East of Scotland Deanery prior to this. She was also one of the speakers at the CVS Annual Symposium, held virtually this year on 18 June. Find out more about Anda's current research:

Myocardial injury is common and can be associated with a variety of cardiac and non-cardiac causes. Furthermore, myocardial injury can lead to adverse clinical outcomes. Understanding the aetiology and mechanism of myocardial injury can help to risk stratify patients. In the DEMAND-MI (BHF funded study) we are evaluating the mechanism of myocardial injury and the role of coronary artery disease in patients with type 2 myocardial infarction. The findings from this study will inform further research in the assessment and management of patients with type 2 myocardial infarction.

The global pandemic has brought changes to the direction of our research and over the past few months we have been concentrating on new studies to evaluate the effects of COVID-19 on the heart. Our understanding of the clinical manifestations of COVID-19 is improving with increasing scientific evidence. So far, we know that elderly patients and those with heart problems are susceptible to particularly poor outcomes from this infection. Furthermore, evidence suggests that acute myocardial injury is common and associated with severe illness. The frequency of myocardial injury and the underlying mechanisms of acute myocardial injury in COVID-19 are currently not well understood, but a range of potential direct and indirect causes are likely to be involved (Figure 1).

Figure 1: Potential mechanisms of acute myocardial injury in COVID-19 and related cardiac phenotypes



Chapman, et al. Circulation. 2020;141:1733-1735

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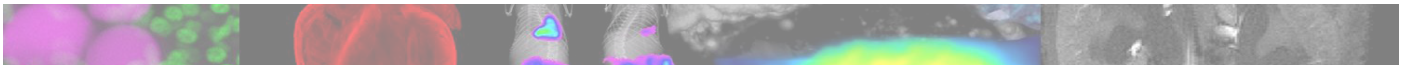
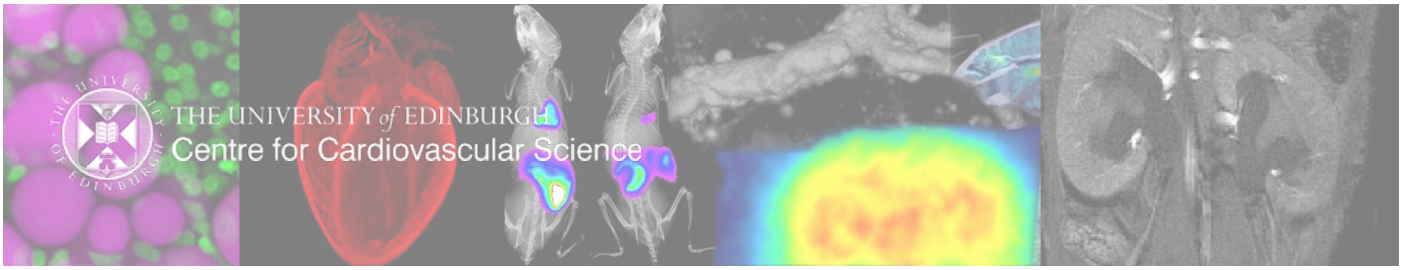
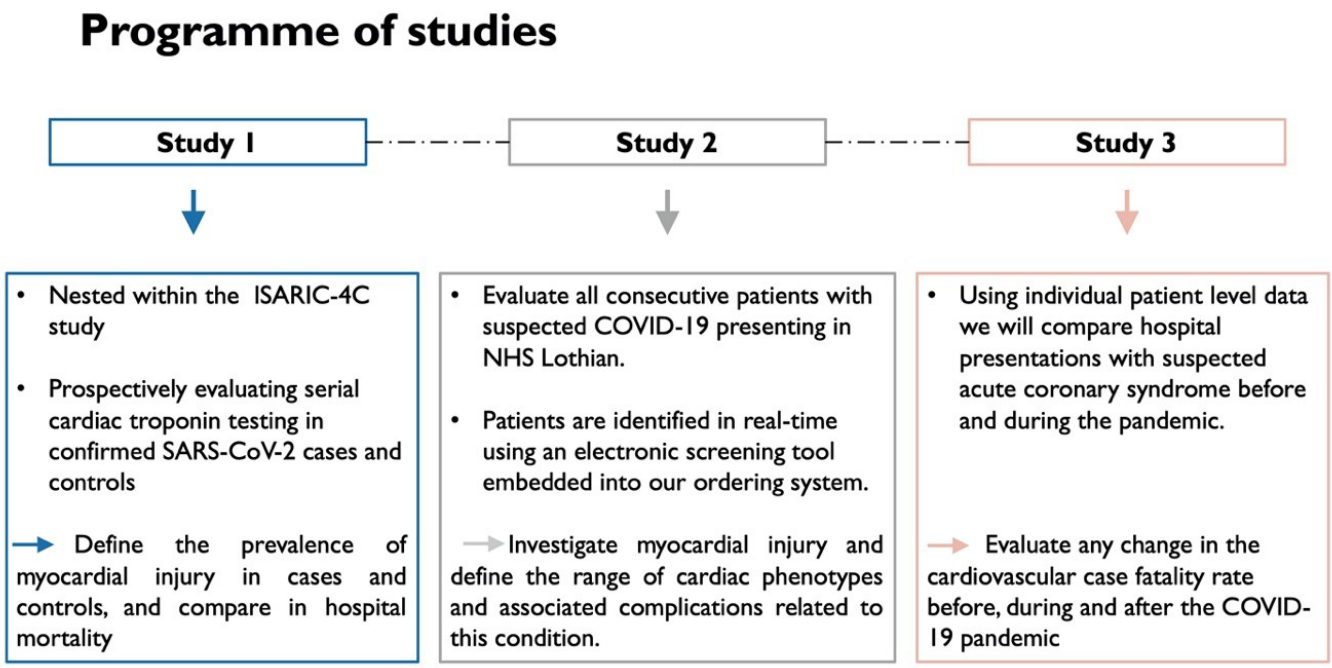




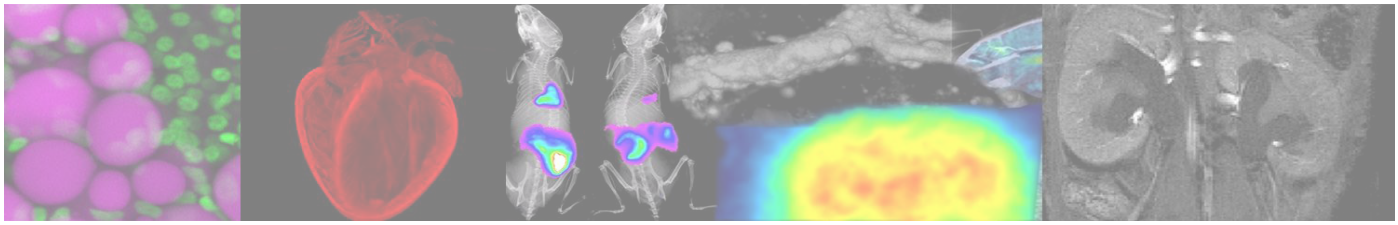
The indirect consequences of this pandemic on cardiac care may be as important as the direct effects of the infection, as patients with established cardiovascular disease are encouraged to self-isolate to reduce their risk.

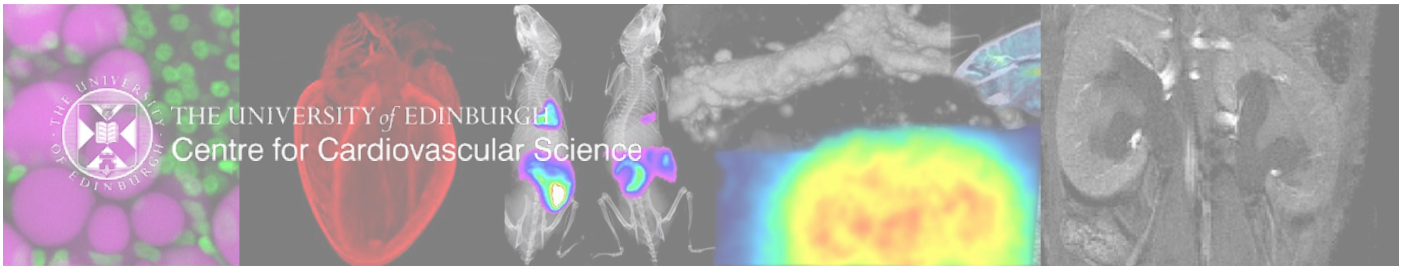
Through the use of routinely collected linked electronic health record data and systematic cardiac biomarker testing in this series of cohort studies (COVID – HEART, Figure 2) we aim to evaluate the direct and indirect consequences of COVID-19 on the heart and the provision of acute cardiac care. Our integrated programme of studies will provide generalisable findings to define the true prevalence of acute myocardial injury in COVID-19 and the range of cardiac manifestations associated with this condition. Furthermore, we will provide insight into the indirect consequences of this pandemic and ensure that pressures on the provision of care do not compromise the decades of progress we have made here in improving survival for patients with cardiovascular disease.

Figure 2: COVID-HEART Programme of Studies



The British Heart Foundation REA3 provides excellent training, collaboration and flexible funding opportunities for early career researchers, such as myself. I am very grateful for the support offered by REA3, which has enabled me to continue my research training at this challenging time. It has been a great opportunity to work as part of an interdisciplinary team (DataLoch COVID-19 Collaborative) towards a common goal to improve our understanding of the effects and consequences of this novel infection on the cardiovascular system.





BRITISH HEART FOUNDATION(BHF) VIRTUAL EVENT SERIES

The BHF are launching a brand new virtual event series, bringing research to life for the public! Over the next six months they will be featuring an array of inspiring speakers, telling their research stories for a lay audience.

The first will be taking place on the 29th July at 4pm. This event, called The Inflamed Heart, will involve:

- An introduction from the BHF's CEO, Dr Charmaine Griffiths, on the BHF today and how they've navigated the pandemic
- A short introduction from the BHF's Medical Director, Professor Sir Nilesh Samani, on BHF's research mission and the future of BHF research at this time
- A deep-dive into BHF Professor Federica Marelli-Berg's research into the inflamed heart where she'll be sharing her inspiring work into heart transplant rejection and myocarditis. She's also be touching on her pivot to Covid-19 research during the pandemic.

More information and how to register can be found on the BHF website:
https://www.bhf.org.uk/what-we-do/in-your-area/public-engagement-events

CVS VIRTUAL EXTERNAL SEMINARS

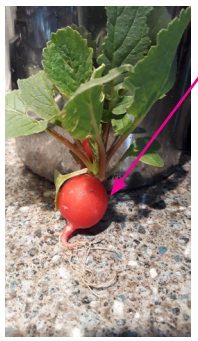
Two of our REA3 SAB members are providing talks after the summer break as part of this virtual series. Keep an eye out on further details being circulated in email communications:

Thursday 3rd September: Professor Anna Krook, Karolinska Institute
Thursday 17th September: Professor Calum MacRae, Harvard University
Titles and Moderators: TBC

FINALLY.....

Did you know that indoor tomato plants need tickled to encourage self-pollination? Yes? Well, not Gillian Joyce who jumped on the lockdown bandwagon and grew some stuff:

Minnie Mouse Pencil - Chief Tomato flower tickler



Not a tomato, a mighty radish. One survived.