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Title: Invasive Group A Streptococcus: changing epidemiology, optimised management, and effective chemoprophylaxis

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Scientific Abstract

Background

Group A streptococcus (GAS) infection is responsible for over 500,000 annual fatalities[1]. In 2023, Ireland saw a fivefold increase in invasive group A streptococcus (iGAS) cases compared to pre-pandemic levels[2]. This trend was observed worldwide[3], but reasons for this are poorly understood.

Primary Aim

Investigate the molecular epidemiology of iGAS in Ireland using laboratory and clinical data

Secondary Aims
- Identify genomic markers that correlate with severity, complications and outcomes in iGAS cases
- Evaluate the role of intravenous immunoglobulin (IVIG) use in iGAS treatment
- Investigate the efficacy of clindamycin as an anti-toxin agent in clindamycin-resistant GAS isolates
- Explore the facilitators and barriers to compliance with iGAS chemoprophylaxis in patients and prescribers

Methods

Study 1: An observational study using data from the Health Protection Surveillance Centre (HPSC) and the Irish Meningitis and Sepsis Reference Laboratory (IMSRL). Statistical analysis and bioinformatics will be employed to establish the molecular epidemiology, genomic diversity and emerging lineages of iGAS in Ireland and how this compares internationally.

Study 2: A multidisciplinary approach will be used to establish if genomic markers correlate with severity, complications and outcomes in iGAS.

Study 3: A systematic review and meta-analysis to evaluate the impact of IVIG on iGAS mortality.

Study 4: A laboratory-based study using an *in vitro* human whole blood model of streptococcal toxic shock syndrome to establish if the anti-toxin effect of clindamycin therapy is maintained in clindamycin-resistant GAS isolates.

Study 5: A two-phase qualitative study, investigating the facilitators and barriers to compliance with iGAS chemoprophylaxis from a prescriber and patient/contact perspective.

Conclusion

This study will assist in understanding the molecular epidemiology of iGAS nationally and provide information regarding correlations between GAS isolates and outcomes, data to inform optimised iGAS treatment and prophylaxis. Ultimately the aim is to improve patient outcomes and to minimise cross-transmission.

Lay Summary

Group A streptococcus (GAS) is a bug/germ which can be found in the throat and on the skin. Infections are typically mild, like strep throat or skin infections. Occasionally, GAS can cause life-threatening infections, known as invasive GAS (iGAS). Since October 2022, iGAS cases in Ireland have increased unexpectedly. Our study aims to figure out why this is happening, how best to treat and reduce the spread of these infections. We will look at these bugs in more detail using special DNA tests to see if any specific/new types of GAS are circulating in Ireland. We will also look at how good some of the treatments for these infections are by looking at published research and by doing some laboratory testing ourselves. Lastly, we aim to find out what factors help or hinder people in contact with iGAS patients receiving recommended antibiotics after exposure to prevent spreading GAS.

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Determining activity and disease progression in morphea using advanced imaging (IMAGINE Study)

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Scientific Abstract

Background

Morphea is a rare autoimmune disorder characterized by inflammation and sclerosis of the skin and soft tissues.[1] It has the potential to cause extreme disfigurement with both neurologic and ocular complications.[2,3] Once fibrosis takes hold it is irreversible. Pathogenesis is poorly understood however vascular injury is thought to play a central role.

Morphea is difficult to diagnose and difficult to monitor making management decisions challenging. The Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) score is the validated measure of morphea activity,[4] however as a clinical scoring tool, it is vulnerable to bias and interrater variability. Objective measurements including multispectral imaging and tissue viability imaging may provide greater information on the microvascular architecture in lesional skin providing a deeper, more accurate measurement of activity. Accurate methods of identifying activity and disease progression are required to prevent diagnostic delays and inform treatment decisions.

The aim of this study is to describe the microvascular architecture of morphea lesions compared to unaffected skin using advanced imaging to further our understanding of the pathogenesis of the condition and demonstrate the use of these methods in detecting disease activity.

Objectives
1. Determine the difference spectral response between lesional and non-lesional skin using multispectral imaging
2. Determine the difference on blood volume between lesional and non-lesional skin using tissue viability imaging
3. Retrospectively analyse 3-D images in patients with morphea
4. Explore the use of multimodal machine learning to objectively detect activity in morphea lesions

Methods

Multi-site prospective study of adult and paediatric patients with morphea. LoSCAT scores, serum levels of CXCL9 & CXCL10, multispectral images and tissue viability imaging will be collected serially. Control images will be taken from the unaffected contralateral side.
3D images of craniofacial morphea will be retrospectively analysed. A multimodal machine learning model will be used to incorporate clinical, serological and imaging data to better quantify activity.

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Lay Summary

Morphea is a scarring skin condition which appears subtle at first but can progress to involve the deeper layers of skin, muscle, and bone. Once scarring takes hold it is irreversible. Head and face involvement is disfiguring and can cause neurological problems including seizures.

As the condition is subtle at first, it is hard to diagnose and very difficult to track. It is important for doctors to be able to tell when the disease is active, so we know when to treat. This is crucial to prevent further destruction.

I plan to use specialized cameras which can 'see through' the top layer of skin and measure the volume of blood in the damaged skin compared to healthy skin. I plan to use an artificial intelligence model incorporating the different test results to help us to pick-up activity more effectively.

Interrogation of Overlapping Mechanisms of Epileptogenesis and GliomAgenesis in Human Brain Tumours (OMEGA)

Healy, Vincent. O'Connor, Kate. Sweeney, Kieron. Cunningham, Mark.

Scientific Abstract

The OMEGA project aims to understand overlapping mechanisms of epileptogenesis and gliomagenesis in human brain tumours.

Brain tumour related epilepsy is debilitating and common, occurring in up to 100% of low grade and >60% of high grade gliomas.[1–4] Brain tumours are increasing in incidence globally, and lead youth cancer mortality in many countries including the US and UK.[5–8]
An emerging focus has developed, to understand shared mechanisms for seizure generation (epileptogenesis) and glioma growth (gliomagenesis), recently appreciated as 'two sides of the same coin'.[9–13] However, there are many unknowns.

This project will utilise human tissue from the National Neurosurgery Centre to determine overlapping mechanisms of epileptogenesis and gliomagenesis via multimodal analysis including neuropathology, immunohistochemistry, electrophysiology and proteomics. Samples will include epileptogenic and non-epileptogenic i) high grade gliomas and ii) low grade gliomas, in addition to iii) LEATs (long-term epilepsy associated tumours). Both tumour and peritumoural samples will be independently analysed to understand the role of the peritumoural region and tumour microenvironment. A focus will be placed on brain tumour subtypes, recently recharacterized by the WHO 2021 Brain Tumour Classification, which particularly acknowledges IDH mutant status. This analysis will inform mechanistic and animal model studies, towards developing therapeutics directed towards both processes.

As an exploratory and novel analysis, this multidisciplinary, cross-institutional project may contribute much to our understanding of glioma and glioma-related seizures.

Lay Abstract

This research aims to understand how seizures are caused by brain tumours.

Glioma is the most common form of brain cancer. Quite often, the first sign of a glioma is a seizure. Seizures are a disabling quality of life issue for patients. Currently, there are no specific treatments specifically designed to treat brain tumour related epilepsy. In addition, we do not have a complete understanding of how brain tumour growth contributes to seizures, or how seizures contribute to brain tumour growth. We believe that these processes are connected and fuel one another.

Using human brain tumour samples from consented patients in the National Neurosurgery Centre in Beaumont Hospital, we will apply advanced methods to understand the overlapping processes of brain tumour growth and the generation of seizures. We hope to gather new information to design targeted treatments for brain tumour related epilepsy.

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Gram-negative bacteria and the progression of feline oral squamous cell carcinoma: a comparative investigation into the role of lipopolysaccharide, toll-like receptor 2 and toll-like receptor 4 in tumour progression.

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Scientific Abstract

Background

Feline oral squamous cell carcinoma (FOSCC) is a devastating disease of cats due to its invasive growth and lack of effective treatments. Its biologic behaviour is similar to human oral squamous cell carcinoma (HOSCC). In humans, periodontal disease has been established as a risk factor for HOSCC and various studies have investigated oral bacteria, lipopolysaccharide (LPS) and toll-like receptors (TLRs) in this context. In cats, the contribution of oral inflammation to FOSCC progression remains unstudied, despite the high prevalence of periodontal disease in this species.

Aims and objectives

To investigate the impact of LPS from Gram-negative oral bacteria on FOSCC progression via TLR2 and/or TLR4 activation.

1. Investigate TLR2 and TLR4 expression and the presence of Gram-negative oral bacteria in FOSCC.
2. Examine the response of FOSCC and HOSCC cell lines to LPS *in vitro* using a comparative approach.
3. Evaluate the impact of LPS on FOSCC progression *in vivo*.

Methods

1: Archived biopsies of FOSCC tissue will be interrogated for the presence of a) TLR2 and TLR4 via immunohistochemistry and b) for *Porphyromonas* and *Fusobacteria* via fluorescent in-situ hybridisation.

2: FOSCC and HNSCC cell lines will be cultured *in vitro* and exposed to LPS derived from human or feline oral Gram-negative bacteria. Response to LPS will be assessed via cell migration, invasion, and proliferation assays and via RT-PCR, RNA-seq and ELISA for cytokine and TLR expression.

3: An *in vivo* chorioallantoic membrane (CAM) model of FOSCC will be established and exposed to LPS. Response to LPS will be determined via semi-quantitative assessment of tumour growth parameters (size, weight, depth of invasion) and of angiogenesis.

Impact
This study will enhance our understanding of the potential impact of periodontal disease on the progression of FOSCC. This will help inform future prevention strategies, diagnostic techniques and treatments, improving animal health and welfare. This will also highlight the potential of companion animals as natural models of disease in oncology research.

Lay summary

Feline oral squamous cell carcinoma (FOSCC) is the most common oral tumour of cats. It is usually incurable and affected animals are often euthanased at diagnosis. Periodontal disease may contribute to the development of a similar oral tumour in humans, but it is unknown if the same is true in cats.

This research project will investigate the potential link between feline periodontal disease and the progression of FOSCC. We will test FOSCC samples for bacteria and proteins that bacteria bind to. We will also grow tumour cells in the laboratory and stimulate them with bacterial products, to investigate whether this causes the tumour cells to grow faster and become more invasive.

This will improve our understanding of why FOSCC develops, and help to guide vets in preventing and managing this condition in the future, thus improving animal health and welfare.

Title: Liquid biopsy to optimise treatment for HER2 amplified oesophagogastric cancer

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Background

Increasing understanding of the molecular biology of oesophagogastric adenocarcinoma (OGA) has led to the development of several effective targeted therapies. Human epidermal growth factor receptor 2 (HER2) is a receptor tyrosine protein kinase encoded by the ERBB2 gene, which acts in an oncogenic fashion to accelerate tumour proliferation. Overexpression of HER2 is associated with a more aggressive tumour phenotype in OGA, and recent trials have demonstrated the efficacy of HER2-directed therapies for patients with advanced and metastatic disease. Patient selection is currently guided by the presence of HER2 overexpression as determined by immunohistochemistry or fluorescence *in situ* hybridization, however intratumoural heterogeneity may limit the utility of these approaches, while increasing evidence indicates that the spectrum of HER2-overexpression may have major predictive relevance following biomarker-directed therapy. Liquid biopsy techniques such as the evaluation of circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA) present promise for the non-invasive molecular profiling of oesophagogastric adenocarcinoma to enhance patient selection.

Hypothesis

Liquid biopsy techniques such as assessment of CTCs and ctDNA may provide a non-invasive means to assess HER2 status in oesophagogastric adenocarcinoma, to provide important prognostic insights and determine eligibility for targeted treatments.

Aims & Objectives

1. Outline the impact of HER2 status on clinicopathological outcomes in OGA in a large international cohort
2. Determine the clinical significance of ctDNA-detected ERBB2 amplification as a novel predictive biomarker of HER2 status in OGA, implications for metastatic potential and primary-metastatic tumoural heterogeneity
3. Assess the clinical utility of CTC evaluation for the identification of HER2 overexpressing OGA, implications for metastatic potential and primary-metastatic tumoural heterogeneity

Outcomes

This project will determine the utility of emerging liquid biopsy techniques for the evaluation of tumour and metastatic HER2 status in OGA. Ultimately this strategy may optimise patient selection for targeted therapies, by enhancing the detection of in transit HER2 overexpressing metastatic clones, and improving our understanding of treatment resistance mechanisms among patients with OGA.

Lay Summary

Oesophageal cancer is a tough cancer to treat and it has a very poor survival rate. However, scientists are making progress in creating personalised cancer treatments. They've found special markers on the surface of cancer cells, one of which is called HER2. Think of these markers like bullseyes that treatments can aim for to destroy cancer cells. In the past, doctors could only find these markers after surgery or by taking tissue samples. But now, they've found a way to spot these markers in a patient's blood.

In this project, we want to see how HER2 markers show up in the blood of oesophageal cancer patients. Second, we will be working on better ways to spot HER2 on the surface of cancer cells using blood samples. The ultimate goal is to improve the chances of survival for people with oesophageal cancer. This research project aims to help us understand the disease better and create more accurate treatments that could save lives.

ATLANTIS - Identification of AutoimmuniTy reversaL in ANca vasculiTIS

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Scientific abstract

Background

ANCA associated vasculitis (AAV) is an archetypal autoimmune disease, resulting in immune-mediated organ damage. Immunosuppressive drugs (ISDs) have transformed AAV from a progressively fatal condition into chronic relapsing-remitting disease. However, infection post ISDs is now the primary cause of death among patients with autoimmune diseases. The greatest unmet need in AAV is to devise personalised strategies for precise tailoring of ISDs. ISDs could be reduced if it were possible to quantify relapse risk and to identify patients in whom treatment could be stopped safely.

Aims

The aim of this study is to quantify the immunological state in AAV remission and to identify factors that signify a return to normal, with re-establishment of tolerance to the relevant autoantigens, myeloperoxidase (MPO) or proteinase-3 (PR3).

The objectives are to:
1. Perform an in-depth comparison of the immune status of AAV patients in long-term remission off therapy (LTROT) with (a) patients with active disease, (b) patients with anti-GBM disease, a monophasic "one-hit" autoimmune disease, and (c) healthy controls.

2. Test whether the cluster of "tolerance markers" are present at various time points in the AAV disease course in LTROT patients.

3. Build a statistical model, incorporating a longitudinal dataset and the parameters identified above, and assess whether this identifies those remaining in remission when applied at the point of treatment discontinuation.

Methods

The RITA-Ireland Vasculitis RIV Registry and Biobank includes over 900 patients with vasculitis, approximately 50 meet LTROT criteria. This longitudinal dataset has serial biological samples obtained at diagnosis, remission and relapse (PBMC, serum, plasma, urine, DNA, Paxgene).
The experimental methods to define LTROT immune tolerance signature include dimensional flow cytometry using stored PBMCs, including identification of antigen specific B- and plasma-cells (Aurora cytometer), ELISA for soluble markers of immune exhaustion, proteomic screening (o-link), single cell RNA sequencing, PCR and measurement of Torque Teno Virus levels. Validation will be performed by testing international cohorts e.g. UCL, IDIBELL, Barcelona and Czech vasculitis biobank.
Impact

Tailored ISD use will benefit low-relapse-risk patients, enhance societal productivity, and reduce healthcare costs, patient/carer burden, and physician clinical time.

Lay Summary

Autoimmune disease affects 10% of adults, most of whom are women, and two of the top five medications with the highest cost globally are used to keep these recurring conditions in remission. These medications suppress the immune system, leaving the patient exposed to increased infection and cancer risk. Patients have highlighted a desire to tailor these treatments to each patient and to stop these medications where safe.

What is the aim of ATLANTIS?
ATLANTIS delivers a practical response to this challenge.
We aim to closely examine the immune system characteristics of patients who have infrequent disease flares by performing tests in laboratories. This may help us identify patients in which immunosuppressant medications can be stopped.

We use systemic vasculitis as a typical autoimmune disease to answer these questions.

Improving antenatal diagnosis of coarctation of the aorta

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Scientific summary

Background

Coarctation of the aorta (CoA) is a discrete narrowing usually in the region of the aortic isthmus and accounts for approximately 8% of all live births with congenital heart disease (CHD). CoA results in cardiogenic shock following closure of the ductus arteriosus and requires urgent surgery in the neonatal period. Despite vast improvements in antenatal detection of CHD, CoA remains notoriously difficult to accurately diagnose in fetal life, with high rates of both false positives and false negatives. The strong evidence base for improved outcomes following antenatal diagnosis serves as a driving force to improve current detection rates of 20-40%.

Aims

1. Establish the first open-source dataset of fetal echocardiograms labelled for the presence or absence of postnatal CoA.
2. Develop a set of novel machine-learning algorithms which demonstrate explainability using visualisation techniques to accurately predict postnatal coarctation.
3. Explore attitudes of patients and screening practitioners towards AI in clinical practice, as well as the human-AI interaction.

Methods

1) Create a dataset of cases and controls at varying gestations. Perform pre-processing to bring the images to MIDaR (medical imaging data readiness) level A – this is a standardised approach to preparing images for machine learning tasks.
2) Experiment with novel machine learning techniques to develop a model to detect coarctation on fetal ultrasound scans. Use visualisation techniques to provide insights into the model's decision-making process.
3) Conduct separate online surveys of a) screening practitioners and b) pregnant people to explore their attitudes towards the use of AI in fetal screening. Conduct an online scenario-based simulation study to assess the interaction between users, the AI tool and explainability techniques.

Impact

This study may improve our antenatal detection rate of CoA, therefore improving patient outcomes. It will also provide insights which may improve translatability of AI into real-world clinical practice.

Lay summary

Almost 1 in 1000 babies are born with a structural problem affecting their heart – congenital heart disease. Coarctation of the aorta (CoA) describes a narrowing in the main blood vessel which supplies oxygenated blood to the body. This is one of the most common forms of congenital heart disease but also one of the most difficult to detect before birth. We know that diagnosing CoA prior to delivery improves outcomes for the baby by allowing stabilisation and prompt surgical repair.

Our research aims to harness novel artificial intelligence techniques to improve the diagnosis of CoA before birth using fetal ultrasound. We will include all fetal cardiology units on the island of Ireland as well as collaborating with international centres of excellence (Evelina Children's Hospital, London; Queen Silvia Children's Hospital, Gothenburg). We will also explore pregnant people and screening practitioners' attitudes towards and interaction with artificial intelligence tools, to improve our ability to use our findings in real-world clinical practice.

Characterisation of High-Risk Multiple Myeloma and An Exploration of CAR-Cellular Therapeutics in this Cohort (CHaRM-CAR)

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Scientific Abstract

Background

Multiple myeloma (MM) is an incurable haematological malignancy characterised by clonal proliferation of plasma cells in the bone marrow. There is a cohort of high-risk myeloma (HRMM) patients, with disease characteristics which predispose them to worse clinical outcomes and poor therapeutic response. The 5-year survival rate for HRMM is significantly worse than standard risk disease (30% vs 82%).[1]

Defining and identifying HRMM is complex but essential for accurate prognostication and to facilitate the use of targeted treatment strategies in this cohort. There is a need to define the specific genomic factors characterising HR disease and to understand the downstream oncogenic impact of these aberrations.

Cellular therapies, including chimeric antigen receptor T-cell therapy (CAR-T), have demonstrated promising clinical results. However, challenges associated with CAR-T therapy have prompted consideration of the application of CAR technology to natural killer (NK) cells, which could have multiple conceptual advantages. There is a need to evaluate the efficacy of CAR-NK therapy in HR patients, particularly following relapse through prior lines of treatment, including cellular therapies.

Aims

1. Interrogate the tumour microenvironment in high-risk multiple myeloma, using a genomic and metabolomic approach, to identify specific features of high-risk disease at a molecular level.
2. Utilise a computational biology approach to validate genomic results and to predict the clinical impact of identified genomic alterations.
3. Design and evaluate an adoptive CAR-NK therapy that demonstrates in-vitro effectiveness against high-risk multiple myeloma.

Methods

The project will be divided into 3 work packages:

1. Multi-omic (genomic and metabolomic) interrogation of the tumour microenvironment of patients with HRMM. Genomic analysis will be completed on bone marrow aspirate samples from HRMM patients. Samples from HRMM patients who have relapsed following CAR-T therapy will undergo both genomic and metabolomic analysis.

2. Results of genomic profiling in HRMM will be validated within a large cohort using the international CoMMpass database (Multiple Myeloma Research Foundation/MMRF).

3. Dual-target CAR-NK cells will be generated using a validated retroviral transduction method. In-vitro efficacy of dual-target CAR-NK cells against primary MM cells derived from high-risk patients (HRMM) will be assessed using flow cytometry-based cytotoxic assays.

Lay Summary

Multiple myeloma (MM) is a cancer that develops in a type of white blood cell called a plasma cell. The clinical outcomes for patients with MM have significantly improved in the most recent decade, resulting in an improved quality of life and prolonged survival. However, it remains a largely incurable disease with inevitable relapse and the development of treatment resistance. There is significant variability regarding the duration of treatment response and overall survival. In particular, there is a cohort of high-risk patients, who possess disease characteristics which result in poor response to treatment and significantly worse clinical outcomes. The overarching aim of this project is to evaluate possible causes of high-risk disease at a genetic and cellular level and to explore a potential cutting-edge cellular therapy in a laboratory-based model of high-risk MM.

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The RolE oF androgen excess in mUscle Energy metaboLism in women with PolyCystic Ovary Syndrome (REFUEL PCOS study)

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Scientific Abstract

Polycystic ovary syndrome (PCOS) is a prevalent metabolic disorder affecting approximately 10% of women worldwide, resulting in a significant healthcare and economic burden, estimated at $15 billion annually in the US in 2023. While traditionally viewed as a reproductive disorder, increasingly PCOS is associated with severe metabolic health consequences throughout a woman's life. Androgen excess, a key characteristic of PCOS, correlates directly with the risk of developing type 2 diabetes, non-alcoholic fatty liver disease, and other metabolic complications. However, the specific mechanistic role of androgens in the pathophysiology of metabolic disease in PCOS remains unclear.

Insulin resistance conditions are linked to lipid accumulation in non-adipose tissues. Skeletal muscle, liver, and pancreatic beta cells are particularly affected, impairing insulin signalling and glucose metabolism. Lipid droplets, including triglycerides and cholesterol esters, play a crucial role in cellular metabolism by fuelling fatty acid oxidation, and lipid droplet dysfunction has been linked to metabolic disturbances. Skeletal muscle is a major site of lipid storage, and the interplay between lipid droplets and mitochondria is essential for maintaining energy balance and metabolic homeostasis. Recent proteomic analyses of luteal cells identifying steroidogenic enzymes within lipid droplets, notably HSD3B and CYP11A1, have shed light on a potential new role for these organelles. When combined with findings from other proteomic investigations examining lipid droplets in diverse tissues outside the adrenal gland, the hypothesis that lipid droplets may play a pivotal role in the metabolism of steroid hormones emerges.

PCOS is known to be associated with lipotoxicity; thus investigating the impact of androgen excess on lipid droplet biology in skeletal muscle is crucial. By exploring lipid droplet size, number, and distribution changes, we can gain insights into lipid and steroid metabolism alterations and potential lipotoxic effects associated with PCOS. This line of investigation adds an important dimension to our understanding of metabolic dysfunction in PCOS and may provide further insights into the mechanisms contributing to the pathogenesis of PCOS.

Lay Abstract

Polycystic ovary syndrome (PCOS) is a common condition affecting approximately 10% of women worldwide, with substantial economic costs. It was once considered primarily a reproductive issue, but we now recognise its broader health implications. PCOS is characterised by elevated androgens (male hormones), increasing the risk of type 2 diabetes, liver complications, and metabolic issues. The exact link between androgens and health outcomes is still under investigation.

PCOS often involves insulin resistance, leading to fat accumulation in non-adipose tissues like muscles, the liver, and the pancreas. This disrupts glucose utilisation for energy, especially in skeletal muscle. Recent studies have identified hormone-related enzymes within tiny fat-storage structures called lipid droplets in ovarian cells. This suggests a new role for these structures in hormone regulation.

Understanding how excess androgens impact fat storage is important. We plan to investigate changes in lipid droplet size, number, and location in skeletal muscle to provide valuable insights into how PCOS affects fat and hormone metabolism, potentially shedding light on this condition's underlying mechanisms.

Why do kidney transplants fail so early in young people?

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Scientific Abstract

Background
The burden of End-Stage Kidney Disease in young people is severe. Renal transplantation is the gold-standard treatment. Recipients <30 years old have the best short-term outcomes following transplantation but paradoxically have the worst long-term graft survival rates. Why kidney transplant fail so early in young people is poorly understood.

Aim

To explore whether the difference in long-term kidney transplant outcomes between younger (< 30 years old) vs older (≥30 years old) recipients is associated with variations in epidemiological risk factors, proteomic profiles and subsets of immunological cell types.

Objectives

1.) Identify epidemiological factors associated with long-term kidney transplant outcomes and variation in these between younger and older recipients.
2.) Investigate variation in proteomic profiles between younger recipients with/without evidence of immunological injury and comparing with older recipients with/without evidence of immunological injury.
3.) Investigation of subset variance of T- regulatory, B-regulatory and natural killer cells between recipients <30 and ≥30 years old with functioning transplants.

Methods
Study-1: Data will be extracted from a prospective clinical database of renal transplant recipients. Statistical analysis will identify variation in transplant graft outcome and demographic associations with graft loss.
Study-2: Using the OLINK 384 inflammation platform, proteomic profiling of stored samples from young recipients with (n=50) and without (n=50) evidence of immunological injury will be performed. A control group of older recipients with (n=50) and without immunological injury (n=50) will enable cross-sectional comparisons to identify proteins associated with immunological injury in both age categories.
Study-3: Patients with functioning transplants will be recruited (n=25 <30 years old, n=25 ≥ 30 years old) to provide serum samples. High-dimensional multi-colour flow cytometry will enable subset analysis of T-regulatory, B-regulatory and Natural Killer cells identifying variation between younger and older recipients.

Conclusion
This study will assist in the understanding of why long-term outcomes in younger transplant recipients are poorer. The research may help identify ways of risk stratifying for immunologically mediated transplant loss.

Lay Summary

Kidney transplantation is the best treatment for people with end-stage kidney disease; providing improved quality of life and much longer survival. Unfortunately, younger people appear to be at higher risk of losing their transplant; having a devastating impact on their health. It remains unclear why kidney transplants fail so early in young people.

The aims of my PhD are: 1.) Identify the reasons for kidney transplant loss in younger people and determine whether other details about their health can be linked to their increased risk of transplant loss. 2.) Use new technology to measure difference in proteins (proteomics) in transplant recipients to better understand their increased risk of transplant failure. 3.) Measure different types of cells that affect transplant outcomes to see if their expression varies between younger and older transplanted patients

I hope by better understanding why young people suffer from earlier transplant loss we will be able to improve their care and ultimately reduce transplant loss.

An implantable, Closed-Loop Antihypertensive Drug-Delivery Algorithm in Hypertension (The CLADDAGH study)- Translational and Innovation Approach

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Scientific abstract

Background

Suboptimally controlled hypertension remains the leading cause of cardiovascular morbidity and mortality, affecting >1 billion adults. Oral antihypertensives are the mainstay of treatment, but blood pressure (BP), internationally, remains uncontrolled in approximately 63% of patients. BP variability between clinic visits can lead to challenges in appropriate dosing of antihypertensives, particularly in non-dipping hypertension and resistant hypertension. With the advent of novel wearable BP measurement devices, it is likely that there will be a shift to more of a self-management support model for hypertension. However, the technology to integrate monitoring with dose modifications has not yet been realised.

Aims/Objectives

1. Develop a soft robotic drug delivery device for on-demand delivery of Esmolol (an antihypertensive) and test this in vitro and in vivo. Drug release will be controlled by pressure applied to the device.
2. Develop dose-response relationships between Esmolol, BP and heart rate response in a hypertensive animal model.
3. Test this control system in a simulated cardiovascular model of human physiology and in an animal model, using radiotelemetry measurement and subcutaneous implantable drug release.

Methods

(i) Stroke-prone spontaneously hypertensive rats (SHRSP) will be administered a fixed dose of Amlodipine orally until steady state BP lowering is achieved. Varying doses of Esmolol will be administered via pump in a bolus manner with washout between doses, to establish a time-course and response curve. Outputs of heart rate, systolic and diastolic blood pressure will be measured, using radiotelemetry.
(ii) Using data collected in (i), a control system using a closed-loop design will be created. The system components will include the radiotelemetry device which will transmit data to a mini-processor and micro-controller, which will run the control algorithms that determine the timing and release of Esmolol and wirelessly communicates this to the subcutaneous device containing Esmolol. This closed-loop system will be tested in SHRSP models, with assessment of mean BP, BP variability and heart rate.

Discussion

My presentation will focus on the translational elements of my work, building on the research performed in the Duffy laboratory.

Lay summary

High blood pressure (hypertension) is one the main causes of ill health and death. Despite treatments, many people's blood pressure (BP) stays uncontrolled, leading to challenges in prescribing medications effectively. Wearable BP monitors offer a promising solution, yet integrating monitoring with dose adjustments is a challenge.

Our goal is to create a drug delivery device for Esmolol, an antihypertensive. It would lie over the skin and administer the drug under the skin through a tube. We'll test it in lab settings and in animals. By administering varying Esmolol doses in hypertensive rats, we'll study BP and heart rate responses. Using this data, we'll develop a control system. This system will collect BP data, process it through a mini-processor, and control the release of Esmolol, through the pump, wirelessly.

My presentation will highlight how this work builds on prior research, focusing on its potential to advance hypertension management by developing a smart system for personalised drug delivery.

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Scientific abstract

Objective
To report a novel paraneoplastic encephalitis associated with calmodulin kinase-like vesicle associated (CAMKV)-IgG antibody.

Background
Uterine cancer is historically associated with paraneoplastic cerebellar ataxia but not encephalitis. High-throughput protein microarrays expedite novel neural antibody discovery.

Methods
Microarrays helped identify novel antigens for unclassified antibodies identified by murine brain-based indirect immunofluorescence assay (IFA) October 2022-September 2023. A serum with unclassified cerebrum-restricted IgG staining (cerebellum negative) had CAMKV as high-ranking candidate antigen. Additional patient samples were obtained retrospectively (serum, 3; CSF, 3). Western blot, dual confocal microscopy, immune-absorption and mass spectrometry were performed to elucidate CAMKV specificity further. Recombinant protein-specific assays (cell-based assay [CBA], western blot) provided additional molecular confirmation.

Results
Five patients with CAMKV-IgG were identified, 3 women; 2 men (median symptom-onset age was 59 years; range, 53-74). All samples (serum 4, CSF 3) were tissue IFA and CAMKV CBA positive. Onset was subacute (4) or acute (1). All had encephalitis manifesting with ≥1 of: behavioral change (3), seizures (3), psychosis (2), amnesia (2), hyperkinetic movements (3), insomnia (2). None had cerebellar ataxia. CSF revealed lymphocytic pleocytosis (median, 17; range, 8-74 [normal, ≤5]) in all 4 available. EEG was abnormal in 3 of 4 (subclinical electrographic seizures [2], bilateral epileptiform discharges [1]). T2 hyperintensities present in all patients were: mesial temporal (4), bilateral basal ganglia (3). Diffusion weighted lesions affected right paramedian frontal and parietal lobes (1), and bilateral anterior cingulate gyri (1). Cancers detected were uterine (3 patients: adenocarcinoma [2; poorly differentiated, 1], neuroendocrine [1]), bladder (1), non-Hodgkin lymphoma (1). Two patients developed encephalitis following immune checkpoint inhibitor cancer therapy (atezolizumab [1], pembrolizumab [1]). All 5 demonstrated an initial response to immunotherapy (corticosteroids [4], IVIG [2]); 3 patients died from cancer.

Conclusion
CAMKV-IgG is a biomarker of immunotherapy-responsive paraneoplastic encephalitis (limbic and extra-limbic) notably associated with uterine cancer.

Lay Summary

Autoimmune encephalopathies are disorders which occur when the body's immune system attacks the brain.

Doctors are guided by the specific antibody associated with the patient's symptoms as it provides information on the natural course of the disorder, the treatment needed and which cancer (if any) to screen for. In many patients the antibody is not known and discovering these antibodies helps in diagnosis and treatment.

CAMKV IgG is a newly discovered antibody which associates with a subset of patients with autoimmune encephalitis. These patients usually have psychiatric problems, confusion, and seizures. They also have striking abnormalities on MRI. All women with CAMKV encephalitis described to date have uterine cancer. In the future, testing patients for this new antibody will help doctors diagnose this disorder. CAMKV encephalitis should be suspected in women with uterine cancer who present with new-onset confusion and/or seizures.

Moderate alcohol consumption is associated with progression of left ventricular dysfunction in those with Pre-Heart failure.

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Scientific abstract

Background: There is limited evidence of the longitudinal impact of alcohol dose and progression of structural cardiac changes amongst European populations at risk of heart failure or with pre-heart failure (pre-HF). Current European heart failure (HF) guidelines describe beneficial effects in the general population of light alcohol usage on risk of HF[1].

Methods: This is a secondary analysis of the St Vincent's Screening TO-Prevent Heart Failure (STOP-HF) trial [3], amongst patients at risk or with pre-HF, with documented alcohol intake and echocardiography at both baseline and follow up ≥18 months. The main outcome measure was the relationship between progression of HF (left ventricular dysfunction and/or development of HF symptoms), stratified according to whether patients were classified as at risk or with pre-HF at baseline, and 3 categories of alcohol dose: no alcohol usage; low alcohol use (1 unit daily or 70g/week); moderate-high alcohol usage (>1 unit daily or >70g/week).

Results: Of 744 patients included in the analysis (mean age 66.5 (9.8) years), 395 (53.1%) were female, 556 (74.7%) had hypertension, 145 (19.5%) had diabetes and 260 (34.9%) had pre-HF at baseline. Overall, a total of 201 (27.0%) patients reported no alcohol usage, 356 (47.8%) reported low alcohol intake and n=187 (25.1%) reported moderate-high alcohol usage alcohol intake. Over a median follow up period of 5.44 [IQR 4.33;6.73] years, 84 (11.3%) patients had progression of HF. Moderate-high alcohol usage was associated with an adjusted 4.5-fold (95% CI 1.7- 15.9, p=0.004) increased risk of progression of HF amongst those with pre-HF at baseline. Increased progression of HF was also evident in moderate (70-140g/week) and high (>140g/week) alcohol use subgroups. Finally, there was no protective associations of low alcohol usage (<70g/week) and progression of HF in any patient group.

Conclusion: Moderate alcohol (>70g/week) usage appears to be associated with progression of HF in European patients in the STOP-HF study and we did not observe protective benefits of low alcohol usage.

Lay summary

2.3 billion people worldwide consume alcohol, but despite its common use, there is mixed evidence of how different doses of alcohol are associated with the risk of developing heart failure. Different cardiology guidelines advise for differing amounts of safe or even beneficial levels of alcohol. This study included people who were at risk of heart failure [asymptomatic but with cardiovascular risk factors, and no structural/functional heart changes on echo scan] and those with pre-heart failure (pre-HF), [asymptomatic, with risk factors and structural/functional heart changes as seen on echo scan]. This study found over the course of 5.4 years, that those with pre-HF who consumed more than ~1 bottle of wine a week, were 4.5x more likely to have progressive negative changes in the heart and/or develop symptomatic heart failure compared to those who did not drink alcohol. We found no protective benefits on the risk of heart failure related to any dose of alcohol consumption, contrary to current guidelines.

Subphenotypes in critical care: translation into clinical practice
Supervisors: Prof Danny McAuley (QUB), Prof Cecilia O'Kane (QUB)
Secondary supervisors: Prof Carolyn Calfee (University of California San Francisco), Dr Pratik Sina (Washington University at St. Louis), Dr David Antcliffe (Imperial College London)

Scientific abstract

Subphenotypes of acute respiratory distress syndrome (ARDS) have been identified through latent class analysis (LCA) of randomised controlled trials (RCTs). The hyperinflammatory and hypoinflammatory subphenotypes have prevalence, mortality rates, biomarker profiles, and clinical characteristics that are reproducible across ARDS populations and respond differently to treatment in retrospective analyses of trial data. These subphenotypes are a key focus of interest in ARDS precision medicine but, at present, can only be identified retrospectively using large datasets. Now, a parsimonious model incorporating plasma measurement of interleukin-6 (IL-6), bicarbonate, and soluble tumour necrosis factor-1 (sTNFR-1) can accurately allocate individual patients' subphenotype (AUC 0.94). This model is employed in combination with a point-of-care chemiluminescence assay (Randox Inc, Co. Antrim, Northern Ireland) to prospectively identify ARDS subphenotypes at the bedside in the PHIND study (NCT04009330), which has now closed to recruitment, recruiting 518 patients with ARDS and an exploratory cohort of 140 patients with acute hypoxaemic respiratory failure (AHRF). In addition to providing a platform for the development of precision medicine trials in ARDS and AHRF, PHIND will shed light on subphenotypic mechanisms, the interaction between known subphenotyping schema, and the extensibility of ARDS subphenotypes to other critical care populations. The upcoming PANTHER trial will build on insights from PHIND. PANTHER will recruit patients with ARDS, prospectively identifying the hypo- and hyperinflammatory subphenotypes and randomising both subphenotypes to treatment with multiple anti-inflammatory medications (initially simvastatin and baricitinib) in an international, parallel-arm, Bayesian adaptive platform trial design.

Lay Summary
Acute respiratory distress syndrome (ARDS) is a severe and often deadly condition of lung failure in the intensive care unit that has no treatment. Researchers have not been able to find medications that work for ARDS, perhaps because there are two subtypes of ARDS and the right treatment for one subtype might not be the right treatment for the other. We can now quickly determine what subtype a patient belongs to in the recently finished PHIND study. The PANTHER trial will follow and build on PHIND by using a new type of trial design called a Bayesian adaptive platform trial. This type of trial allows multiple medications to be tested at the same time in both ARDS subtypes and allows us to find an answer as to which medications are effective more quickly.

A strategic approach to establishing a new regional head and neck cancer patient and public involvement group in Northern Ireland

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Scientific abstract

Background
Patient and public involvement (PPI) is an integral part of research. People with lived experience of head and neck cancer (HNC) have historically been underrepresented within existing PPI groups, including those in Northern Ireland (NI). There are unique challenges experienced by these patients such as difficulties with speech and facial disfigurement. Given the increasing incidence of HNC it is important to ensure this patient group is represented and patient-focused research initiatives established.

Objectives
This initiative aims to adopt a strategic approach to establishing a regional HNC PPI group within NI. This new group will include patients with lived experience of HNC and their family members. It will be facilitated by researchers across academic institutions and healthcare trusts, providing a sustainable approach to building these relationships and linking into existing PPI initiatives.

Methods
Throughout the planning phase, the current landscape of HNC PPI was scoped throughout the United Kingdom and Ireland, garnering knowledge from Liverpool and Cork on their operational frameworks. After stakeholder consultation we approached the Northern Ireland Cancer Research Consumer Forum (NICRCF), a well-established regional PPI group, proposing the creation of a unique HNC subgroup. Following agreement, a public information and awareness event was held in August 2023.

Results
The new NICRCF HNC PPI subgroup has been established, with an inaugural meeting in October 2023. Currently there are 14 HNC PPI members, encompassing a diverse range of HNC sub-sites, treatment modalities, age range and educational status. To consolidate and sustain regular group meetings for the initial 18 months, £2500 of grant funding has been secured. The group is currently supporting three HNC projects, with a further two in the pipeline. It has also been approached by organisations seeking input regarding HNC campaigns and educational initiatives.

Impact
Creation of this new group has already resulted in a significant contribution to the HNC research landscape and provided an opportunity for interested individuals to become involved in HNC research.

Lay summary

The number of people diagnosed with head and neck cancer (HNC) is increasing. Patients with this type of cancer often face many unique challenges after treatment, including facial disfigurement and difficulties with swallowing and/or eating.

Patient and public involvement (PPI) relates to experts with lived experience of a disease, or those who care for them, who can make research more accessible and relevant. Within Northern Ireland (NI) there was a lack of HNC PPI involvement in research. To address this gap a new regional HNC PPI group was created. A key role for this group is to link with researchers and clinical staff to improve the quality and relevance of HNC research. After securing funding to establish this new group, known as the NI Cancer Research Consumer Forum HNC PPI subgroup, 14 members have been recruited and training has been provided. This newly formed group is currently supporting three HNC research projects.

UNEARTH: Understanding Adherence in Apparent Treatment-Resistant Hypertension

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Scientific abstract

Background

Hypertension care providers report having little time and few tools to support detecting and improving adherence in their patients.[25] Measurement of adherence to medication is fraught and presents a clinical challenge.[14] High performance liquid chromatography tandem mass spectrometry (LC-MS/MS), can accurately measure anti-hypertensives and their metabolites within patient urine or blood samples, providing accurate point-in-time estimation of anti-hypertensive adherence.[6,19,20]

Tailoring adherence-supporting interventions to the individual according to their particular beliefs and capacity is likely to improve the efficacy of such an intervention.[24]

Aims

1. To describe and critically evaluate the "when, where and how" of biochemical adherence testing use to date.
2. To investigate psychosocial and clinical characteristics associated with patients' partial and complete anti-hypertensive non-adherence within a tertiary care setting using mixed methods.
3. To provide the evidence required to inform policy and planning care pathways for this patient group.

Methods

1. A prospective cohort study will recruit patients from two separate specialist hypertension clinics and gain detailed assessment of clinical and psychological factors including (beliefs about medicines, adherence, anxiety/depression, health literacy, treatment coherence, physician communication, detailed demographics, clinical assessment and LC-MS/MS of urine for anti-hypertensive drugs and their metabolites.
2. A descriptive qualitative approach using semi-structured interviews of participants purposefully sampled from the cohort study will be used to further investigate these issues as existing quantitative measures for medication adherence are insufficient to capture the complexity of medication-taking behaviour in patients with apparent treatment-resistant hypertension. Qualitative description aims to describe participants' perceptions, responses and concerns and to comprehensively summarise these; it is particularly suitable for this type of exploratory work as it can provide useful data to tailor future clinical care.
3. Cost analysis studies. Our 2022 study, now published, reports on the cost of providing care in a multidisciplinary hypertension clinic which manages patients with suspected secondary hypertension and/or apparent treatment-resistant hypertension. We are now recruiting for a follow-on study to assess the cost to patients attending clinic.

Lay summary

Hypertension (high blood pressure) is a common health problem that contributes to several serious health complications such as heart attack, stroke and kidney disease. Hypertension can usually be controlled with medication, but many people do not take hypertension medication as prescribed (this is called medication adherence). Doctors consider that someone has 'resistant' hypertension when their blood pressure is not controlled despite being on at least 3 blood pressure medicines. Previous research has shown that up to 70% of people labelled as having 'resistant' hypertension are not taking their medicines as prescribed and

perhaps do not have 'resistant' hypertension at all. This means that the healthcare service is spending significant resources investigating and treating hypertension when those resources could perhaps be better spent addressing adherence.

This research aims to better understand why some people do not take their medicines as prescribed. Using a technique called liquid chromatography mass spectrometry, we can analyse patients' urine to detect whether patients are taking their medicines as prescribed. We will compare those findings with what patients tell us themselves about their adherence to medication and their blood pressure control. We will also ask participants to complete a number of questionnaires relating to their attitudes and beliefs about medicines, their levels of anxiety and depression, and their perceptions of their interaction with their healthcare provider. This will allow us to explore what features of a person affect their adherence to medication so that healthcare providers can better predict who will have difficulty taking medicines as prescribed and provide support when and where it is most needed.

Associations between the gut microbiome, inflammation and cardiovascular profiles in People with HIV (PWH).

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Scientific abstract

Background:

Systemic inflammation and innate immune activation are associated with chronic HIV infection, despite effective antiretroviral therapy. We aimed to explore the relationship between the gut microbiome, inflammation and HIV infection from participants of the Understanding the Pathology of Bone Disease in HIV-infected (UPBEAT)-CAD study.

Methods:

The UPBEAT-CAD sub-study examined cardiovascular disease (CVD) risk in people with HIV (PWH) and HIV negative participants. Gut microbial diversity was explored by 16SrDNA analysis of biobanked stool samples. Taxonomic repertoires were derived and diversity analysis was performed. Analysis of Compositions of Microbiomes with Bias Correction (ANCOM-BC) was applied to identify the differentially abundant (DA) species based on absolute abundance while adjusting the covariates. 36 biomarkers were analysed in matched plasma by bead-based ELISA (Luminex) and chemiluminescence (MesoScale Devices). Correlations between biomarkers, metadata and abundant bacterial species was conducted using Spearman correlation. All analysis was conducted in R ver 4.3.2.

Results:

The median age of the 81 participants included in the analysis was 51 (46,56) and three-quarters were male (73%) and Caucasian (74%). A significant difference in β-diversity was observed between PWH and HIV negative participants (PERMANOVA <0.001). ANCOM-BC analysis identified 42 species that were DA, with depletion of 17 species and enrichment of 25 species. PWH displayed a distinct pattern of inflammation with bacterial species compared to HIV negative participants. Elevated I-FABP was associated with an enrichment of several bacterial species associated with CVD measures. Conversely, a depletion of several butyrate-producing bacteria was correlated with elevation of different inflammatory markers (CRP, d-dimer), endothelial markers (vWF, VCAM, E-selectin) as well as CVD markers (HDL, cholesterol and triglyceride:HDL ratio).

Conclusion:

This study describes distinct microbiome and biomarker patterns linking CVD risk in PWH, providing further evidence of an important role for the microbiome in modifying a persistent inflammatory state and influencing clinical outcomes in HIV infection.

Lay summary:

This study explored the connections between gut bacteria and inflammation in people with HIV (PWH) and HIV negative participants. 81 participants were enrolled from the Understanding the Pathology of Bone Disease in HIV-infected (UPBEAT)-CAD study, which matched participants for traditional cardiovascular risk factors. Stool and blood samples were collected and analysed. The diversity of the gut bacteria differed between the HIV positive and HIV negative groups and 17 bacterial species were found to be significantly lower while 25 species were significantly higher overall. In PWH, a lower level of some healthy bacteria were positively correlated with higher inflammation markers and a higher level of some bacteria were associated with higher level of I-FABP, a marker of gut inflammation and cardiovascular risk outcomes. In contrast, these changes were not seen in the HIV negative group. This research reveals patterns of gut bacteria and biomarkers that affect cardiovascular risk in PWH.

Public and Patient Involvement Strategy in the 'Cognitive Impairment in People who are long-term Homeless: Evidence and Relationships (CIPHER)' Study.

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Scientific Abstract

Background
Social exclusion & poverty result in adverse health outcomes & increased mortality in people experiencing homelessness (PEH). Internationally, evidence suggests that PEH acquire significant cognitive impairment at higher rates and at a younger age than the general population. This has not been investigated in Ireland, and the mechanisms driving this have not been elucidated. The CIPHER study aims to identify the characteristics, associations and potential mechanisms of acquired cognitive impairment in PEH, and will provide information to inform local policy and practice.

Public and patient involvement (PPI) is recognised as an important component of high-quality clinical research. PPI is crucial in research in socially excluded groups, including PEH, to minimise the power imbalance between researcher and participant, and to ensure that research is relevant, accessible and feasible.

Aim
The aim of PPI in CIPHER is to consult, collaborate with, and co-produce research with PPI contributors with lived experience of homelessness, throughout the research process, to foster trust and maximise study inclusivity, relevance, applicability, and feasibility.

Methods
A general and study-specific information leaflet for PPI contributors with lived experience of homelessness, based on INVOLVE Guidance, was created and disseminated to inform contributors about the role of PPI in research. A PPI group with lived experience of homelessness was created, and the study design incorporated regular, subsidised meetings with this group featuring the provision of regular feedback to the contributors.

Results
2 PPI consultations have been held to date: prior to research proposal submission & prior to the CIPHER pilot study. This has significantly informed the study design, recruitment posters & study materials.

Plan for further involvement
The PPI contributors have agreed to collaborate with the research team as lay contacts for study participants, to facilitate peer-to-peer discussion of the study when desired by participants/potential participants. Continued PPI consultation is planned during recruitment and following data analysis to ensure recruitment is maximised, to assist with interpretation of the results and to steer plans for & to collaborate in their dissemination to PEH.

Lay Summary

The CIPHER study is being carried out to look at problems with thinking and memory that people experiencing homelessness might pick up over the course of their lives. In order to make this research as relevant and acceptable as possible to its potential participants (people experiencing homelessness), a strategy to include public and patient involvement in this research has been designed. This will ensure that people with lived experience of homelessness can have their say about how the research is going to be conducted and what to do with its results. So far two meetings with people with lived experience have been held, and this has influenced the design of the study and the study materials that will be given to participants. A plan for more meetings has been made to make sure that the voices of people with lived experience continue to influence the CIPHER study until it is completed & its results have been disseminated.

Scientific abstract

Background
Respiratory viruses are associated with significant morbidity and mortality in immunosuppressed patient populations. Increased viral load and prolonged viral shedding. Complications include pneumonia, respiratory failure and superimposed bacterial infection. Vaccination remains the most effective prevention strategy against influenza and SARS CoV-2. However, vaccine effectiveness is reduced and inconsistent in those with altered immune system function as a result of haematopoietic stem cell transplant (HSCT) and chimeric antigen receptor (CAR)-T cell therapy compared with young, healthy members of the population. Studies to date have shown inconsistent seroconversion and seroprotection rates in HSCT recipients. Correlation of findings with clinical outcomes is unclear. Furthermore, this cohort is frequently excluded from clinical trials evaluating vaccine responsiveness and so findings cannot be extrapolated.

Aims and objectives

1. Characterise the humoral and cellular responses to influenza vaccination
2. Characterise the humoral and cellular response to SARS CoV-2 vaccination when co-administered with influenza vaccine
3. Assess vaccine effectiveness and correlation with immune response observed in aims 1 and

Methods
Patients who have undergone allogeneic HSCT or CAR-T-cell therapy for haematological malignancy are administered one dose of commercially available quadrivalent inactivated influenza vaccine. Peripheral blood is drawn on days 0, 7, 28, 60, 180 for PBMC preparation and antibody studies. PBMCs will be stimulated with influenza and SARS CoV-2 peptides and T cell responses measured by flow cytometry and ELISA. Haemagglutination inhibition tires and specific anti-influenza antibodies with be measured. Fortnightly nasopharyngeal swabs are collected to assess for infection and carriage of respiratory viruses throughout the winter season and clinical episodes of influenza-like illness are captured.

Impact
It is anticipated that the results of this study will provide greater understanding of the mechanisms of vaccine response and anti-viral immunity in patients receiving these therapies

Lay summary
Medications used to treat certain medical conditions such as cancer, autoimmune and inflammatory conditions alter the function of the immune system leaving patients at higher risk of developing infection and complications of infection. Vaccines have been one of the most important advances made in medicine, protecting populations against developing infection or severe complications of infection. It is known however that patients receiving immunosuppressive medications do not respond to vaccines as well, or as consistently, as those with healthy immune systems. My research aims to characterise how patients respond to vaccines in the post-transplant period including influenza vaccination. Influenza is a common, seasonal respiratory virus. It is a cause of significant morbidity and mortality worldwide, particularly in this patient group, and has potential to cause future pandemics. The results of this research will inform vaccination strategies for these patients in the future.

Transforming Radiology: Artificial Intelligence for Change Detection in Longitudinal Imaging Data

Scientific Abstract

Multiple Sclerosis (MS) is a chronic progressive idiopathic demyelinating disorder whose diagnosis is contingent on the interpretation of MRI. New MRI lesions are an early biomarker of disease progression. Artificial Intelligence (AI) is increasingly applied to clinical radiology. Although initial Radiology AI research concentrated on a limited set of applications, there is now growing interest in incorporating the concept of temporality. Interpreting medical images is dynamic, involving comparisons between different time points, a focus of increasing research interest.

In the computer science literature there have been many recent advances in Time Series and Change Detection tasks using methods such as Siamese Neural Networks and more recently Vision Transformers. However, the application to medical imaging has been limited, partly due to the scarcity of longitudinal data.

Initially, a comprehensive stakeholder and patient engagement project was undertaken to align research objectives with the needs of those most affected. We built a longitudinal dataset with over 40,000 images. Then AI methodologies including radiomics and deep learning were employed to compare radiologic images at different points in time for the purposes of both prediction and change detection.

We reconceptualize the identification of new MS lesions in MRI scans as a change detection challenge, proposing new evaluative metrics aimed at minimizing the costs linked to diagnostic decisions. We also describe a novel Siamese U-transformer (NeU-Former) which can have a lower expected cost than the current state of the art, especially for small lesions.

In conclusion, incorporating AI and temporality in our approach holds the potential for more prompt and precise diagnoses and prognoses in MS MRI.

Lay Summary

Multiple Sclerosis (MS) is a condition where the body's immune system attacks its own nerves. Diagnosing MS involves looking at MRI scans to find changes in the brain or spinal cord. One sign of MS getting worse is finding new spots (lesions) on MRI. Traditionally, doctors have to compare scans taken at different times to find these changes. Artificial Intelligence (AI), could help by analysing scans more efficiently.

We gathered over 40,000 MRI images from MS patients and trained AI systems to not just look at a single image, but to compare images from different times. We developed "NeU-Former" a kind of AI that's particularly good at spotting small changes, potentially making it more effective than current methods.

Our work shows that by using AI to focus on changes over time, we could make the diagnosis and monitoring of MS more effective, helping patients get the care they need sooner.

Analysis of the platelet proteome reveals insights into the pro-inflammatory and pro-thrombotic state associated with the Philadelphia chromosome-negative myeloproliferative neoplasms

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Scientific Abstract

Introduction

Myeloproliferative neoplasms (MPN) are clonal haematopoietic cell malignancies characterised by myeloid proliferation and thrombocytosis. Patients with polycythaemia vera (PV) and essential thrombocythaemia (ET) have an increased risk of thrombosis. We hypothesised that platelet proteomics would provide a snapshot into the observed haemostatic derangements experienced by patients.

Methods

Platelet samples from patients with a known diagnosis of MPN (ET, n= 59; PV, n= 41) were obtained from an established biobank of patients. Prospective recruitment of individuals referred for investigation of thrombocytosis/erythrocytosis formed a cohort of patients with newly diagnosed MPN (n= 31) and a control group with transient/reactive thrombocytosis (n= 23). Platelets were isolated from whole blood. Differential proteomic signatures were established using label-free quantification (LFQ) mass spectrometry (MS).

Results

We evaluated the platelet proteome in 100 patients with an established diagnosis of PV & ET compared to 40 healthy controls. 1995 proteins from platelet lysates were quantified, with 227 and 166 proteins significantly differentially expressed (false discovery rate <0.05; fold change >1.5) in ET & PV respectively. Mediators of inflammation and effectors of platelet pro-coagulant activity were overexpressed in MPN. Functional analysis of platelets using gene set enrichment demonstrated proteins from the MTOR signalling pathway and unfolded protein response were enriched in the PV & ET cohorts.

Next, we aimed to capture the unique pattern of protein expression in a cohort of untreated patients at the time of MPN diagnosis. Unsupervised principal component analysis of platelet proteins separated patients with MPN from those with reactive thrombocytosis. Proteomic analysis of platelets from newly diagnosed patients demonstrated prothrombotic signatures.

Conclusions

We describe the untargeted proteomic profile of platelets from two large, independent MPN cohorts. This is the first such characterisation from newly diagnosed patients with ET & PV.

Lay Summary

Myeloproliferative Neoplasms (MPNs) are chronic blood cancers characterised by increased numbers of circulating blood cells, arising due to an acquired genetic mutation affecting the bone marrow. Patients with MPN have an increased risk of blood clots and progression to bone marrow fibrosis and/or acute leukaemia. Blood clotting risk is highest around the time of initial diagnosis; however, it remains elevated despite treatment and represents the greatest risk to life expectancy and quality of life. Platelets are essential for blood coagulation however it is also known that they play an important role in several inflammatory diseases through expression/release of protein signals. Taking platelets from chronically treated patients with MPN and as well as from newly diagnosed patients, we have shown that platelet proteins with known inflammatory and thrombotic function are increased in patients with MPN compared to people without MPN. We have also shown overexpression of proteins associated with important biologic pathways, including but not limited to coagulation. In conclusion we highlight prothrombotic platelet proteins in untreated MPN patients, however in keeping with the observation that clotting risk remains high amongst treated patients, we also show evidence of altered platelet proteins in that group despite standard therapy.

Targeted Inhibition of Phosphodiesterase (PDE) 4 in Endothelial Cells as a Novel Therapy for Von Willebrand disease

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Scientific Abstract

Background
Desmopressin (DDAVP) is widely used to treat von Willebrand Disease (VWD). DDAVP activates V2 receptors on endothelial cells (EC), stimulating cAMP generation and VWF release. However, DDAVP has significant limitations, including lack of oral formulation and sub-optimal responses in some patients.

Aims
Identify EMA-approved drugs that can trigger cAMP-dependent VWF secretion from EC to repurpose as novel haemostatic therapeutic agents.

Methods
Candidate agents identified by mechanistic screening of EMA-approved databases were tested for capacity to induce VWF (VWF:Ag) release from Human Umbilical Vein Endothelial Cells (HUVEC). VWF string formation on HUVEC under flow conditions was determined using fluorescent anti-VWF antibodies and confocal microscopy. Washed platelet capture was visualized by bright-field microscopy. Platelet aggregation was assessed by light transmission aggregometry.

Results
In vitro screening determined a lead candidate drug class: PDE-4 inhibitors. Non-selective PDE-inhibitor IBMX significantly increased VWF release from HUVEC (median fold increase VWF:Ag 1.49,$p<0.0001$). PDE-2 and PDE-3 inhibitors had no effect. In contrast, selective PDE-4 inhibition with Roflumilast (ROF) significantly increased VWF release (1.51-fold,$p<0.0001$), including at therapeutically relevant nanomolar concentrations. Critically, although IBMX markedly attenuated platelet aggregation, ROF had no inhibitory effect, consistent with lack of PDE-4 isoform expression in platelets.

Pre-incubation of HUVEC with ROF triggered VWF string formation under flow conditions, with fluorescent strings visualized in most fields of view. Consistently, platelet capture was confirmed upon ROF-treated HUVEC (Median string number/field of view; ROF-vs-NC; 4-vs-0,$p<0.0001$).

Although HUVEC do not express V2 receptors, ROF exhibited synergistic activity with cAMP-elevating agents Isoprenaline ($p=0.0140$) and Forskolin ($p=0.0029$), suggesting combination therapy with DDAVP as a potential therapeutic approach.

Conclusion
Our novel findings demonstrate that ROF, an EMA-approved orally available PDE-4 inhibitor, stimulates VWF release without deleterious effects on platelet aggregation. Our data highlight the therapeutic potential of PDE-4 inhibitors, alone or in combination with DDAVP, in the treatment of VWD.

Lay summary

von Willebrand Factor (VWF) is a protein that is important for blood clotting. Cells that line blood vessel walls, called "endothelial cells", produce VWF. Some people have low levels of VWF and suffer from Von Willebrand Disease (VWD), which causes bleeding. DDAVP is a drug that is used to treat VWD. It stimulates endothelial cells to release VWF into the bloodstream. This allows patients with VWD to safely undergo surgery. However, DDAVP doesn't work in all patients and isn't available as a tablet. We aimed to find other drugs that can stimulate endothelial cells to release VWF. We studied drugs that are already used to treat other medical conditions. This means they are safe in humans. We found that the drug Roflumilast can stimulate VWF release. Therefore, Roflumilast might have potential in the future as a treatment of VWD.

Machine learning for the investigation of optic neuropathies

The central hypothesis of my thesis is that a smaller scleral opening as the optic nerve passes into the eye results in worse visual outcome in patients with optic neuropathies. I have been working alongside collaborators in Mount Sinai, New York and the University of Iowa to analyse a database of patients with non-arteritic ischaemic optic neuropathy (NAION) who were followed up longitudinally from disease-onset for one year. Using archetypal analysis, a method of dimensionality reduction, we have analysed the typical patterns of vision loss in this disease. I aim to link this to objective structural changes such that, at disease onset, we will be able to predict the natural course that patients will likely have without any intervention.

A related piece that I have been working on is to develop an algorithm for assessment of papilloedema (optic nerve swelling secondary to raised intracranial hypertension) in patients with idiopathic intracranial hypertension (IIH). In IIH, the Frisén grading system is used to give an indicator of papilloedema severity. Changes between grades can be very subtle and thus a very specialised skillset is needed to be able to analyse the optic nerve accurately. This assessment is prone to high inter-examiner variability when the interpretation is done by non-neuro-ophthalmologists. With the increased prevalence of fundus photography, this interpretation is now primed to be assisted by computer vision techniques. By utilising transfer learning of a pre-trained vision-transformer-based architecture fine-tuned on images taken from the Idiopathic Intracranial Hypertension Treatment Trial, we have developed a model that can objectively grade papilloedema to aid in monitoring this condition. This model has an accuracy of 93% and an F1-score of 81.5% at predicting papilloedema Frisén grade. In conjunction with this I have been assessing the morphology of the retinal vasculature in papilloedema to see how it changes with increasing Frisén grade.

Future work will look to transfer these models across for assessment of ischaemic optic neuropathies and analyse the impact of neural canal opening size on visual outcome in ischaemic optic neuropathy and papilloedema.

Lay Summary

Papilloedema is optic nerve swelling as a result of raised pressure around the brain. By tweaking a large pre-trained algorithm we have developed a machine learning model to identify and grade papilloedema to a high degree of accuracy. This model will next be used to help investigate a condition known as non-arteritic ischaemic optic neuropathy (NAION). We have analysed patterns of vision loss in this disease using machine learning and next plan on linking these changes to features of the disease that we see when we look at the back of patients' eyes. At the moment we do not know what outcome a patient will have until it is too late to intervene. With this work we hope to be able to predict whether a patient will have a good outcome or a poor outcome at the moment of first presentation to hospital so that in the future we can assess whether treatments in clinical trials are effective.

Digitisation of the INTERSTROKE paper-based ECG records: A step closer to Machine Learning Analysis

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Scientific Abstract

Background
Stroke is a leading cause of death worldwide and leaves most survivors with permanent disability. Stroke presents diagnostic challenges, which limits access to effective reperfusion therapies in the form of thrombolysis or endovascular thrombectomy. Previous studies have identified electrocardiogram (ECG) abnormalities associated with acute stroke. These are most frequently seen in the haemorrhagic subtype, and include T-wave abnormalities, QTc prolongation, arrhythmias, pathologic Q-waves, ST-segment depression/elevation, and prominent U waves. These changes have been seen in up to 92% of stroke patients, even in those without underlying cardiovascular disease. Machine learning (ML) has previously proven to out-perform cardiologists in recognising certain ECG abnormalities. We aim to explore the ECG for early identification of stroke neurology via ML analysis from the INTERSTROKE ECG data.

Aims
The first step in utilising the INTERSTROKE ECG data, is converting it from paper-based images to a digitised signal.

Methods
We performed an extensive literature search of previously developed ECG digitization tools. 35 papers have been published in the area, each outlining various approaches to the extraction of the ECG signal. Of these, only 5 papers have their ECG digitization tool code as open-source or had their software accessible.

Results and Discussion
Of the ECG digitization tools currently developed, no tool has successfully handled every component to extract an accurate signal i.e. deskewing the image, binarization, lead detection, signal extract and noisy image treatment. Significant strides have been made in the last 12 months by different groups to focus on improving individual components. Using a random sample of the INTERSTROKE ECGs, we have begun assessing the ability of open-source codes to generate an accurate ECG signal. These codes provided a strong foundation for building in this area. Further work, and modification, of the code is required to facilitate the use of noisy, skewed or degraded ECGs.

Lay Summary

Stroke is a leading cause of death and disability. Differentiating an ischaemic (clot) from haemorrhagic (bleed) stroke quickly is vital as their treatments differ greatly. A major factor contributing to underutilisation of stroke treatments, is limited access to CT brain scanning which must occur before initialising treatment. 66% of the world does not have access to simple X-rays, let alone CT scans.

Abnormalities in heart rate tracings, known as an ECGs, have been detected in over 90% of patients with strokes. These changes are seen from time of stroke onset, and most commonly in haemorrhagic stroke. Using computer techniques known as machine learning, a tool to analyse ECG information will be developed to help predict stroke type. The first step of is converting our paper-based ECG records to digital signals which the computer can use to learn. This could ultimately lead to the development of rapid, out-of-hospital stroke differentiating technologies.

Investigating the impact of *Fusobacterium nucleatum* on apoptosis and sensitivity to the Inhibitor of Apoptosis Protein antagonist, tolinapant, in colorectal cancer models

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Scientific Abstract

Introduction
Fusobacterium nucleatum, a Gram-negative anaerobic bacterium originating from the oral cavity, can enrich colorectal tumours, exerting a range of pathogenic effects and promoting chemotherapy resistance, culminating in poorer patient outcomes. Using *in vitro* models of colorectal cancer (CRC), including three-dimensional tumour spheroids, we investigated the impact of *F. nucleatum* on apoptosis and potential sensitisation to the clinically relevant Inhibitor of Apoptosis Protein (IAP) antagonist, tolinapant.

Materials & Methods
Human CRC cell lines, HCT116 and HT29 were cultured using standard techniques. Spheroids were generated by seeding cells into ultra-low adherence 96-well plates. Infections were performed with live *F. nucleatum* (subspecies *animalis*, *nucleatum*, *polymorphum* or *vincenti*) or bacterial lipopolysaccharide (LPS). Infected models were treated with combinations of tolinapant, tumour necrosis factor alpha (TNFa) and 5-fluorouracil (5FU). Imaging with light microscopy was analysed using ImageJ software. Apoptosis was measured by quantitative polymerase chain reaction, Western blotting, cell viability (3D-CellTiterGlo) and caspase 3/7 and 8 activity assays as well as annexin V / propidium iodide flow cytometry. The selective Toll-like receptor 4 inhibitor, TAK242, was used to explore the mechanism further.

Results & Discussion
Treatment with *F. nucleatum* significantly increased the expression of the anti-apoptotic protein, cellular Inhibitor of Apoptosis Protein 2 (cIAP2). This effect could be attenuated with a small molecule Toll-like receptor 4 inhibitor. Increased cIAP2 is known to be correlated with a worse response to chemotherapy in CRC. Although the IAP antagonist, tolinapant, could prevent the *F. nucleatum*-induced increase in cIAP2, it did not confer increased chemotherapy sensitivity compared to non-infected controls.

Conclusion
F. nucleatum infection elevated the expression of the poor prognostic, anti-apoptotic protein, cIAP2, in experimental CRC models, likely via TLR4 signalling. Tolinapant successfully degraded cIAP2 but this did not translate into greater cell death in *F. nucleatum* infected cells. An exploratory objective of the upcoming ASTFOX phase 1 clinical trial (Tolinapant combined with chemotherapy in metastatic CRC) is to explore the association between tumour response and intra-tumoural *F. nucleatum*.

Lay summary

Bowel cancer is the 2nd and 3rd most common cause of death from cancer in Ireland and the UK, respectively. Chemotherapy is used to reduce the risk of cancer returning and to prolong life. It works by damaging the DNA (genetic code) of cancer cells causing them to self-destruct by a process called apoptosis.

Unfortunately, bowel cancer cells infected with a bacteria called *Fusobacterium nucleatum* can be resistant to apoptosis meaning that patients are less likely to be cured of their cancer.

A new drug, tolinapant, can switch apoptosis back on when combined with chemotherapy and is soon to be tested in a clinical trial taking place in Belfast, Leicester and Glasgow.

As part of this PhD, I investigated if tolinapant could reverse the bad effects of *Fusobacterium nucleatum* on bowel cancer cells to improve the effects of chemotherapy.

Reduced 11-oxygenated androgens due to reduced activity of 11β-hydroxysteroid dehydrogenase type 2 in patients with chronic kidney disease – preliminary results from CORT-CKD.

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Scientific Abstract

Background

The 11-oxygenated androgen subclass derive from a common substrate, 11β-hydroxyandrostenedione (11OHA4), which is produced by the adrenal gland. 11OHA4 is converted to 11-keto androstenedione (11KA4) in mineralocorticoid target tissues, mainly the kidney, by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2). 11KA4 is released into circulation and converted to the more potent androgens such as 11-ketotestosterone (11KT) and 11-hydroxytestosterone (11OHT) in peripheral tissues.

11-oxygenated androgens are of particular interest in chronic kidney disease (CKD) as 11βHSD2 is a major gatekeeper of 11-oxygenated androgen production[2]. Research focused on glucocorticoid metabolism in CKD has identified both reduced activity and expression of 11βHSD2 in patients with CKD[6-10]. Relative deficiency of 11βHSD2 is likely to have a significant impact on 11-oxygenated androgen metabolism, with possible clinical consequences for patients with CKD.

Methods

In this cross-sectional multicentre cohort study of patients with CKD, basal serum steroid profiling by liquid chromatography with tandem mass spectrometry (LC-MS/MS) was performed to measure the concentration of cortisol, cortisone, and 11-oxygenated androgens. Ratios of steroid hormone concentrations were calculated as predictors of 11βHSD2 activity. Statistical analysis using spearman correlation analysis and Kruskal Wallis tests was performed using R version 4.3.1.

Results

90 patients (65% male) with a median age of 64 years (IQR 52-70), and median eGFR of 23ml/min (IQR 13-39) participated in the study. LC-MS/MS revealed significant positive correlation between serum cortisone (r 0.77, p <0.01), 11OHT (r 0.36, p <0.01), and 11KT (r 0.56, p<0.01) and eGFR. Reduced eGFR was also associated with an increase in cortisol/cortisone ratio indicating reduced 11βHSD2 activity (r-0.59, p<0.01). Reduced 11βHSD2-derived 11-oxygenated androgen production was reflected by increased 11OHA4/(11KA4 + 11KT + 11OHT) ratio with declining eGFR (r-0.64, p<0.01)

Discussion

The kidney is the major site of 11βHSD2 activity which has significant implications for corticosteroid metabolism in chronic kidney disease. We have identified reduced 11βHSD2 activity with declining eGFR. This is the first study to demonstrate abnormalities in 11-oxygenated androgen metabolism in patients with CKD and further analysis to include urine steroid profiling and the clinical consequences of these findings is pending.

Lay summary

Chronic kidney disease has multiple consequences for the functioning of the endocrine system. Cortisol, produced in the adrenal gland, is usually inactivated by an enzyme, 11βHSD2, present in the kidney. With a decline in kidney function, the activity of 11βHSD2 is impaired. As a result, patients with kidney disease have reduced ability to inactivate cortisol which may lead to high blood pressure, weight gain, diabetes and cardiovascular risk.

11βHSD2 is also required for the activation of a subclass of adrenal androgen hormones. We have identified that patients with chronic kidney disease have reduced levels of these androgen hormones. The possible clinical consequences of this are yet to be described, but, reduced androgen levels may contribute to frailty and poor bone health seen in patients with chronic kidney disease.

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Randomised controlled trials of antihypertensive therapy: does exclusion of orthostatic hypotension alter treatment effect? A systematic review and meta-analysis

Scientific Abstract

Background and Purpose
Management of antihypertensive therapy is challenging in patients with symptomatic orthostatic hypotension, a population often excluded from randomised controlled trials of antihypertensive therapy. In this systematic review and meta-analysis, we sought to determine whether the association of antihypertensive therapy and adverse events (e.g. falls, syncope), differed among trials that included or excluded patients with orthostatic hypotension.

Methods
We performed a systematic review and meta-analysis of randomised controlled trials comparing blood pressure lowering medications to placebo, or different blood pressure targets on falls or syncope outcomes and cardiovascular events. A random-effects meta-analysis was used to estimate a pooled treatment-effect overall in subgroups of trials which excluded patients with orthostatic hypotension and trials which did not exclude patients with orthostatic hypotension, and tested P for interaction. The primary outcome was fall events.

Results
46 trials were included, of which 18 trials excluded orthostatic hypotension and 28 trials did not. The incidence of hypotension was significantly lower in trials that excluded participants with orthostatic hypotension (1.3% versus 6.2%, P <0.001) but not incidences of falls (4.8% v 8.8%; P=0.40) or syncope (1.5% v 1.8%; P=0.67). Antihypertensive therapy was not associated with an increased risk of falls in trials that excluded (OR 1.00, 95% CI; 0.89-1.13) or included (OR 1.02, 95% CI; 0.88-1.18) participants with orthostatic hypotension (P for interaction=0.90).

Conclusions
The exclusion of patients with orthostatic hypotension does not appear to affect the relative risk estimates for falls and syncope in antihypertensive trials.

Lay summary

The management of hypertension (high blood pressure) and orthostatic hypotension (low blood pressure on standing) is challenging. These two conditions commonly co-exist, however some trials of anti-hypertensive medications did not include individuals with both conditions. The objective of our study was to compare rates of adverse events (side effects) in trials which excluded individuals with orthostatic hypotension, compared to trials which did not exclude individuals with orthostatic hypotension. We found that the exclusion of people with orthostatic hypotension did not significantly alter safety effects (e.g. falls/fracture), however the number of hypotension (low blood pressure) and falls events was lower in trials which excluded individuals with orthostatic hypotension.