ANTIPLATELETS AND RISK OF CANCER: A NATIONAL PROPENSITY-SCORE WEIGHTED COHORT ANALYSIS

1Clare Oliver-Williams, 2Catherine Welch, 2Paul Lambert, 3Mick Peake, 1David Adam, 2Michael Sweeting. 1University of Leicester, Department of Health Sciences, George Davies Centre, University Road, Leicester, LE1 7RH, UK; 2University of Leicester

10.1136/heartjnl-2022-BCS.214

Introduction Common cardiovascular therapies have been suggested to have a protective effect against cancer. Aspirin, an antiplatelet, has been shown to reduce the incidence of some cancers, possibly because platelets are needed for tumour cells within a solid cancer to survive. The effect on cancer incidence of newer antiplatelets, such as thienopyridine inhibitors like Prasugrel and P2Y12 inhibitors like Ticagrelor is unclear.

Methods The Virtual Cardio-Oncology Research Initiative (VICORI) data resource of linked English national cancer and cardiovascular disease audits was used to assess the risk of total cancers as well as breast, colorectal, lung, and prostate cancer for myocardial infarction patients who had received thienopyridine inhibitors or ticagrelor during admission between 2000–2018. Time-varying Cox proportional hazards regression models estimated the risk of the outcomes for individuals who received the medications compared to those who did not. Propensity score weights were used to adjust for differences between individuals who did and did not receive the relevant medication.

Results Among 228,495 cardiac patients, those discharged on thienopyridine inhibitors were at lower risk of cancer than those who did not, HR=0.90 (0.84–0.96). Cancer risk for individuals discharged on thienopyridine inhibitors was lowest in the first year after discharge. There were no differences in risk of breast, colorectal, prostate or lung cancer by thienopyridine inhibitors. Ticagrelor was not associated with risk of cancer, HR=0.96 (0.89–1.04) and the risk of cancer over time for individuals discharged on ticagrelor did not vary over time. Ticagrelor was associated with a lower risk of breast cancer, HR=0.60 (0.40–0.92), but not colorectal, prostate or lung cancer.

Conclusions Cardiac patients who received thienopyridine inhibitors were at lower risk of cancer, and those who received ticagrelor were at lower risk of breast cancer, specifically. These findings should be further validated in large-scale cohort studies and prospective clinical trials.

THE ROLE OF THE LNCRNA EINCR1 AND MAPK SIGNALLING IN THE HEART

1Hayden Jones, 1Andrew Sharrocks, 1Bernard Keavney. 1The University of Manchester, AV Hill Building, Upper Brook Street, Manchester, M13 9PT, UK; 2University of Manchester

10.1136/heartjnl-2022-BCS.215

The mitogen-activated protein kinase pathway (MAPK) transduces signals to affect a variety of biological processes, including, proliferation, differentiation, and cellular survival. It is known to be key during cardiovascular development and during physiological cardiovascular function, indicated by the congenital heart defects that are typical of Noonan syndrome and other diseases that affect MAPK signalling. A previous group have shown that a long non-coding RNA, the EGF-inducible non-coding RNA 1 (EINCR1) regulates the MEK/ERK branch of the MAPK pathway, which usually responds to growth factors and other mitogenic signals. However, the exact mechanism is unknown. Due to the importance of the MEK/ERK pathway in various cardiovascular physiological and pathological processes, and because EINCR1 expression is highest in the heart, we wanted to investigate how EINCR1 regulates the MEK/ERK kinase cascade. Current pharmacological inhibitors of the MEK/ERK pathway have significant side effects, and the identification of alternative regulatory mechanisms could prove to be beneficial for patients with a variety of diseases. In the first phase of this study, we had three main aims. First, to confirm that EINCR1 expression is induced by MAPK activation via EGF treatment and transfection with a constitutively active MEK. Second, to characterise the EINCR1 locus using Nanopore long-read sequencing because previous studies have suggested that the current gene annotation is not complete. Finally, we aimed to identify any enhancers in the locus that could be contributing to its regulatory effects, and once identified, to use CRISPRi to downregulate the activity of these enhancers and use RT-qPCR to identify the genes affected. First, we confirmed that EINCR1 expression is induced following EGF treatment. Nanopore sequencing then revealed that the transcripts that arise from the EINCR1 locus are not well defined, with no consistent spliced structure, like other lncRNAs, such as MALAT1. The enhancer assays indicated that two regions near the EINCR1 locus have potential enhancer ability when compared to a random region of DNA that was used as a control. Our initial findings indicate that MAPK signalling activates enhancers near and within the EINCR1 gene body. Nanopore sequencing revealed that the EINCR1 transcript lacks a consistent splicing pattern in a bladder cancer cell line. However, future studies are aimed at assessing the structure of the EINCR1 transcript in the heart, as there is some evidence that suggests it may be consistently spliced in the cardiomyocytes. A consistent structure in the heart may indicate that the transcript is functional in addition to the enhancers. Analysis of our CRISPRi work is ongoing, and we hope to identify genes that are regulated by this locus soon. Understanding the entire MAPK signalling pathway, including its regulatory mechanisms, could be key in the prevention of disease and for the development of novel treatments of cardiovascular diseases.

ACUTE ARTERIAL HAEMODYNAMICS ACTIVATION OF ENDOTHELIAL TO MESENCHYMAL TRANSITION IN LONG SAPHENOUS VEINS. IMPACT ON VEIN GRAFT DISEASE

1Shameem Ladak, 1Liam McQueen, 1Lathishia JoelDavid, 1Gavin Murphy, 1Mustafa Zakkar. 1University of Leicester, Department of Cardiovascular Sciences, University of Leicester, Glenfield Hosp, Leicester, LE3 9QP UK; 2University of Leicester; 3NIHR Leicester Biomedical Research Centre (BRU2), cardiovascular theme, Glenfield Hospital

10.1136/heartjnl-2022-BCS.216

Introduction The long saphenous vein (LSV) is frequently used in cardiac surgery; however, its use is complicated by late stenosis or occlusion due to the development of intimal hyperplasia (IH). TGF-β has been implicated in the process of IH
however the impact of acute haemodynamic changes on the activation of TGF-β endothelial-to-mesenchymal transition (EndMT) has not been assessed and it’s the focus of this study.

**Methods** Surplus LSV were exposed to acute arterial haemodynamics using a perfusion bioreactor. Changes in EndMT markers at the RNA and protein level evaluated by quantitative real time PCR, RNASecope and immunofluorescence.

**Results** The acute exposure of veins to arterial haemodynamics ex-vivo induced significant increase in inflammatory marker IL-8 expression and transcription factor TWIST1 in LSV (both p≤0.01, Figure 1A) endothelium. Furthermore, immunostaining demonstrated the activation of pSMAD (p≤0.01, Figure 1B) acutely in endothelium after 45 minutes of exposure to arterial haemodynamics. This was followed by significant increase of SMC related markers (Vimentin and α-SMA; Figure 1C, both p≤0.001) and the suppression of endothelial cell related marker CD31 after 4 hours of LSV exposure to acute arterial haemodynamics. RNASecope and IHC results showed localisation of TWIST1 RNA and protein in CD31+ (p≤0.001) and VECAD+ (p≤0.001) cells respectively following exposure to acute arterial haemodynamics (Figure 1D). Furthermore, TGFβ pathway phosphorylation array identified the activation of Smad1 (p≤0.05) but not TAK1 in LSV endothelial cells indicating that acute arterial haemodynamics activates the TGFβ-SMAD pathway specifically (Figure 1E).

**Conclusion** The exposure of LSV to acute arterial haemodynamics is associated with the activation of TGFβ-SMAD pathway leading to EndMT changes in the endothelium of vein grafts ex-vivo. This contributes to our understanding of the changes that occur in veins after implantation into arterial circulation and that the acute changes in the endothelium and suggests that strategies to modulate TGFβ-SMAD can be utilised to modulate IH in vein grafts.

Abstract BS36 Figure 1 Changes in inflammatory and EndMT marker expression in LSV subjected to acute arterial haemodynamics. Surplus LSV were subjected to acute arterial haemodynamics for 45 minutes and 4 hours and changes in EndMT marker expression were evaluated at the RNA and protein level (clockwise). Changes in IL8 and TWIST1 expression was examined using quantitative real time PCR (A). Protein changes of EndMT markers was evaluated using immunofluorescence (B&C). TWIST1 RNA and protein expression was also studied in LSV using RNASecope and IHC technique respectively (D). TGFβ pathway phosphorylation protein array was quantified using ImageQuant Lass 400 software and changes in EC SMAD1 and EC TAK expression was studied. Data was also plotted as a heap map (E). Data was analysed by paired t-test (*=p≤0.05, **=p≤0.01, ***=p≤0.001) and compared to the control (static). Images were quantified using Image J software and graphs were plotted using GraphPad Prism 9 software.