Project: **ALL-HEART**

Title of paper: **Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial**

Reference: The Lancet Vol 400, Issue 10359, 2022, 1195-1205

Authors: Isla S Mackenzie, Christopher J Hawkey *et al* on behalf of the ALL-HEART Study Group

url: https://doi.org/10.1016/S0140-6736(22)01657-9

Summary: **Background**: Allopurinol is a urate-lowering therapy used to treat patients with gout. Previous studies have shown that allopurinol has positive effects on several cardiovascular parameters. The ALL- HEART study aimed to determine whether allopurinol therapy improves major cardiovascular outcomes in patients with ischaemic heart disease.

Methods: ALL-HEART was a multicentre, prospective, randomised, open-label, blinded-endpoint trial done in 18 regional centres in England and Scotland, with patients recruited from 424 primary care practices. Eligible patients were aged 60 years or older, with ischaemic heart disease but no history of gout. Participants were randomly assigned (1:1) to receive oral allopurinol up-titrated to a dose of 600 mg daily (300 mg daily in participants with moderate renal impairment at baseline) or to continue usual care. The primary outcome was the composite cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The hazard ratio (allopurinol vs usual care) in a Cox proportional hazards model was assessed for superiority in a modified intention-to- treat analysis. The safety analysis population included all patients in the modified intention-to-treat usual care group and those who took at least one dose of randomised medication in the allopurinol group.

Findings: Between Feb 2014, and Oct 2017, 5937 participants were randomly assigned to receive allopurinol or usual care. 5721 participants (mean age 72·0 years [SD 6·8], 4321 [75·5%] males, and 5676 [99·2%] white) were included in the modified intention-to-treat population. Mean follow-up time was 4·8 years. There was no evidence of a difference between the randomised treatment groups in the rates of the primary endpoint. 314 (11·0%) participants in the allopurinol group (2·47 events per 100 patient-years) and 325 (11·3%) in the usual care group (2·37 events per 100 patient-years) had a primary endpoint (hazard ratio [HR] 1·04 [95% CI 0·89–1·21], p=0·65). 288 (10·1%) participants in the allopurinol group and 303 (10·6%) participants in the usual care group died from any cause (HR 1·02 [95% CI

0·87–1·20], p=0·77).

Interpretation: In this large, randomised clinical trial in patients aged 60 years or older with ischaemic heart disease but no history of gout, there was no difference in the primary outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death between participants randomised to allopurinol therapy and those randomised to usual care.

Project: **Discussing cancer risk**

Title of paper: **Patient and practitioner views on cancer risk discussions in primary care: a qualitative study**

Reference: British Journal of General Practice Open 2022; 6 (1)

Authors: David N Blane, Sara MacDonald and Catherine A O'Donnell

url: https://doi.org/10.3399/BJGPO.2021.0108

Summary: **Background**: It is estimated that nearly 600 000 cancer cases in the UK could have been avoided in the past 5 years if people had healthier lifestyles, with the principle modifiable risk factors being smoking, obesity, alcohol consumption, and inactivity. There is growing interest in the use of cancer risk information in general practice to encourage lifestyle modification.

Aim: To explore the views and experiences of patients and practitioners in relation to cancer prevention and cancer risk discussions in general practice.

Design & setting: Qualitative study among patients and practitioners in general practices in Glasgow, UK.

Method: Semi-structured interviews were conducted with nine practitioners (five GPs and four practice nurses), and 13 patients (aged 30–60 years, with two or more specified comorbidities).

Results: Currently, cancer risk discussions focus on smoking and cancer, with links between alcohol and/or obesity and cancer rarely made. There was support for the use of the personalised cancer risk tool as an additional resource in primary care. Practitioners felt practice nurses were best placed to use it. Use in planned appointments (for example, chronic disease reviews) was preferred over opportunistic use. Concerns were expressed, however, about generating anxiety, time constraints, and widening inequalities.

Interpretation: Health behaviour change is complex and the provision of information alone is unlikely to have significant effects. Personalised risk tools may have a role, but important concerns about their use remain, particularly in areas of socioeconomic disadvantage

Project: **GP burnout Survey**

Title of paper: **A national study of burnout and spiritual health in UK general practitioners during the COVID-19 pandemic**

Reference: PLoS ONE 17(11): e0276739

Authors: Ishbel Orla Whitehead, Suzanne Moffatt, Carol Jagger and Barbara Hanratty

url: https://doi.org/10.1371/journal.pone.0276739

Summary: Objectives: To quantify the burnout and spiritual health of GPs in the UK who worked during the Covid-19 Pandemic.

Design: Online survey, April/May 2021, distributed via emails to general practices, CCGs, Health boards, Clinical Research Networks, professional groups, social media GP groups and networks.

Participants: 1318 GPs who worked in the NHS during the COVID-19 pandemic. 169 GP respondents were working in Scotland.

Main outcome measures: Burnout scores, measured by the Maslach Burnout Inventory (MBI) for Medical Personnel; spiritual health, measured using the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being, Non-Illness (FACIT-SP-NI).

Results: 19% of surveyed GPs were at the highest risk for burnout, using accepted MBI 'cut off' levels. There was no evidence of a difference in burnout by gender, ethnicity, or length of service. GP burnout was associated with GP spiritual health, regardless of identification with a religion. GPs with low spiritual health were five times more likely to be in the highest risk group for burnout.

Interpretation: Burnout is at crisis levels amongst GPs in the UK NHS. A comprehensive response is required, identifying protective and precipitating factors for burnout. The potentially protective impact of spiritual health merits further

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Project: **HEAT**

Title of paper: **Helicobacter pylori eradication for primary prevention of peptic ulcer bleeding in older patients prescribed aspirin in primary care (HEAT): a randomised, double-blind, placebo-controlled trial**

Reference: The Lancet 2022; Vol 400, Issue 10363, 597–606

Authors: Chris Hawkey, Anthony Avery, Carol A C Coupland, Colin Crooks, Jennifer Dumbleton and F D Richard Hob

url: https://doi.org/10.1016/S0140-6736(22)01843-8

Summary: **Background**: Peptic ulcers in patients receiving aspirin are associated with H pylori infection. We aimed to investigate whether H pylori eradication would protect against aspirin- associated ulcer bleeding.

Methods: We conducted an RCT (Helicobacter Eradication Aspirin Trial [HEAT]) at 1208 primary care centres in the UK, using routinely collected clinical data. Eligible patients were aged 60 years or older who were receiving aspirin at a daily dose of 325 mg or less and had a positive C13 urea breath test for H pylori at screening. Patients receiving ulcerogenic or gastroprotective medication were excluded. Participants were randomly assigned (1:1) to receive either a combination of oral clarithromycin 500 mg, metronidazole 400 mg, and lansoprazole 30 mg (active eradication), or oral placebo (control), twice daily for 1 week. Follow-up was by scrutiny of electronic data in primary and secondary care. The primary outcome was time to hospitalisation or death due to definite or probable peptic ulcer bleeding and was analysed by Cox proportional hazards methods in the intention-to-treat population.

Findings: Between Sept 2012 and Nov 2017 30,166 patients had breath testing for H pylori, 5367 had a positive result, and 5352 were randomly assigned to receive active eradication (n=2677) or placebo (n=2675) and were followed up for a median of 5·0 years (IQR 3·9–6·4). Analysis of the primary outcome showed a significant departure from proportional hazards assumptions (p=0·0068), requiring analysis over separate time periods. There was a significant reduction in incidence of the primary outcome in the active eradication group in the first 2·5 years of follow-up compared with the control group (six episodes adjudicated as definite or probable peptic ulcer bleeds, rate 0·92 [95% CI 0·41–2·04] per 1000 person-years vs 17 episodes, rate 2·61 [1·62–4·19] per 1000 person-years; hazard ratio [HR] 0·35 [95% CI 0·14–0·89]; p=0·028). This advantage remained significant after adjusting for the competing risk of death (p=0·028) but was lost with longer follow-up (HR 1·31 [95% CI 0·55–3·11] in the period after the first 2·5 years; p=0·54).

Interpretation: H pylori eradication protects against aspirin-associated peptic ulcer bleeding, but this might not be sustained in the long term

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Project: **Hep C: developing a GP-led pathway**

Title of paper: **Developing a primary care-initiated hepatitis C treatment pathway in Scotland: a qualitative study**

Reference: British Journal of General Practice 2022; 72 (722)

Authors: David Whiteley, Elizabeth M Speakman, Lawrie Elliott, Helen Jarvis, Katherine Davidson and Michael Quin

url: https://doi.org/10.3399/BJGP.2022.0044

Summary: **Background**: The ease of contemporary hepatitis C virus (HCV) therapy has prompted a global drive towards simplified and decentralised treatment pathways. In some countries, primary care has become an integral component of community-based HCV treatment provision. In the UK, however, the role of primary care providers remains largely focused on testing and diagnosis alone.

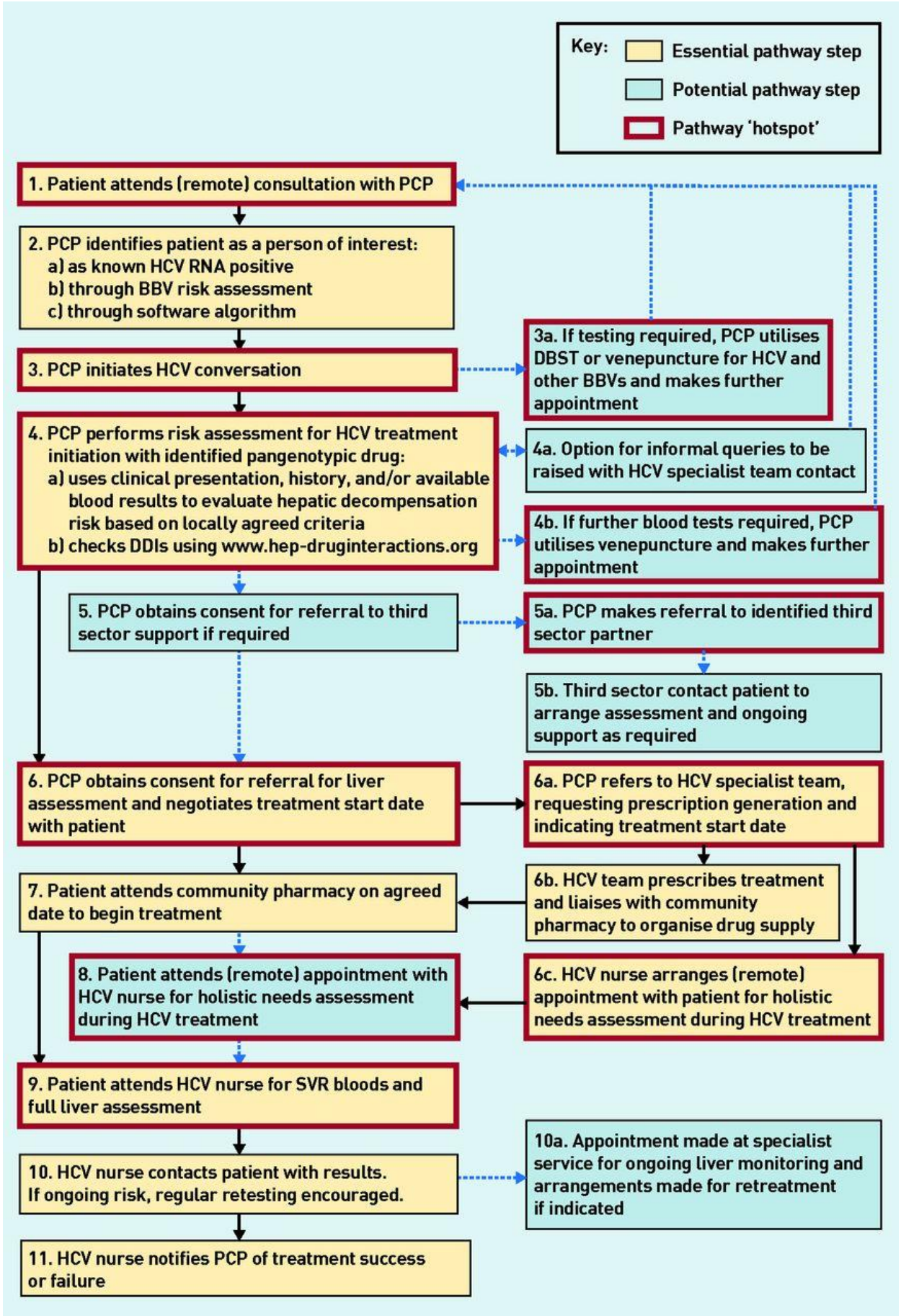
Aim: To develop a primary care-initiated HCV treatment pathway for people who use drugs and recommend theory-informed interventions to help embed that pathway into practice.

Design and setting: A qualitative study informed by behaviour change theory. Semi-structured interviews were undertaken with key stakeholders (n = 38) primarily from two large conurbations in Scotland.

Method: Analysis was three-stage. First, a broad pathway structure was outlined and then sequential pathway steps were specified; second, thematic data were aligned to pathway steps, and significant barriers and enablers were identified; and, third, the Theoretical Domains Framework and Behaviour Change Wheel were employed to systematically develop ideas to enhance pathway implementation, which stakeholders then appraised.

Results: The proposed pathway structure (see figure below) spans broad, overarching challenges to primary care- initiated HCV treatment. The theory-informed recommendations align with influences on different behaviours at key pathway steps, and focus on relationship building, routinisation, education, combating stigmas, publicising the pathway, and treatment protocol development

Interpretation: This study provides the first practicable pathway for primary care-initiated HCV treatment in Scotland and provides recommendations for wider implementation in the UK. It positions primary care providers as an integral part of community-based HCV treatment, providing workable solutions to ingrained barriers to care


Key:
Essential pathway step
Potential pathway step
Pathway 'hotspot'
1. Patient attends (remote) consultation with PCP
2. PCP identifies patient as a person of interest:
a) as known HCV RNA positive
b) through BBV risk assessment
c) through software algorithm
3. PCP initiates HCV conversation
3a. If testing required, PCP utilises DBST or venepuncture for HCV and other BBVs and makes further appointment
4. PCP performs risk assessment for HCV treatment initiation with identified pangenotypic drug:
a) uses clinical presentation, history, and/or available blood results to evaluate hepatic decompensation risk based on locally agreed criteria
b) checks DDIs using www.hep-druginteractions.org
4a. Option for informal queries to be raised with HCV specialist team contact
4b. If further blood tests required, PCP utilises venepuncture and makes further appointment
5. PCP obtains consent for referral to third sector support if required
5a. PCP makes referral to identified third sector partner
5b. Third sector contact patient to arrange assessment and ongoing support as required
6. PCP obtains consent for referral for liver assessment and negotiates treatment start date with patient
6a. PCP refers to HCV specialist team, requesting prescription generation and indicating treatment start date
6b. HCV team prescribes treatment and liaises with community pharmacy to organise drug supply
7. Patient attends community pharmacy on agreed date to begin treatment
8. Patient attends (remote) appointment with HCV nurse for holistic needs assessment during HCV treatment
6c. HCV nurse arranges (remote) appointment with patient for holistic needs assessment during HCV treatment
9. Patient attends HCV nurse for SVR bloods and full liver assessment
10. HCV nurse contacts patient with results.
If ongoing risk, regular retesting encouraged.
10a. Appointment made at specialist service for ongoing liver monitoring and arrangements made for retreatment if indicated
11. HCV nurse notifies PCP of treatment success or failure

Project: **RAACENO**

Title of paper: **Reducing asthma attacks in children using exhaled nitric oxide (RAACENO) as a biomarker to inform treatment strategy: a multicentre, parallel, randomised, controlled, phase 3 trial**

Reference: The Lancet Respiratory Medicine Vol 10, Issue 6, 2022, 584-592

Authors: Steve Turner, Seonaidh Cotton *et al*.

url: https://doi.org/10.1016/S2213-2600(21)00486-0

Summary: **Methods**: RAACENO was a multicentre, parallel, randomised, controlled, phase 3 trial in the UK. Patients with a confirmed asthma diagnosis, aged 6–15 years, prescribed inhaled corticosteroids, and who received a course of oral corticosteroids for at least one asthma exacerbation during the 12 months before recruitment were included. Participants were randomly assigned to either FeNO plus symptom-guided treatment (intervention) or symptom-guided treatment alone (standard care). A web-based algorithm gave treatment recommendations based on the Asthma Control Test or Childhood ACT score; current asthma treatment; adherence to study treatment in the past 3 months; and use of FeNO (in the intervention group). Follow-up occurred at 3-month intervals for 12 months. The primary outcome was any asthma exacerbation treated with oral corticosteroids in the 12 months after randomisation.

Findings: Between June 2017, and Aug 2019, 509 children were recruited and at baseline, the mean age of participants was 10·1 years (SD 2·6), and 308 (60·5%) were male. The median FeNO was 21 ppb (IQR 10–48), mean predicted FEV1 was 89·6% (SD 18·0), and median daily dose of inhaled corticosteroids was 400 µg budesonide equivalent (IQR 400–1000). Asthma was partly or fully controlled in 256 (50·3%). The primary outcome occurred in 123 (48·2%) of 255 participants in the intervention group and 129 (51·4%) of 251 in the standard care group, the intention-to-treat adjusted odds ratio (OR) was 0·88 (95% CI 0·61 to 1·27; p=0·49). The adjusted difference in the percentage of participants who received the intervention in whom the primary outcome occurred compared with those who received standard care was −3·1% (−11·9% to 5·6%). In 377 (21·3%) of 1771 assessments, the algorithm recommendation was not followed.

Interpretation: We found that the addition of FeNO to symptom-guided asthma treatment did not lead to reduced exacerbations among children prone to asthma exacerbation. Asthma symptoms remain the only tool for guiding treatment decisions.

Project: **Spiro-CKD**

Title of paper: **Effects of Spironolactone and Chlorthalidone on Cardiovascular Structure and Function in Chronic Kidney Disease**

Reference: Clinical Journal of the American Society of Nephrology October 2021, 16 (10) 1491-1501

Authors: Nicola C. Edwards, Anna M. Price *et al*

url: https://doi.org/10.2215/CJN.01930221

Summary: **Background and objectives**: In a randomized double-blind, placebo-controlled trial, treatment with spironolactone in early-stage CKD reduced left ventricular mass and arterial stiffness compared with placebo. It is not known if these effects were due to BP reduction or specific vascular and myocardial effects of spironolactone.

Design, setting, participants, & measurements: A prospective, randomized, open-label, blinded end point study conducted in four UK centers comparing spironolactone 25 mg to chlorthalidone 25 mg once daily for 40 weeks in 154 participants with nondiabetic stage 2 and 3 CKD (eGFR 30–89 ml/min per 1.73 m2). The primary end point was change in left ventricular mass on cardiac magnetic resonance imaging. Participants were on treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and had controlled BP (target ≤130/80 mm Hg).

Results: There was no significant difference in left ventricular mass regression; at week 40, the adjusted mean difference for spironolactone compared with chlorthalidone was −3.8 g (95% confidence interval, −8.1 to 0.5 g, P=0.08). Office and 24-hour ambulatory BPs fell in response to both drugs with no significant differences between treatment. Pulse wave velocity was not significantly different between groups; at week 40, the adjusted mean difference for spironolactone compared with chlorthalidone was 0.04 m/s (−0.4 m/s, 0.5 m/s, P=0.90). Hyperkalemia (defined ≥5.4 mEq/L) occurred more frequently with spironolactone (12 versus two participants, adjusted relative risk was 5.5, 95% confidence interval, 1.4 to 22.1, P=0.02), but there were no patients with severe hyperkalemia (defined ≥6.5 mEq/L). A decline in eGFR >30% occurred in eight participants treated with chlorthalidone compared with two participants with spironolactone (adjusted relative risk was 0.2, 95% confidence interval, 0.05 to 1.1, P=0.07).

Interpretation: Spironolactone was not superior to chlorthalidone in reducing left ventricular mass, BP, or arterial stiffness in nondiabetic CKD

Project: **TIME**

Title of paper: **Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial**

Reference: The Lancet Vol 400, Issue 10361, 2022, 1417-1425

Authors: Isla S Mackenzie, Amy Rogers *et al* on behalf of the TIME Study Group

url: https://doi.org/10.1016/S0140-6736(22)01786-X

Summary: **Background**: Studies have suggested that evening dosing with antihypertensive therapy might have better outcomes than morning dosing. The Treatment in Morning versus Evening (TIME) study aimed to investigate whether evening dosing of usual antihypertensive medication improves major cardiovascular outcomes compared with morning dosing in patients with hypertension.

Methods: The TIME study is a prospective, pragmatic, decentralised, parallel-group study in the UK, that recruited adults (aged ≥18 years) with hypertension and taking at least one antihypertensive medication. Eligible participants were randomly assigned (1:1) to take all of their usual antihypertensive medications in either the morning (0600–1000 h) or in the evening (2000–0000 h). Participants were followed up for the composite primary endpoint of vascular death or hospitalisation for non-fatal MI or non-fatal stroke. Endpoints were identified by participant report or record linkage to National Health Service datasets. The primary endpoint was assessed as the time to first occurrence of an event in the intention-to-treat population. Safety was assessed in all participants who submitted at least one follow-up questionnaire.

Findings: Between Dec 2011, and June 2018, 21 104 individuals were randomly assigned to evening (n=10 503) or morning (n=10 601) dosing groups. Mean age at study entry was 65·1 years (SD 9·3); 12 136 (57·5%) participants were men; 8968 (42·5%) were women; 19 101 (90·5%) were White; 98 (0·5%) were Black, African, Caribbean, or Black British (ethnicity was not reported by 1637 [7·8%] participants); and 2725 (13·0%) had a previous cardiovascular disease. By the end of study follow-up (March 31, 2021), median follow-up was 5·2 years (IQR 4·9–5·7), and 529 (5·0%) of 10 503 participants assigned to evening treatment and 318 (3·0%) of 10 601 assigned to morning treatment had withdrawn from all follow-up. A primary endpoint event occurred in 362 (3·4%) participants assigned to evening treatment (0·69 events [95% CI 0·62–0·76] per 100 patient-years) and 390 (3·7%) assigned to morning treatment (0·72 events [95% CI 0·65–0·79] per 100 patient-years; unadjusted hazard ratio 0·95 [95% CI 0·83–1·10]; p=0·53). No safety concerns were identified

Interpretation: Evening dosing of usual antihypertensive medication was not different from morning dosing in terms of major cardiovascular outcomes. Patients can be advised that they can take their regular antihypertensive medications at a convenient time that minimises any undesirable effects.

Project: **VERTIS**

Title of paper: **Efficacy of Ertugliflozin on Heart Failure–Related Events in Patients With Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease. Results of the VERTIS CV Trial**

Reference: Circulation December. 2020; Vol 142:23: 2205–2215

Authors: Francesco Cosentino, Christopher P. Cannon *et al* on behalf of the VERTIS investigators

url: https://doi.org/10.1161/CIRCULATIONAHA.120.050255

Summary: **Background**: In patients with type 2 diabetes mellitus, sodium-glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure (HHF). We assessed the effect of ertugliflozin on HHF and related outcomes.

Methods: VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial), a double-blind, placebo-controlled trial, randomly assigned patients with type 2 diabetes mellitus and atherosclerotic cardiovascular (CV) disease to once-daily ertugliflozin 5 mg, 15 mg, or placebo.

Prespecified secondary analyses compared ertugliflozin versus placebo on time to first event of HHF and composite of HHF/CV death, overall and stratified by prespecified characteristics. Cox proportional hazards modeling was used with the Fine and Gray method to account for competing mortality risk, and Andersen-Gill modeling to analyze total (first+recurrent) HHF and total HHF/CV death events.

Results: 8246 patients were randomly assigned to ertugliflozin (n=5499) or placebo (n=2747); n=1958 (23.7%) had a history of heart failure (HF) and n=5006 (60.7%) had pretrial ejection fraction (EF) available, including n=959 with EF ≤45%. Ertugliflozin did not significantly reduce first HHF/CV death (hazard ratio [HR], 0.88 [95% CI, 0.75–1.03]). Overall, ertugliflozin reduced risk for first HHF (HR, 0.70 [95% CI, 0.54–0.90]; P=0.006). Previous HF did not modify this effect (HF: HR, 0.63 [95% CI, 0.44–0.90]; no HF: HR, 0.79 [95% CI, 0.54–1.15]; P interaction=0.40). In patients with HF, the risk reduction for first HHF was similar for those with reduced EF ≤45% versus preserved EF >45% or unknown. However, in the overall population, the risk reduction tended to be greater for those with EF ≤45% (HR, 0.48 [95% CI, 0.30–0.76]) versus EF >45% (HR, 0.86 [95% CI, 0.58–1.29]). Effect on risk for first HHF was consistent across most subgroups, but greater benefit of ertugliflozin was observed in 3 populations: baseline estimated glomerular filtration rate <60 mL·min–1·1.73 m–2, albuminuria, and diuretic use (each P interaction <0.05). Ertugliflozin reduced total events of HHF (rate ratio, 0.70 [95% CI, 0.56–0.87]) and total HHF/CV death (rate ratio, 0.83 [95% CI, 0.72–0.96]).

Interpretation: In patients with type 2 diabetes mellitus, ertugliflozin reduced the risk for first and total of hospitalisation for heart failure and total of hospitalisation for heart failure /CV death, adding further support for the use of sodium-glucose cotransporter 2 inhibitors in primary and secondary prevention of HHF.