Importance of protection and prevention in cardiorenal disease

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On average, a 50-year old with diabetes but no history of vascular disease is ~6 years younger at time of death than a counterpart without diabetes.

“It is observable, that the hypertrophy of the heart seems, in some degree, to have kept pace with the advance of disease in the kidneys; for in by far the majority of cases, when the heart was increased, the hardness and contraction of the kidney bespoke the probability of long continuance of the disease.”

- R Bright, 1836
Novel treatments can improve cardio-renal outcomes in patients with diabetes

Prevention is important as long term exposure to risk factors drives cardio-renal disease

Leveraged gain from early intervention on common pathways to disease

Emerging early role for new drugs?

Never Too Late…Never Too Early…!!
Evidence Based Cardiorenal Risk Reduction

- Statins
- BP Lowering
- Metformin
- ACEi / ARB

GLP1-RA  SGLT2-i
Empagliflozin, CV Outcomes and Mortality in T2DM

Primary Outcome

Death from Cardiovascular Causes

Hazard ratio: 0.86 (95% CI, 0.74–0.99)
P = 0.04 for superiority

Death from Any Cause

Hazard ratio: 0.68 (95% CI, 0.57–0.82)
P < 0.001

Hospitalization for Heart Failure

Hazard ratio: 0.65 (95% CI, 0.50–0.85)
P = 0.002

GLP-1RA CV Outcome Trials

**LEADER**

Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

**SUSTAIN 6**

HR: 0.74  
(95% CI: 0.58 ; 0.95)  
*p<0.001 for non-inferiority*  
*p=0.02 for superiority*


Diabetes Treatment for CVD Reduction

SGLT-2 Inhibitors

- Preload
- Afterload
- Epicardial Fat

GLP-1R Agonists

- Satiety
- Nausea

Glycosuria
- Natriuresis
- Uricosuria

Hemodynamic Effect

- Major Adverse Cardiovascular Events
- Nephropathy
- Weight
- Blood Pressure

Anti-Atherogenic Effect

- Gastric motility
- Chylomicrons

Vasodilation

Post-prandial Glucose

Insulin

Glucagon

Renal Benefit from GLP-1RA and SGLT-2i

9,900 individuals with T2DM and eGFR of ≥ 15mL/min; Dulaglutide v Placebo; > two thirds primary CV prevention

Source: Hertzel C Gerstein, Lancet x.doi.org/10.1016/S0140-6736(19)31150-X
Exciting New Era for CVD Management in DM

- Diabetologists
- Cardiologists
- Primary Care
- Nephrology
A Thought…

“Why just strive to treat a disease like Diabetes better when you could *prevent* it?”
Diabetes Epidemic: Risk Factors start Early!

Source: IDF Diabetes Atlas. 7th edn. 2015

The Ticking Clock: ↑ CV Risk Before ↑ Glucose (Nurses’ Health Study)

20 yr F/U of 117,629 women: n=1,508 diabetes at B/L; n=5,894 developed diabetes; n=110,227 free from diabetes

Source: Hu et al, Diabetes Care 2002; 25: 1129-1134
Primary Care-led Weight Management For Remission of T2DM (DiRECT)

> 10kg Weight Loss  ➞  64% Remission

Source: Lean, M et al, Lancet 2018; 391: 541–51
Impact of GLP1-RA on Obesity

Four Weeks Of Liraglutide Inhibits Progression Of Atherosclerotic Lesions In ApoE-/- mice


Lesion development

Haemotoxylin and eosin staining in the aortic arch

Vehicle  |  Lira  |  Lira + Ex-9

Lipid deposition

Oil red O staining performed in the aorta

N=13–16

Vehicle  |  Lira  |  Lira + Ex-9

N=6–10

IMR analysis performed in the aortic arch

Vehicle  |  Lira  |  Lira + Ex-9

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SELECT: GLP1-RA in high CVD risk Non Diabetics

N=17,500 patients
Male or female
≥45 years of age
BMI ≥27

Semaglutide s.c. 2.4 mg once-weekly

Placebo s.c. once-weekly

Randomisation (1:1)
Event driven
1225 first MACEs

Prior MI
Prior stroke
PAD

Primary endpoint:
Time from randomisation to first occurrence of a composite endpoint consisting of either:
- CV death
- Non-fatal myocardial infarction
- Non-fatal stroke
CV RFs Drive Multiple Diseases Through Common Pathways

- Stress
- Obesity
- BP
- Smoking
- Cholesterol
- Systemic Inflammation
- Oxidative Stress
- Ageing
- Stroke
- Diabetes
- CKD
- CVD
- Dementia
- Cancer
Impact of Periodontitis Treatment on Glucose Control, Vascular and Renal Function in T2DM

In UK population
- Severe in 5-10%
- Mild/mod. in 40%

Source: D’Aiuto  Lancet Diabetes 2018
How Early Should Prevention Start? "Poor Start in Life"
Obesity at 2 yrs Predicts Status at 35 yrs...

BMI During Adolescence and CV Mortality

Diabetes and Hypertension

Source: Twig G et al, NEJM 2016;374:2430-40
Cardio-renal Disease in Diabetes: Protection & Prevention

New era for treatment of cardio-renal disease

Earlier management is needed to target disease in the population

Emerging role for new drugs and lifestyle in pre-clinical disease
Final Thought…

“It should be the function of medicine to have people die young as late as possible”

- Ernest L. Wynder M.D.