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A novel role of SGLT2 inhibitors to increase circulating proangiogenic progenitor cells in patients with type 2 diabetes and cardiovascular disease: A sub-study of the EMPA-HEART CardioLink-6 Trial

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Background: SGLT2 inhibitors (SGLT2i) have been demonstrated to reduce major adverse cardiovascular events and mortality in patients with type 2 diabetes (T2D) who are at high risk for cardiovascular disease (CVD). However, the mechanism(s) of the underlying benefit remain unclear. Since regenerative cell exhaustion resulting in impaired vascular homeostasis has been proposed as a key driver of CV events in T2D, we hypothesised that modulation of circulating vascular regenerative cell content by SGLT2i may be a novel basis of cardioprotection.

Purpose: To evaluate the effects of the SGLT2i, empagliflozin (EMPA), vs placebo on circulating vascular regenerative and pro-inflammatory cells in patients with T2D and CVD.

Methods: This was a biomarker sub-study of the EMPA-HEART Cardiolink-6 randomised trial of EMPA (10mg QD) vs placebo in patients with T2D and a history of coronary artery disease (prior myocardial infarction and/or coronary revascularisation). Blood samples (baseline N=48; study end N=26) underwent multiparametric progenitor cell analyses by flow cytometry. Circulating cells were assessed for aldehyde dehydrogenase (ALDH) activity, a self-protective enzyme highly expressed in several proangiogenic progenitor cell lineages, as well as cell surface co-expression of the primitive progenitor (CD34, CD133) or M1/M2 macrophage (CD80, CD163) markers.

Results: Individuals with increased inflammatory burden (ALDHhi granulocytes above the baseline median) were older (61±2 vs 67±2 years), more likely to be current or past smokers (21% vs 42%) and had reduced LV function, assessed by echocardiography. The placebo- and EMPA-assigned groups were equivalent at baseline with respect to the frequency and distribution of proangiogenic progenitor cells (ALDHhiSSClo), monocyte/macrophage (ALDHhiSSCmid) and inflammatory granulocyte (ALDHhiSSChi) precursors. Following 6-months of treatment with EMPA, there was a marked increase in the number of circulating primitive ALDHhiSSClo cells with CD133 (Placebo: -2.8±3.8%, EMPA: +8.6±2.5%, P<0.02) or CD133 / CD34 (Placebo: 0.4±4.5%, EMPA: +13.3±3.8%, P<0.05) co-expression. Furthermore, EMPA treatment was associated with an increase in the frequency of circulating anti-inflammatory cells with M2 macrophage polarisation marked by CD163 (Placebo: - 0.7±0.8%, EMPA = +3.9±1.3%, P<0.01) expression. Non-significant increases in circulating proangiogenic monocytes, and decreases in the frequency of circulating inflammatory granulocytes were also observed after EMPA treatment (vs placebo).

Conclusion: We provide the first evidence showing that SGLT2i treatment with EMPA alters the balance of key circulating vascular progenitor and inflammatory cells in patients with T2D and CVD. We suggest that SGLT2i may afford cardioprotection through a novel and previously unrecognised capacity to limit regenerative cell exhaustion in T2D.
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