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**Do the Favorable Effects of Digoxin and SGLT2 Inhibitors Really Differ in Patients with Heart Failure and a Reduced Ejection Fraction?
A Provocative Side-by-Side Comparison of Trial Outcomes**

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Do the Favorable Effects of Digoxin and SGLT2 Inhibitors Really Differ in Patients with Heart Failure and a Reduced Ejection Fraction? A Provocative Side-by-Side Examination of Trial Outcomes

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In the 2021 heart failure guidelines from the European Society of Cardiology, there is a striking difference in the recommendations for the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors and digoxin. SGLT2 inhibitors have a class IA recommendation, and their use is strongly advocated for all patients with heart failure and a reduced ejection fraction (HFrEF). In contrast, digoxin carries a class IIB recommendation that suggests its possible consideration in patients with HFrEF in sinus rhythm.

Does the clinical trial evidence support the marked differences in how these drugs are regarded? There have been two large-scale trials of SGLT2 inhibitors in HFrEF (DAPA-HF and EMPEROR-Reduced) and one large-scale trial of digoxin in HFrEF and sinus rhythm (the DIG trial).¹⁻³ In all three trials, patients were routinely treated with conventional inhibitors of the renin-angiotensin system, but the use of beta-blockers and mineralocorticoid receptor antagonists as background therapy was documented only in the trials with SGLT2 inhibitors. The effect of treatment on all-cause and cause-specific deaths and hospitalizations is shown (Table 1).

The primary benefit of SGLT2 inhibitors in patients with heart failure is to reduce the risk of hospitalizations for heart failure. This effect was the principal driver of success in the DAPA-HF and EMPEROR-Reduced trials.^{2,3} The effect of SGLT2 inhibitors on cardiovascular death has not been a consistent finding with these drugs, either in trials of patients with heart failure or in trials of patients with in type 2 diabetes. The mortality benefit reported in a meta-analysis of two heart failure trials was modest (< 15% risk reduction) and borderline significant,⁴ a pattern that differs meaningfully from the mortality reduction seen with other foundational drugs for HFrEF. The effect of SGLT2 inhibitors to reduce hospitalizations is specific for hospitalizations due to heart failure. When hospitalizations are defined more broadly, the magnitude of the hospitalization benefit of SGLT2 inhibitors diminishes, although it remains significant.

The primary benefit of digoxin in patients with HFrEF and sinus rhythm is to reduce the risk of hospitalizations for heart failure. When hospitalizations are defined more broadly, the magnitude of the hospitalization benefit of digoxin diminishes but remains significant. When given in doses up to 0.375 mg daily to achieve a broad range of serum concentrations (including those >1.2 ng/ml), digoxin had no significant effect on all-cause mortality in the DIG trial, although the risk of heart failure deaths was modestly lower (12% risk reduction, $P=0.06$). In post hoc analyses, the achieved serum digoxin concentrations measured early in the trial influenced the effect of the drug on survival. When compared with placebo, patients in the digoxin group with a serum digoxin concentration <0.9 ng/ml had a reduction in all-cause mortality (hazard ratio 0.80 [0.68-0.94]) after multivariable adjustment.⁵ Low doses of digoxin may act primarily to reduce neurohormonal activation and be devoid of the deleterious positive inotropic and proarrhythmic effects seen with high doses.

It is true that the DIG trial was carried out in an era where there was little routine use of beta-blockers and mineralocorticoid receptor antagonists. Furthermore, the need for blood tests to ensure that patients have a serum digoxin concentration <0.9 ng/ml might discourage the use of digoxin among some physicians. Perhaps for these reasons, there has been a progressive downgrading of the recommendations for digoxin in guideline documents. In the US heart failure guidelines, digoxin carried a class IA recommendation in 2001, a class IIA recommendation in 2009 and 2013, and a class IIB recommendation in 2016 and 2021. Interestingly, these changes occurred in the absence of any new evidence from randomized controlled clinical trials.

Does this downgrading make sense? Current guidelines provide a class IA recommendation for angiotensin converting-enzyme inhibitors, even though their efficacy in patients with

chronic heart failure receiving beta-blockers and mineralocorticoid receptor antagonists has not been established. Furthermore, inhibitors of the renin-angiotensin system and mineralocorticoid receptor antagonists require periodic blood tests to ensure their safe and effective use.

It should also be noted that there are at least two positive randomized trials of digoxin in heart failure. Both digoxin and SGLT2 inhibitors are given once daily and are well-tolerated, but digoxin is less expensive than dapagliflozin and empagliflozin.

Do the available data justify a striking difference in the recommendations for digoxin and SGLT2 inhibitors for the treatment of HFrEF? If the principal benefit of these drug classes is to reduce heart failure hospitalizations without a consistent effect to reduce mortality, why are cardiologists thinking of these drugs so differently?

Disclosures

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Table 1. Outcomes in Large-Scale Trials of SGLT2 Inhibitors and Digoxin in Patients With Heart Failure and a Reduced Ejection Fraction

	DIG	DAPA-HF	EMPEROR-Reduced
Number of randomized patients	7372	4744	3730
Median duration of double-blind therapy	37 months	18 months	16 months
Effect on all-cause mortality	0.99 (0.91-1.07)	0.83 (0.71-0.97)	0.92 (0.77-1.10)
Effect on cardiovascular deaths	1.01 (0.93-1.10)	0.82 (0.69-0.98)	0.92 (0.72-1.12)
Effect on heart failure deaths	0.88 (0.77-1.01)	Not reported	Not reported
Effect on all-cause hospitalizations	0.92 (0.87-0.98)	Not reported	0.82 (0.74-0.90)
Effect on cardiovascular hospitalizations	0.87 (0.81-0.93)	Not reported	0.75 (0.67-0.85)
Effect on heart failure hospitalizations	0.72 (0.66-0.79)	0.70 (0.59 to 0.83)	0.69 (0.59-0.81)