CONTEMPORARY REVIEW

Molecular, Cellular, and Clinical Evidence That Sodium-Glucose Cotransporter 2 Inhibitors Act as Neurohormonal Antagonists When Used for the Treatment of Chronic Heart Failure

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ABSTRACT: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure. Initially, these drugs were believed to have a profile similar to diuretics or hemodynamically active drugs, but they do not rapidly reduce natriuretic peptides or cardiac filling pressures, and they exert little early benefit on symptoms, exercise tolerance, quality of life, or signs of congestion. Clinically, the profile of SGLT2 inhibitors resembles that of neurohormonal antagonists, whose benefits emerge gradually during sustained therapy. In experimental models, SGLT2 inhibitors produce a characteristic pattern of cellular effects, which includes amelioration of oxidative stress, mitigation of mitochondrial dysfunction, attenuation of proinflammatory pathways, and a reduction in myocardial fibrosis. These cellular effects are similar to those produced by angiotensin converting enzyme inhibitors, β-blockers, mineralocorticoid receptor antagonists, and neprilysin inhibitors. At a molecular level, SGLT2 inhibitors induce transcriptional reprogramming of cardiomyocytes that closely mimics that seen during nutrient deprivation. This shift in signaling activates the housekeeping pathway of autophagy, which clears the cytosol of dangerous cytosolic constituents that are responsible for cellular stress, thereby ameliorating the development of cardiomyopathy. Interestingly, similar changes in cellular signaling and autophagic flux have been seen with inhibitors of the renin-angiotensin system, β-blockers, mineralocorticoid receptor antagonists, and neprilysin inhibitors. The striking parallelism of these molecular, cellular, and clinical profiles supports the premise that SGLT2 inhibitors should be regarded as neurohormonal antagonists when prescribed for the treatment of heart failure with a reduced ejection fraction.

Key Words: heart failure ■ neurohormonal antagonists ■ SGLT2 inhibitors

First proposed in 1992, the neurohormonal hypothesis postulates that heart failure with a reduced ejection fraction should be regarded as a neurohormonal disorder and that these patients should benefit from the use of drugs that interfere with the deleterious effects of neurohormonal systems. At the time of its formulation, angiotensin-converting enzyme (ACE) inhibitors were the only neurohormonal antagonist that had been approved for use in patients with chronic heart failure. However, since 1992, numerous large-scale clinical trials have demonstrated the benefits of β-blockers, mineralocorticoid receptor antagonists, and sacubitril/valsartan. These drugs interfere with the deleterious effects of excessive activation of the sympathetic nervous system, aldosterone, and neprilysin that characterizes patients with heart failure and impaired systolic function.

Combination therapy with multiple neurohormonal antagonists represents the cornerstone of class I recommendations in current heart failure guidelines based on compelling evidence that these drugs prolong survival in a broad spectrum of patients with heart failure.
Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| ACE          | angiotensin-converting enzyme |
| Akt          | protein kinase B |
| AMPK         | adenosine monophosphate-activated protein kinase |
| AMPKa2       | adenosine monophosphate-activated protein kinase isoform alpha 2 |
| DAPA-HF      | Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure |
| EMPEROR-Reduced | Empagliflozin Outcome Trial in Chronic Heart Failure With Reduced Ejection Fraction |
| mTOR         | mammalian target of rapamycin |
| mTORC1       | mammalian target of rapamycin complex 1 |
| mTORC2       | mammalian target of rapamycin complex 2 |
| SGLT2        | sodium-glucose cotransporter 2 |
| SIRT1        | sirtuin-1 |

and a reduced ejection fraction in trials that recorded a meaningful number of serious cardiovascular events.3 Other drugs that are recommended for use in chronic heart failure (eg, digoxin, ivabradine, and hydralazine/isosorbide dinitrate) act primarily to reduce the risk of heart failure hospitalizations or have been reported to reduce the risk of death based only on small numbers of events or in select groups.3,4

In recent years, sodium-glucose cotransporter 2 (SGLT2) inhibitors were shown to reduce the risk of heart failure hospitalizations (and often cardiovascular death) in high-risk patients with type 2 diabetes mellitus who generally did not have heart failure at the time of enrollment in the trials.5 Furthermore, in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, dapagliflozin reduced the risk of cardiovascular death in patients with established heart failure and a reduced ejection fraction, including those without diabetes mellitus. A second large-scale trial (EMPEROR-Reduced [Empagliflozin Outcome Trial in Chronic Heart Failure With Reduced Ejection Fraction]) that is evaluating the effects of empagliflozin in patients with advanced disease is nearing completion.6 If the DAPA-HF and EMPEROR-Reduced trials yield concordant findings, then SGLT2 inhibitors will likely join the ranks of the current class I recommended drugs for heart failure; but should SGLT2 inhibitors be regarded as neurohormonal antagonists, akin to how we currently think about angiotensin receptor neprilysin inhibitors, β-blockers, and mineralocorticoid receptor antagonists?

WHAT FEATURES OF A DRUG IDENTIFY IT AS A NEUROHORMONAL ANTAGONIST?

In the 1970s and 1980s, heart failure was regarded primarily as a hemodynamic disorder.7 Decreases in cardiac output and increases in left ventricular filling pressures were attributed to an impairment in cardiac contractility and constriction of arterial resistance and venous capacitance vessels. Treatment focused on the use of diuretics, systemic vasodilators, and positive inotropic agents; these drugs produced immediate changes in hemodynamic variables, often with rapid relief of dyspnea. However, the immediate actions of positive inotropic and systemic vasodilator drugs often failed to predict their long-term effects. Sustained treatment with hemodynamically active drugs often stimulated deleterious neurohormonal systems or mimicked their adverse actions on the myocardium.8 As a result, the short-term benefits of these agents were frequently not sustained,9 and prolonged therapy often acted to accelerate progression of the underlying disease and increase the risk of hospitalization and death.10,11

Neurohormonal antagonists (which interfere with the actions of deleterious endogenous mechanisms) exhibit a strikingly different pattern of response. The benefits of these drugs emerge slowly and typically require prolonged treatment to become apparent. In many instances, these drugs produce no immediate benefit on cardiac output or left ventricular filling pressures or lead to unwanted hemodynamic responses, for example, hypotension with ACE inhibitors, carvedilol and neprilysin inhibitors, and worsening heart failure with β-blockers. Any favorable effect on left ventricular remodeling or ejection fraction is often delayed for 6 to 12 months or longer.12 During the first weeks or months of treatment, patients often report little improvement in quality of life or exercise tolerance.13,14 Nevertheless, long-term treatment is accompanied by striking effects to reduce the risk of death and hospitalization. Interestingly, prior treatment with ACE inhibitors and β-blockers has not precluded the benefits of mineralocorticoid receptor antagonists and neprilysin inhibitors,2 suggesting that simultaneous antagonism of different deleterious pathways is needed to produce optimal effects on survival.

The features and time course of the response to treatment distinguish neurohormonal antagonists from diuretics or hemodynamically active agents.
The benefits of neurohormonal interventions emerge slowly, presumably because the heart needs time to recover once it is shielded from endogenous influences that are injurious to cardiomyocyte function and survival. Viewed from this perspective, neurohormonal antagonism in chronic heart failure represents a form of pharmacological cardioprotection.

### SGLT2 INHIBITORS DO NOT EXERT THEIR BENEFITS IN CHRONIC HEART FAILURE BY AN ACTION ON HEMODYNAMIC VARIABLES

When first introduced into clinical use, SGLT2 inhibitors were believed to have immediate and clinically relevant hemodynamic effects. These drugs inhibit sodium reabsorption in the proximal renal tubule by an action to block glucose reuptake (via SGLT2) and possibly by an effect to interfere with sodium-hydrogen exchanger isofom 3.15 In patients with acute heart failure, SGLT2 inhibitors promote an increase in urine volume that persists for several days,16 and this natriuretic action may lead to decreases in plasma and/or interstitial volume.17 In addition, SGLT2 inhibitors exert vasodilator effects that may underlie their action to lower blood pressure.18 Accordingly, it was suggested that SGLT2 inhibitors act primarily to lower cardiac filling pressures. However, the effect of SGLT2 inhibitors on urinary sodium excretion in chronic heart failure appears to be modest and transient, and any reduction in plasma volume is often short lived.19-21 As a result, these drugs do not produce the immediate and striking decreases in circulating natriuretic peptides that are typically seen with loop diuretics, and treatment does not alleviate pulmonary or systemic congestion.22 In addition, the effects of loop diuretics have been associated with an increased risk of cardiovascular death,23 whereas SGLT2 inhibitors decrease cardiovascular mortality, both in patients with type 2 diabetes mellitus as well as those with chronic heart failure.5

Some have proposed that SGLT2 inhibitors may produce hemodynamic benefits by enhancing the production of ketone bodies.24 The short-term infusion of β-hydroxybutyrate in supraphysiological doses increases both cardiac contractility and heart rate in patients with a reduced ejection fraction.25 However, the clinical significance of this finding remains uncertain because SGLT2 inhibitors do not appear to produce positive inotropic and chronotropic effects in clinical trials. The failing heart already preferentially consumes ketone bodies as a fuel,26 and in experimental models, SGLT2 inhibition does not consistently improve myocardial ketone body use.27-29 Importantly, any improvement in cardiac performance that might result from the increase in myocardial adenosine triphosphate produced by SGLT2 inhibitors is not related to enhanced ketone body metabolism.28,29 In hemodynamic studies, the cardiovascular benefits of these drugs are not related to changes in cardiac contractility or ventricular loading conditions.30

The cardioprotective effects of SGLT2 inhibitors evolve slowly, and their actions to reduce left ventricular mass and cardiac volumes are seen during prolonged therapy.31,32 Furthermore, in a manner akin to conventional neurohormonal antagonists, SGLT2 inhibitors do not act rapidly to improve symptoms and show little effect on exercise tolerance or quality of life in trials of 3 months’ duration (Table).22 Any benefits of SGLT2 inhibitors on functional capacity33 may result from (rather than precede) the effects of these drugs to favorably influence the underlying cardiomyopathy.

### Table. Clinical, Cellular, and Molecular Features That Distinguish Hemodynamically Active Drugs, Established Neurohormonal Antagonists, and SGLT2 Inhibitors

| Effect | Diuretics, Systemic Vasodilators, and Positive Inotropic Drugs | Established Neurohormonal Antagonists | SGLT2 Inhibitors |
|--------|---------------------------------------------------------------|--------------------------------------|------------------|
| Immediate effects on cardiac output, filling pressures, and natriuretic peptides | Present and desirable | Often absent and frequently undesirable | Generally absent in clinically stable patients |
| Ability to rapidly improve symptoms, exercise tolerance, and quality of life | Frequently present | Frequently absent | Generally absent |
| Effect to reduce the risk of cardiovascular death | Usually absent | Characteristically present | Usually present |
| Effect to ameliorate oxidative stress, organellar dysfunction, and cellular inflammation | Usually absent | Characteristically present | Characteristically present |
| Enhancement of SIRT1/AMPK and attenuation of Akt/mTOR signaling | Inconsistent and not characteristic | Present with several drug classes | Characteristic of members of the drug class |
| Augmentation of autophagic flux | Inconsistent and not characteristic | Reported with several drug classes | Noted with several members of the drug class |

Akt indicates Akt/protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; SGLT2, sodium-glucose cotransporter 2; and SIRT1, sirtuin-1.

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SGLT2 inhibitors exert cardioprotective effects in numerous models of diabetic and nondiabetic cardiac injury. Regardless of the inciting cause, treatment leads to the amelioration of oxidative stress, mitigation of mitochondrial dysfunction, attenuation of proinflammatory pathways, and a reduction in myocardial fibrosis. The pattern of these effects is similar to that produced by ACE inhibitors, β-blockers, mineralocorticoid receptor antagonists, and neprilysin inhibitors. ACE inhibitors reduce oxidative stress, preserve mitochondrial function, and mitigate proinflammatory pathways, effects that are superior to those seen with angiotensin receptor blockers. β-blockers attenuate the generation of reactive oxygen species, inhibit mechanisms that trigger cellular inflammation, and promote mitochondrial biogenesis. Mineralocorticoid receptor antagonists alleviate oxidative stress and reduce the inflammatory responses that lead to fibrosis. Neprilysin inhibitors stabilize mitochondrial function and protect the heart from the injurious effects of reactive oxygen species and inflammation. The striking parallelism in the cellular effects of SGLT2 inhibitors and established neurohormonal antagonists support the hypothesis that the actions of SGLT2 inhibitors are akin to those produced by drugs that interfere with endogenous neurohormonal systems (Table).

The ability of SGLT2 inhibitors to exert cardioprotective effects on a cellular level is intriguing because the healthy or failing heart does not express SGLT2, and SGLT2 inhibitors do not bind to cardiac tissue. In contrast, cardiomyocytes have identifiable receptors for angiotensin II, norepinephrine, aldosterone, and natriuretic peptides, and interaction with these receptors is generally required for the effect of neurohormonal antagonists to ameliorate cellular stress and organelar dysfunction. Although SGLT2 inhibitors may modestly attenuate the sympathetic response to volume depletion, the direct measurements of sympathetic activity have demonstrated little inhibitory action of these drugs. Furthermore, SGLT2 inhibitors activate the renin-angiotensin-aldosterone system, suggesting that these drugs do not inhibit the mechanisms that are targeted by conventional neurohormonal antagonists.

Therefore, the benefits of SGLT2 inhibitors to alleviate cellular stress and organelar dysfunction result from interference with endogenous mechanisms that adversely affect the heart, but these are not the conventional pathways that are targeted by established drugs, and they are not mediated by identifiable receptor in the heart. What is the identity of the injurious mechanisms that are blocked by SGLT2 inhibitors?

**IMPORTANCE OF AUTOPHAGIC FLUX IN ATTENUATING CELLULAR STRESS AND MITIGATING THE DEVELOPMENT OF CARDIOMYOPATHY**

In chronic heart failure (regardless of etiology), glucose and lipid intermediates accumulate in cardiomyocytes, and play a critical role in causing oxidative and endoplasmic reticulum stress. These stresses directly impair the structural integrity and normal functioning of mitochondria and peroxisomes, thus promoting the generation of reactive oxygen species and activating proinflammatory pathways, further enhancing cellular stress. These cellular stresses and organelar derangements are normally constrained by a cellular housekeeping pathway known as autophagy.

Autophagy is a lysosome-mediated degradative process that allows cardiomyocytes to clear the accumulation of intracellular glucose and lipid pools, and it also promotes the disposal of dysfunctional and damaged mitochondria and peroxisomes, thus muting oxidative stress and proinflammatory mechanisms. The autophagic capacity of cardiomyocytes is markedly impaired in human heart failure; yet pharmacological stimulation of autophagic flux can directly ameliorate oxidative stress and organelar dysfunction, thereby preventing or reversing cardiomyocyte dysfunction and demise, and mitigating the development of cardiomyopathy. Activation of autophagy represents a major shift in the priorities of cardiomyocytes away from growth toward the preservation of cellular homeostasis and survival. Importantly, the intensity of autophagic flux in cardiomyocytes is finely regulated by the balance of enzymes and transcription factors that are exquisitely sensitive to environmental conditions, particularly states of nutrient and energy deprivation and overabundance.

**Transcription Factors That Modulate Autophagic Flux in Cardiomyocytes and Influence the Evolution of Progression of Myocardial Dysfunction**

Autophagy is stimulated by nutrient depletion because any reduction in environmental fuel requires cells to curtail growth and direct their efforts to support organelar function and cellular homeostasis. The major
sensors of glucose deprivation are SIRT1 (sirtuin-1) and AMPK (adenosine monophosphate–activated protein kinase). SIRT1 is a redox-sensitive nicotinamide adenine dinucleotide–dependent deacetylase that functions to maintain blood glucose. AMPK is sensitive to the balance between adenosine triphosphate and adenosine diphosphate or adenosine monophosphate in the cytosol; its activation promotes the generation of adenosine triphosphate. Both SIRT1 and AMPK are enzymes that regulate the activity of hundreds of genes and proteins that are involved in metabolism and cellular homeostasis; their functions are intertwined, and they suppress energy storage and promote catabolic pathways. Both SIRT1 and AMPK act to stimulate autophagy and thus promote the clearance of dysfunctional organelles and glucose/lipid intermediates, which are the primary sources of cellular stress. In addition, they act directly to preserve organellar integrity and mute inflammasome activation.

In states of energy overabundance, cells prioritize growth over cellular stability and survival, and during such times, autophagic flux is constrained by activation of Akt (protein kinase B) and mTOR (mammalian target of rapamycin). Both Akt and mTOR are serine/threonine protein kinases that function as critical promoters of cell proliferation; mTOR is expressed as 2 protein complexes: mTORC1 and mTORC2. Both Akt and mTORC1 are upregulated by nutrient surplus and by growth factors (eg, insulin), and Akt potentiates the activation of mTORC1. When activated by nutrient surplus, both Akt and mTORC1 enhance glucose and lipid storage, oxidative metabolism, and mitochondrial oxygen consumption, and they promote the anabolic pathways that are required for cellular hypertrophy and replication.

Therefore, whereas SIRT1 and AMPK signaling promotes autophagy and cellular homeostasis and survival during nutrient deprivation, Akt and mTORC1 act to suppress autophagy and facilitate cellular expansion during nutrient overabundance. The actions of the Akt and mTORC1 pathway counterbalance those of SIRT1 and AMPK.

Abnormalities of Nutrient-Sensitive Transcription Factor Signaling in Experimental and Clinical Heart Failure and Their Modulation by Conventional Neurohormonal Antagonists

Both experimentally and clinically, heart failure is characterized by the simultaneous impairment of signaling through SIRT1 and AMPK and by enhanced activation of the Akt/mTORC1 pathway in cardiomyocytes. SIRT1 and AMPK activation are reduced in experimental and human heart failure. A recent body of evidence has focused on the potential for SIRT1/AMPK to modulate the adverse effects of myocardial ischemia and reperfusion injury. Treatment with AMPK activators or SIRT1 activators before myocardial ischemia reduces infarct size by improving cardiac contractility and reducing the severity of adverse remodeling. Additionally, SIRT1 and AMPK activation may improve myocardial function and survival in experimental and clinical heart failure.

In contrast with the actions of the Akt/mTOR pathway, activation of SIRT1/AMPK prioritizes cellular survival over growth. Signalings through SIRT1/AMPK prevent excessive hypertrophy, mitigate inflammation, promote mitochondrial health, and preserve cardiac function during diverse forms of cardiac stress.

The activity of SIRT1 and AMPK is reduced in experimental and human heart failure, and the severity of heart failure is positively correlated with SIRT1 and AMPK activity. Experimental heart failure is characterized by a decrease in SIRT1 and AMPK activity, and SIRT1 and AMPK activation is reduced in clinical heart failure. In contrast, SIRT1 and AMPK activation is increased in experimental and clinical heart failure, and SIRT1 and AMPK activation is reduced in experimental and clinical heart failure. The activity of SIRT1 and AMPK is reduced in experimental and human heart failure, and the severity of heart failure is positively correlated with SIRT1 and AMPK activity. Experimental heart failure is characterized by a decrease in SIRT1 and AMPK activity, and SIRT1 and AMPK activation is reduced in clinical heart failure. In contrast, SIRT1 and AMPK activation is increased in experimental and clinical heart failure, and SIRT1 and AMPK activation is reduced in experimental and clinical heart failure.

Interestingly, activation of the renin-angiotensin system, sympathetic nervous system, and aldosterone as well as downregulation of natriuretic peptide signaling also cause SIRT1/AMPK suppression and Akt/mTORC1 activation. ACE inhibitors can counteract the adverse effects of angiotensin II by signaling through SIRT1/AMPK activation because SIRT1 upregulation may interfere with the injurious actions of angiotensin II on heart.

The benefits of angiotensin receptor blockers may be mediated by activation of AMPK and inhibition of Akt/mTORC1; the latter effect underlies the action of these drugs to promote autophagy. β-adrenergic receptor stimulation leads to the suppression of AMPK and β-blockade is accompanied by the upregulation of AMPK, and additionally, carvedilol exerts anti-inflammatory effects by an action to promote autophagy through a stimulatory effect on SIRT1 and AMPK.

SGLT2 Inhibitors as Neurohormonal Antagonists
activation of AMPK,120,121 and intriguingly, nephrilysin can directly activate Akt/mTOR signaling independent of its effect on natriuretic peptides.122,123 Therefore, the ability of established neurohormonal antagonists to influence the interplay of SIRT1/AMPK and Akt/mTOR so as to promote autophagy may contribute to the benefits of these drugs.

**SGLT2 Inhibitors Modulate the Effects of Transcription Factors That Regulate Cellular Stresses and Autophagy and Can Influence the Development of Cardiomyopathy**

SGLT2 acts as a sensor of nutrient overabundance,124 and thus there is an inverse relationship between SGLT2 and SIRT1125 (which functions as the principal sensor of nutrient deprivation126); simultaneously, there is a direct relationship between the intensity of proximal tubular sodium-glucose reabsorption and the activation of Akt/mTOR.54 When the actions of SGLT2 are inhibited, the resulting urinary loss of calories triggers systemic transcriptional reprogramming that closely mimics that seen during states of nutrient deprivation.127 The depletion of tissue nutrients that follows glycosuria leads to the activation of SIRT1 and AMPK and the suppression of kinases that are normally activated by nutrient excess (Akt and mTOR) (Figure).127,128 Several SGLT2 inhibitors have been shown to upregulate SIRT1 and AMPK while suppressing the Akt/mTOR pathway,38,127–132 thus explaining the ability of these drugs to promote autophagy in diverse organs, including the heart.36 The induction of autophagy underlies the ability of SGLT2 inhibitors to mute oxidative stress, promote organellar integrity, suppress proinflammatory pathways, and ameliorate the course of cardiomyopathy.34–39 Importantly, because nutrient deprivation signaling is a system-wide response, these benefits do not depend on the expression of SGLT2 in the heart.

**CONCLUSIONS**

Drugs that act primarily as diuretics or on hemodynamic variables can exert rapid effects on cardiac output, cardiac filling pressures, systemic vascular tone, or natriuretic peptides, and they can produce immediate effects to alleviate symptoms of congestion. However, long-term treatment with these drugs often produces little benefit on the progression of heart failure and may increase the risk of death. In contrast, neurohormonal antagonists typically exert little immediate effect on symptoms or quality of life, but over time, they act to reduce morbidity and mortality because they shield the myocardium from the effects of endogenous mechanisms that can cause cellular stress and injury.

The pattern of responses to SGLT2 inhibitors closely mimics that of established neurohormonal antagonists. These drugs have limited immediate benefits on symptoms, quality of life, or natriuretic peptides, but sustained therapy reduces the risk of serious heart failure events. Experimentally, SGLT2 inhibitors ameliorate cellular stress, preserve mitochondrial integrity, and attenuate proinflammatory pathways, a profile of effects similar to that seen with inhibitors of the renin-angiotensin system, β-blockers, mineralocorticoid receptor antagonists, and nephrilysin inhibitors. In addition, SGLT2 inhibitors promote the activation of SIRT1/AMPK and inhibit signaling through Akt/mTOR, thereby enhancing the cellular housekeeping process of autophagy and its effects to ameliorate cytosolic stress, enhance cellular survival, and ameliorate the development of cardiomyopathy. Similar effects on SIRT1/AMPK and Akt/mTOR as well as on autophagy have been noted with conventional neurohormonal antagonists. The striking parallelism of these molecular, cellular, and clinical profiles suggests that SGLT2 inhibitors should be regarded as neurohormonal antagonists when they are prescribed for the treatment of chronic heart failure with a reduced ejection fraction.

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Disclosures
Dr Packer has recently consulted for Abbvie, Actaxis, Akcea, Amgen, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Johnson & Johnson, NovoNordisk, Pfizer, Sanofi, Synthetic Biologies, and Theravance.

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SGLT2 Inhibitors as Neurohormonal Antagonists

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