

Role of Dapagliflozin in Diabetic and Non-Diabetic Heart Failure

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<u>Abstract</u>

Selective sodium-glucose cotransporter-2 (SGLT-2) has been known for years to be effective in the management of hyperglycaemia in diabetic patients. It results in moderate reduction in HbA1C levels, weight and blood pressure in diabetic patients. Recently, it has become apparent that they have a role in management of patients with heart failure with or without diabetes.

A review of recent literature has been carried out to establish the most current and up-to-date evidence to ascertain their effectiveness and safety. Dapaglifozin has been chosen as the drug to be reviewed, due to its recent approval from FDA for diabetic and non-diabetic heart failure.

Sources such as pubmed central, google-scholar, research gate and the cochrane library have been consulted from 1998 till 31st August 2020 to study data from randomised control trials of Dapagliflozin and SGLT-2, and its effect on heart failure in individuals with or without diabetes. In particular, we looked for evidence for cardiovascular outcome, and additionally we looked at the renal outcome and drug safety profile.

Dapagliflozin has shown significant benefit in cardiovascular outcome in patients with heart failure, in both with or without diabetes. It has shown a marked reduction in hospitalisation, urgent appointments and cardiac death in patients with heart failure. Furthermore, it has demonstrated a reduction in progression of renal disease.

Dapagliflozin shows efficacy and safety in individuals with heart failure. It has recently been approved by FDA for heart failure, which underlines the potential for the use of other SGLT-2 inhibitors in heart failure management. This may indicate changes in the heart failure guidelines accordingly.

Keywords: Diabetic, Non-Diabetic, Heart Failure



الملخص:

يعرف ناقل الحركة الانتقائي للصوديوم -الجلوكوزمنذ سنوات بأنه فعال في علاج ارتفاع السكري لمرضى السكري، حيث يؤدي الى نقصان في مخزون السكر التراكمي ،الوزن وضغط الدم لدى مرضى السكري.

حديثًا وجد من الواضح انه يلعب دور في علاج مرضى عجز القلب الذين يعانون من مرض السكر والذين لا يعانون منه أيضا.

لقد تم حديثًا مراجعة بعض البحوث لمعرفة وتحديد احدث الأدلة للتأكد من فعالية وسلامة استخدام هذه الادوية. وتم اختيار داباكافلوزن لهذا الامر حيث تمت موافقة منظمة الصحة والغذاء الامريكية وأظهر فعالية في مرضى قصور القلب للمرضى المصابين بالسكري والذين لا يوجد عندهم مرض السكري.

تمت استشارة ومراجعة مصادر مثل بومتك سانترو و غو غل سكولار ومكتبة جوكرين من ١٩٩٨ حتى ٢٠٠٠/٨/٣١ لدر اسة البيانات والتي قد تم جمعها عشوائيا من بعض البحوث والدر اسات العلمية لدواء دابكلوفلوزن و باقي ادية ناقل الحركة الانتقائي للصوديوم و مدى تأثير ها على مرضى القصور القلبي الذين لديهم مرض السكر والذين لا يوجد عندهم هذا المرض.

ولقد تم البحث بصورة خاصة على تأثير هذا الدواء علي الاوعية الدموية والكلى ومدى سلامة استخدامه في الامراض التي تصيب هذه الأجهزة. ولقد الضهر استخدام الدباكلوفلوزن فائدة كبيرة على مرضى القصور القلبي الذين يعانون من مرض السكري والذين لا يعانون منه على حد سواء.

حيث اظهر استخدام الدواء انخفاض ملحوظ في دخول هؤلاء المرضى للمستشفيات إضافة الى انخفاض طلب المواعيد. الطارئة بالإضافة الى تقليل خطر توقف القلب لمرضى القصور القلبي وتقليل خطر القصور الكلوي.

يظهر الدباكلوفلوزن فعالية وقوة وامان في الأشخاص المصابين بعجز القلب حيث تم حديثا الموافقة على استخدام هذا الدواء من قبل منظمة الصحة والغذاء الأمريكية للأشخاص الذين يعانون من العجز القلبي مما يؤكد إمكانية استخدام مثبطات (أل أس ج ل ت ٢-) لأخرى في معالجة أي قصور القلب. هذا قد يغير في إرشادات معالجة مرضي قصور القلب وفقا لذلك.

الكلمات المفتاحية: مرضى السكري، غير مرضى السكري، القصور القلبي.



Introduction

Diabetes is a chronic condition in which the pancreas cannot produce insulin or when there is resistance in the body to make good use of the insulin that is produced. Insulin is a hormone produced by the pancreas which facilitates the transport of glucose in the blood, from the food we eat to be utilised at cellular level as energy source. Hence in the absence of insulin or having insulin resistance causes hyperglycaemia. The long-term consequences of hyperglycaemia include damage to various body organs and tissue (international diabetic federation, 2019).

There are three main types of diabetes – Type 1, Type 2 and others:

- **Type 1 diabetes** is when the body produces very little or no insulin. Type 1 diabetes can develop at any age, but most frequently affects children or adolescents and is managed administering insulin, most commonly via subcutaneous injection (international diabetic federation, 2019).
- **Type 2 diabetes** is when the body develops resistance to the Insulin produced. It is more common in adults, and accounts for around 90% of all diabetes (international diabetic federation,2019). Lifestyle interventions such as weight loss and physical exercise play a key role in the management of type 2 diabetes. The vast majority of patients require oral medication to manage their condition and over time a significant proportion require insulin (international diabetic federation,2019).
- Others
- Gestational diabetes (GDM) consists of hyperglycaemia during pregnancy and is associated with complications in both the mother and baby. GDM usually resolves after pregnancy but women and the children both are at higher risk of developing type 2 diabetes later in life (international diabetic federation, 2019).
- Maturity onset diabetes of young (MODY) is an inherited condition, and results from a single gene mutation in the parent. It is an autosomal dominant condition and hence there is 50% chance of any child of the parent with mutated gene to inherit it. The child with the mutated gene usually develops



MODY before the age of 25 years (Maturity Onset Diabetes of the Young (MODY) Diabetes UK, 2020)

• Latent autoimmune diabetes in adult (LADA) is currently not been classed as a separate form of diabetes. It sorts of sits somewhere in the middle of Type-1 and Type-2 diabetes, hence is sometimes called type-1.5 diabetes. Further research is required to understand how to differentiate LADA from Type 1 and Type 2 diabetes (Latent Autoimmune Diabetes in Adults (LADA) Diabetes UK, 2020).

International Diabetes Federation (IDF) facts and figures have shown the prevalence of diabetes as below in 2019:



Adapted from International Diabetes Federation (IDF) 2019



Literature Review

What are SGLT-2 inhibitors? Their mechanism of action and role in T2DM:

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a fairly new class of oral hypoglycaemic agents (OHA). They have been developed based on the discovery of phlorizin, which is a natural product which inhibits SGLT activity. It was extracted from the bark of the apple tree in 1835, since then with the advancements has caused us to identify SGLTs, and their properties in glucose transport in 1980-1990 (Saisho, 2020).

SGLT-2 inhibitors are absorbed from the gut rapidly and they have a long half-life, hence requiring once daily dose. They are metabolised in the liver through a process of glucuronidation to inactive metabolites. The parent drug has very low excretion though kidneys. Furthermore, it is not known to have clinically significant drug-to- drug interaction (Scheen, 2015).

Human kidney filters 180g of glucose through a glomerular filtration process. SGLT-1 and SGLT-2 are present in proximal tubules, and they absorb almost all the filtered glucose load and ensuing glucose is not excreted in urine. Basolateral sodium/potassium-ATPase causes active extrusion of sodium and glucose uptake by the cell from the tubules against intracellular uphill gradient. Once inside the cell, glucose is transported out of the cell basolaterally via glucose transporter-2 (GLUT2) (Hsia et al., 2017). 90% of filtered glucose is reabsorbed in proximal tubules mainly in segment 1 and 2 by SGLT-2, while the remaining glucose is reabsorbed in proximal tubules segment 3 by SGLT-1. In the event of hyperglycaemia, the glucose reabsorption increases to by 30%, although it is not known if this is due to increased expression of SGLT-2 in diabetic patients. In animal experiments, it has shown that by knocking SGLT-2, the SGLT-1 has compensated and hence increasing its absorption up to 35% of the filtered glucose load (Hsia et al., 2017) (Scheenn, 2015) (Alicic et al., 2019) Figure 1-2.



-10% glu

scending limb of Henle

orption via SGLT1

Sodium-glucose cotransporter 2 (SGLT2)

O Sodium-glucose cotransporter 1 (SGLT1)

P_{sc} = pressure in glomerular capillary

Sodium (Na) Chloride (Cl)

Glucose

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of NaC

Normal nephron B **Diabetic nephron** Α norma ncreased NaCl a glucose filtration increased NaCl and SGLT2 -90% gi via SGLT2 orpt cting tubuk

limb of

Henle

GLUT2

SGLT2



Figure-1 Taken from diabetesjournals.org (Alicic et al., 2019) 13

Capillary

3 Nat

ADP +P 24

ATF

Tubular

lumen

Na*/K*-

ATPase

Tubular epithelial cell

A and B: Glucose reabsorption via SGLT1 and SGLT2 in normal and diabetic kidney. Expressed apically in the epithelium of the proximal convoluted tubule, SGLT2 reabsorbs about 90% of glucose from the urinary filtrate. The remaining 10% is reabsorbed by SGLT1, a high-affinity and low-capacity transporter expressed apically in the epithelium of the straight descending proximal tubule.



Effects of diabetes and SGLT2 inhibition on nephron hemodynamics



Figure-2 Taken from *diabetesjournals.org* (Alicic et al., 2019)

Effects of diabetes and SGLT2 inhibition on nephron hemodynamics. A: Increased reabsorption of glucose by SGLT2 in the proximal convoluted tubule decreases delivery of solutes to the macula densa. The resulting decrease in ATP release from the basolateral membrane of tubular epithelial cells reduces production of adenosine and produces a vasodilatation of the afferent arteriole. B: SGLT2 inhibitors restore solute delivery to the macula densa with resulting adenosine activation and reversal of vasodilation of the afferent arteriole.



Dapagliflozin blocks reabsorption of glucose by inhibition of SGLT-2, as a result, the filtered glucose is not reabsorbed into proximal tubules segment 1 and 2, thus increasing the urinary glucose excretion by approximately 60–80g/day and hence improving hyperglycaemia. This excretion of 60–80g of excess glucose corresponds to the loss of up to 320 kcal from the body which results in weight loss. The weight loss in turn helps to improve obesity and reduce abdominal fat which causes improvement in the insulin resistance and metabolic parameters such as lipid profile, blood pressure and serum uric acid level (Davies et al., 2018) (Figure-3). SGLT-2 inhibitor monotherapy does not increase the risk of hypoglycaemia McGill & Subramanian, 2019).

SGLT-2 like Dapagliflozin are a newer class of medication, and further clinical studies are needed to understand their long-term safety and side effects. The most common problem reported is genital mycotic infection that respond to the standard antifungal treatment. In RCT trials, this adverse effect seldom required to discontinue treatment. The data available for potential risk of UTI in such patients is not clear as some trials have suggested increase in UTIs, while other trials have shown no increased risk compared to the control group. The risk of euglycemic ketoacidosis is low provided that a reasonable intake of carbohydrates and water is maintained (Alicic et al., 2019).



SGLT2 inhibitor Heart failure↓ CV events Arrythmia Renal protection CV mortality↓ Sympathetic nerve EPO1 activation 1 Genital infection/UTI Sodium excretion Urinary glucose excretion↑ Glomerular hyperfiltra Cardiac preload Hypoglycemia + Plasma glucose/HbA1c↓ Energy loss Osmotic diuresis† Glucadon1 Glucotoxicity J Hyperinsulinemia J Visceral fat Body weight Fatty liver↓ Plasma volume Ht↑ Beta cell function↑ Insulin resistance Blood pressure↓ Volume depletion Malnutrition Dehvdration Sarcopenia HDL-C↑ UA↓ TG↓ Acute kidney injury Ketosis Amputation Euglycemic ketoacidosis Fracture

Mechanism of action of SGLT-2 inhibitor

Figure-3- (Saisho, 2020)

SGLT2 inhibitors lower plasma glucose level by increasing urinary glucose excretion. Energy loss by SGLT2 inhibitor treatment promotes weight loss and improves insulin resistance and various metabolic parameters. Possible adverse effects are shown in red. Increased risk of lower-extremity amputation and bone fracture has been reported in a clinical trial with canagliflozin. The cardiorenal benefits shown in CVOTs have revealed additional mechanisms of action of SGLT2 inhibitors that were unknown at the time of launch (highlighted in blue). Osmotic diuresis and natriuresis are likely to be the major mechanisms of the cardiorenal benefits of SGLT2 inhibitors. Increases in blood ketone bodies and hematocrit may also contribute to the cardiorenal benefits. CV; cardiovascular, TG; triacylglycerol, HDL-C; high density lipoprotein cholesterol, UA; uric acid, Ht; hematocrit, UTI; urinary tract infection, EPO; erythropoietin

Beneficial effects of Dapagliflozin in T2DM in general and with Heart Failure

Dapagliflozin is a selective sodium-glucose cotransporter-2 (SGLT-2) inhibitor. It is a very potent inhibitor of SGLT-2 and is reversible in its action (Dhillon, 2019).

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a fairly new class of antidiabetic for the treatment of type 2 diabetes (Hsia et al., 2017) (Wilding et al., 2018).. They act by reducing the reabsorption of glucose in the kidneys and facilitate its excretion in the urine by



inhibiting the high-capacity glucose transporter SGLT2 located in the proximal convoluted tubule, thereby reducing glucose levels independently of insulin action (Dhillon, 2019) (Hsia et al., 2017). Hence Dapagliflozin complements the action when used with other anti-diabetic medication. Dapagliflozin increases the amount of glucose excreted in the urine and hence it improves both fasting and post-prandial plasma glucose levels in patients with type 2 diabetes (Komoroski et al., 2009).

Furthermore, research has shown that Dapagliflozin has reduced the rate of cardiovascular (CV) deaths or hospitalization form heart failure (HHF) and possibly reduced progression of renal disease relative to placebo in patients with established atherosclerotic CV disease (CVD) or multiple risk factors for CVD (Dhillon, 2019).

The DECLARE–TIMI 58 trial was a randomized, double-blind, multinational, placebocontrolled, phase 3 trial of Dapagliflozin in type 2 diabetic patients who had risk factors for atherosclerotic cardiovascular disease or had established cardiovascular disease. Results have shown that Dapagliflozin was non-inferior compared to placebo, in patients type 2 diabetes considering the safety outcome of major adverse cardiovascular events (MACE) i.e. cardiovascular death, myocardial infarction or ischemic stroke. Also, it has also shown that Dapagliflozin has not caused lower rates for those who are at higher risk for MACE compared to placebo. The interesting finding of the trial was that Dapagliflozin has shown lower rate of cardiovascular death or hospitalization for heart failure compared to placebo, and in addition it has shown a possible lower rate of adverse renal outcomes (Wiviott et al., 2019) (Davies et al., 2018)

Therapeutic effect in diabetes and cardiovascular risk factor

Patients with diabetes are at higher risk of developing atherosclerotic cardiovascular disease (Roger et al., 2011) (Donahoe et al., 2007), renal disease and heart failure (Ahmad et al., 2016).



This increased risk of heart failure in patients with diabetes is independent of coronary artery disease. Currently, there is insufficient data to guide treatments for the prevention of heart failure in such patients (Yancy Clyde W. et al., 2017) (2013 ACCF/AHA Guideline for the Management of Heart Failure | Circulation, 2013). Hence it is vital to determine the therapies for diabetes, which in addition to improve glycaemic control, are not only safe but help to reduce the cardiovascular risk (American Diabetes Association, 2018) (8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes, 2018). DECLARE-TIMI 58 was a large trial that evaluated cardiovascular outcomes with the SGLT-2 inhibitor, dapagliflozin. Over 17,000 patients were monitored for a median of 4.2 years including around 10,000 patients without apparent atherosclerotic cardiovascular disease. Prior to this trial, the data on the effects of SGLT-2 inhibitors on this cohort of patients was lacking (Wiviott et al., 2019).On the basis of results from previous trials (American Diabetes Association, 2018) (Ponikowski et al., 2016), current international guidelines for the management of diabetes have focused on the use of SGLT-2 inhibitors in patients with atherosclerotic cardiovascular disease. The results from DECLARE-TIMI 58 trial have shown that dapagliflozin was non-inferior compared to placebo, in patients type 2 diabetes considering the safety outcome of major adverse cardiovascular events (MACE) i.e. cardiovascular death, myocardial infarction or ischemic stroke. Furthermore, it has also shown that dapagliflozin has not resulted in lowering the rates of those who are at higher risk for MACE compared to placebo. As mentioned earlier, the remarkable finding of the trail was that dapagliflozin has shown a lower rate of cardiovascular death or hospitalization for the heart failure compared to placebo (Wiviott et al., 2019) (Davies et al., 2018).

This lower rate of hospitalization and cardiovascular death for heart failure in the dapagliflozin was consistent in multiple groups. Hence dapagliflozin has resulted in preventing cardiovascular events, mainly hospitalisation for heart failure and this is irrespective of a history of atherosclerotic cardiovascular disease or heart failure. Similarly, Dapagliflozin has shown lower rates of progression of renal disease among patients with and without established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease at baseline (Wiviott et al., 2019).



Cardiovascular outcome in non-diabetic heart failure:

As discussed previously, SGLT-2 inhibitors have been shown to reduce the risk of cardiovascular events mainly by decreasing the risk of development or progression of heart failure and hence causing reduction in hospitalisation for heart failure (Wiviott et al., 2019). These results were observed very early after randomization, creating scope for further trials to understand the mechanism of action of dapagliflozin, which is different from the glucose lowering effect(Schnell et al., 2020).

The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial is a prospective study to assess the efficacy and safety of the SGLT2 inhibitor, dapagliflozin, in patients with heart failure and a reduced ejection fraction (HFrEF). The study included 4,744 patients with HFrEF who were investigated for the effect of dapagliflozin (10mg daily) for a median of 1.52 years. This included patients with diabetes mellitus diagnosis (41.8%), and without diabetes mellitus diagnosis (58.2%). Patients who were included had an ejection fraction of \leq 40% and New York Heart Association (NYHA) class II, III, or IV symptoms (Kosiborod Mikhail N. et al., 2020).

The primary outcome that was monitored was composite worsening of heart failure or death from cardiovascular causes as well as unplanned hospitalisation or visit regarding urgent heart failure therapy. The trial showed an improvement in the 55% of patients who did not have diagnosis of type 2 diabetes compared to those who have diagnosis of diabetes. It has been observed in all pre-specified sub-groups that the primary outcome risk was reduced. Hence, patients with HFrEF who received dapagliflozin had reduced risk of worsening of heart failure or death from cardiovascular cause, and have shown improvement in symptoms compared to the placebo group (Kosiborod Mikhail N. et al., 2020).

In an analysis of DAPA-HF trial, patients were examined with the effects of dapagliflozin in HFrEF patient measuring symptoms control, physical function and quality of life using Kansas City Cardiomyopathy Questionnaire (KCCQ), which has indicated that patients did



indeed experience improvement in their health status, whether small, moderate or large (Kosiborod Mikhail N. et al., 2020).

It is hypothesised that the cardiovascular effect of dapagliflozin is due to a mechanism of action other than the effect to improve hyperglycaemia. In addition to the diuretic effect, it has been proposed that there may be changes which affect myocardial metabolism, fibrosis, ion transport, adipokines and vascular function (Alicic et al., 2019) (Verma & McMurray, 2018) (McMurray et al., 2019).

DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in patients with HF with Reduced Ejection Fraction) is a double blinded, randomized and placebo-controlled trial, investigating the effects of dapagliflozin in HFrEF patients with left ventricular ejection fraction (\leq 40%). Dapagliflozin has demonstrated a safety profile as observed in the previous studies. It was well tolerated, and only a minimal number of patients have stopped medication due to any adverse effects. This was the first rigorous study which has shown the effect of drug tolerance in patients with HFrEF without diabetes. The results have shown that use of dapagliflozin over 12 weeks has resulted in significant improvement in patients' experience of heart failure symptoms with or without diabetes. However, it did not affect the mean NT-proBNP (Nassif Michael E. et al., 2019).

Discussion

The purpose of the literature review was to study the recent evidence of SGLT-2 in view of their effect on patients with heart failure with or without diagnosis of diabetes. Dapagliflozin



(SGLT-2) has shown significant reduction in cardiovascular related deaths and hospitalisation in patients with heart failure with diabetes, despite the fact that their effect on long-term glycaemic control is modest. Furthermore, a significant decline is observed in a similar group of patients in end-stage renal disease. In diabetic patient treatment with SGLT-2 like dapagliflozin, causes a 1% reduction in HBA1C with added benefit of arterial blood pressure and weight (Anderson, 2014).

The trial carried out for the effect of Dapagliflozin in diabetic patients have raised the possibility of a mechanism of action other than their glucose lowering effect, to be responsible for the cardiac and renal outcomes in patients with and without diabetes. These multiple non-glycaemic benefits of dapagliflozin have made it favourable in the treatment of diabetic patients with heart failure. As the results were seen quite early in the randomisation, thus the question was raised about dapagliflozin being beneficial in heart failure without diabetes. In view of the strength of evidence gained in the DECLARE-TIMI 58 trial, dapagliflozin has gained approval from FDA in 2019 for patients with type 2 diabetes and multiple cardiovascular risk factors, or established cardiac disease (American College of Cardiology, 2019).

Patients with diabetes are twice as likely to develop chronic kidney disease and are six times more likely to develop end stage kidney disease. In the DECLARE-TIMI 58 trial, dapagliflozin has shown significant reduction in progressive renal failure and renal death (AJMC, 2019).

In a double blinded, randomised, placebo-controlled trial carried out on patients with HFrEF without diabetes has later shown significant improvement with dapagliflozin. There was significant reduction in urgent visits related to heart failure, hospitalisation for heart failure and cardiovascular deaths compared to the control group. The exact mechanism of action by which dapagliflozin improves the cardiovascular outcome in HFrEF is not yet known. It is hypothesised that it is multifactorial as a result of diuretic effect and by influencing myocardial metabolism, fibrosis, ion transport, adipokines and vascular function.



To establish the exact mechanism of action by which the improvement in cadiovacular outcome in HFrEF is achieved would need further studies. Accepting the results from clinical trials, FDA has recently approved dapagliflozin for heart failure with reduced ejection fraction (HFrEF) in adults with and without type 2 diabetes (T2D). As such, for the first time, a medication which was approved for diabetes was approved for heart failure even in the absence of diabetes (AJMC, 2020).

The most commonly reported adverse effects of dapagliflozin are mycotic genital infections both in men and women, which were twice as often in women than men. Most infections are of a mild nature, and respond to usual antifungal treatment. Other common adverse effects reported are volume depletion, UTIs, hypoglycemia (if given with insulin or insulin secretogogue). Less common side effects are acute kidney injury, diabetic ketoacidosis, bladder cancer, lower limb amputation, bone fracture and Fournier's gangrene (Alicic et al., 2019). We have not discussed the adverse effects in detail here as this is not within the scope of this review.



Adverse Effects of SGLT-2 Inhibitor



Figure-2 (McGill & Subramanian, 2019) Summary of adverse events potentially associated with sodium-glucose co-transporter 2 inhibitors



Conclusion

Dapagliflozin is a well known SGLT-2 that has been successfully used in the management of diabetes type 2 for many years. It has a fairly established safety profile and has minimal side effects. There is strong evidence suggesting an improvement in cardiovascular outcome in patients with heart failure in patients with diabetes. Last year, it was approved by FDA for management of heart failure in type 2 diabetes with cardiovascular risk factors or established atherosclerotic cardiovascular disease.

With the recent FDA approval, dapagliflozin now holds a very strong position in the management of heart failure (HFrEF), particularly in view of the evidence from the trial suggesting reduction in heart failure related death, urgent visits and hospitalisation with or without diabetes. This has created an opportunity to explore the potential of other SGLT-2 in the treatment of heart failure. In addition, trials have also shown a strong association with protection from a serious decline in renal function.

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