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**LEARNING OBJECTIVES**

- After reading this issue of **Perspectives in Hypertension<sup>SM</sup>**, participants should be able to:
- Examine the potential for cardiovascular events in diabetic patients with hypertension
  - Initiate and maintain appropriate antihypertensive therapy to prevent disease progression in at-risk patients
  - Describe the dangers associated with untreated and under-treated hypertension across the circulatory, endocrine, and renal systems
  - Select effective strategies to prevent ESRD in patients with hypertension, diabetes, and kidney disease

Intended audience: primary care physicians, cardiologists, endocrinologists

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**DISCLOSURES**

Senior Managing Editor Genevieve Romano has no significant financial interests or affiliations to disclose.

Theodore G. Ganiats, MD, peer-reviewed the case report beginning on this page. He has no significant financial interests or affiliations to disclose.

**C A S E R E P O R T**

## Case of 62-Year-Old Hypertensive Man With Uncontrolled Diabetes

**PRESENTATION**

**C**harlie B. is a 62-year-old caucasian male with a past medical history of high normal blood pressure and borderline dyslipidemia, which are being treated with lifestyle modification (diet and exercise).



Several months earlier, he was given metformin\* to control impaired fasting glucose. His chief current complaint is excessive daytime tiredness. Additionally, he complains of frequent

urination and insatiable hunger. He reports poor sleep in recent weeks, with interruptions for urination and a lack of "deep" sleeping overall. On further questioning, he describes swollen feet in the morning. Patient asks to be given a drug for erectile dysfunction due to his "performance issues," and when pressed describes an inability to achieve an erection for extended periods of time.

Patient does not report any chest pain or shortness of breath, but does become winded during normal conversation. Despite his primary care physician's recommendation of hourly exercise three times a week, he has not done so; nor has he followed the DASH<sup>†</sup> diet given to him. The patient details a diet high in saturated fats and low in vegetables and grains.

**MEDICATIONS:**

Metformin\* 1,000 mg twice daily

**DRUGS AND ALCOHOL USE:**

Seldom drinks, nonsmoker, no illegal drug use.

**FAMILY HISTORY:**

Grandfather died from diabetes. Parents deceased, mother died at age 85 (cancer), father died at age 75 (heart attack). No siblings, one adult daughter in good health.

**SOCIAL HISTORY:**

Works full time as an executive in the aerospace industry. Lives with his wife of 29 years.

**GENERAL:**

Overweight male in no apparent distress.  
**Height:** 70 in  
**Weight:** 203 lbs  
**BMI:** 29.1 kg/m<sup>2</sup>  
**Waist circumference:** 46 in

**VITAL SIGNS:**

**BP:** 138/88 mm Hg  
**HR:** 70 bpm  
**Respiratory rate:** 18/min  
**HEENT:** Pupils equal, round, reactive to light. Extraocular movements intact.  
**Oral and nasal mucosa:** Pink and moist. No ulcers or lesions noted.  
**Neck:** Supple, no adenopathy, no thyromegaly, trachea is midline.  
**Chest:** Bilaterally symmetrical, respiratory excursions bilaterally equal.  
**Lungs:** Clear to auscultation, no crackles or wheezes. Normal to percussion or palpation.  
**CVS:** Regular rate and rhythm, S1 Sw normal, no S3, S4 or murmur. PMI within normal limits.

\*Not FDA-approved for this usage.

<sup>†</sup> Dietary Approaches to Stop Hypertension

## PERSPECTIVES in HYPERTENSION<sup>SM</sup>



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## C A S E R E P O R T

### Case of 62-Year-Old Man With Diabetic Complications of Hypertension

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**Abdomen:** Benign, obese, nontender, no distention, bowel sounds heard, no organomegaly.

**Extremities:** Mild pedal edema. Peripheral pulses normal. No bruits.

**CNS:** Alert and oriented x 3. Cranial nerves II through XII are grossly intact. No focal neurological deficits.

**Reflexes:** Normal deep tendon reflexes present in all limbs.

#### LAB RESULTS:

**TG:** 294 mg/dL

**TC:** 233 mg/dL

**LDL-C:** 146 mg/dL

**HDL-C:** 28 mg/dL

**FPG:** 165 mg/dL

**HbA<sub>1c</sub>:** 8%

**Microalbumin:** 105 mg/g Cr

**Creatinine:** 1.4 mg/dL

**K<sup>+</sup>:** 4.2 mEq/L

**eGFR:** 55 mL/min/1.73 m<sup>2</sup>

#### SYMPTOMS AND ADDITIONAL DIAGNOSTIC TESTS:

1. Charlie B. clearly has uncontrolled diabetes. Which of the following do you recommend? (Choose one or more.)

- A. Dilated eye examination for diabetic retinopathy
- B. Evaluation of urine microalbumin
- C. Evaluation for diabetic neuropathy
- D. Thyroid-stimulating hormone
- E. Electrocardiogram

2. Could the patient's current onset/worsening of diabetes have been prevented using any of the following? (Choose one or more.)

- A. More effective adherence to a diet and exercise regimen
- B. Earlier use of antihypertensive therapy
- C. Aggressive control of lipids
- D. Use of a thiazolidinedione while still at high-normal fasting glucose

3. What should be the main priorities for risk factor reduction?

- A. Better control of blood pressure
- B. Better control of dyslipidemia
- C. Better control of hyperglycemia with a targeted reduction in HbA<sub>1c</sub>

4. Which change(s) in treatment would you make?

- A. A renewed approach to lifestyle modification
- B. Increase metformin to the maximum dose
- C. The addition of sulfonylurea to metformin
- D. Replace metformin with a thiazolidinedione
- E. Begin treatment with an antihypertensive agent

#### REFERENCES FOR ANSWERS ON PAGE 6

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# ADA Takes Close Look at Renoprotection

**T**he 65th convocation of the American Diabetes Association (ADA) took place this June with more than 18,000 physicians in attendance at the San Diego Convention Center. Among the scientific data presented in insulin resistance, genetics, and other areas, were a number of studies looking at diabetic nephropathy and renoprotection. Kidney disease, one of the most common and deadly complications of diabetes, is more prevalent in those patients with hypertension. Continuing study into the renal benefits of antihypertensive therapies that block or inhibit angiotensin is highlighted below in selected presentations from this year's ADA meeting. Other issues from the conference dealt with optimizing care in high-risk groups and avoiding clinical pitfalls in assessing kidney functionality.

## Losartan Improves Proteinuria Independent of BP in Type 2 Diabetes

Angiotensin II receptor blockers (ARBs) have shown renoprotective effects in patients with type 2 diabetes, but it is not known if proteinuria reduction is a result of the ARB directly or if it is a byproduct of lowered blood pressure. In a small Japanese study, investigators looked at whether low-dose losartan therapy could impact diabetic nephropathy without affecting blood pressure. Thirty-four patients were divided into losartan and control groups. Patients were selected based on age ( $\leq 65$  years),  $HbA_{1c} < 8\%$ , serum creatinine  $< 2$  mg/dL, urinary protein dipsticks (-)~(+), negative history of antihypertensive/antiplatelet agents, and home systolic blood pressure (to avoid "white coat syndrome") at waking and bedtime of  $\geq 125$  mm Hg. Treatment group was given 25 mg of losartan once daily for one year. Rising and bedtime home blood pressure (HBP) was followed, with the total HBP calculated as the mean between the two values. In addition, body mass index (BMI),  $HbA_{1c}$ , fasting plasma glucose, total cholesterol, triglyceride level, and ambulatory urinary albumin/creatinine ratio (UACR) were measured.

At follow-up, UACR was significantly lower in losartan group ( $-23.8 \pm 13.7$ ) than in the control ( $15.9 \pm 13.2$ ); mean  $\pm$  SEM,  $P=0.0114$ . UACR also increased in the control with patients who had normoalbuminuria ( $P=0.008$ ) and decreased in the losartan group in patients with microalbuminuria ( $P=0.031$ ). No other statistically significant changes were observed. The findings suggest that low-dose losartan does have a direct effect on kidney function independent of blood pressure effect in type 2 diabetes.

Sawaki H, Terasaki J, Nakagawa S, et al. Low dose losartan has a direct renoprotective effect without lowering blood pressure in patients with type 2 diabetes. *Diabetes*. 2005;54(suppl 1):A547. Abstract 2273-PO.

## Community-Based Clinic Reports Promising Results in High-Risk Population

The growing body of medical literature on preventing renal and cardiovascular outcomes in type 2 diabetes points to a polytherapeutic approach that includes blood pressure, lipid, and glucose control. Statistics show, however, that many patients with diabetes at high risk for renal disease or cardiovascular disease (CVD) are not receiving optimal treatment. A study was conducted on referred patients at five community-based diabetic

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**Table 1. Patients Referred by PCPs to Five Community-Based Diabetic Nephropathy Prevention Clinics**

Measure	Mean	Mean $\pm$ SD
Age	58 y	13 y
Sex	60% male	—
BMI	35.0 kg/m <sup>2</sup>	16.2 kg/m <sup>2</sup>
Type 2 Diabetes	89%	—
Hypertension History	73%	—
CVD History	80%	—
Microalbuminuria	45%	—
Macroalbuminuria	21%	—
HbA <sub>1c</sub>	8.2%	1.99%
Blood Pressure	131/75 mm Hg	18/11 mm Hg
Total Cholesterol	195 mg/dL	55 mg/dL
LDL-C	108 mg/dL	36 mg/dL
HDL-C	43 mg/dL	11 mg/dL
Triglyceride	324 mg/dL	849 mg/dL
s-Cr	1.16 mg/dL	0.41 mg/dL
Albumin:Creatinine Ratio	5.8 mg/mmol	—
Total Hypertension R <sub>x</sub>	2.4	1.1
ACEI/ARB	86%	—
Statin	53%	—
Aspirin	58%	—
Insulin	31%	—
Smoker	20%	—

## ADA Takes Close Look at Renoprotection

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nephropathy prevention clinics to analyze what therapies they had been receiving from their PCPs (Table 1). Investigators looked at glycemia, blood pressure, and lipids in diabetic patients with either micro- or macroalbuminuria (creatinine <2.26 mg/dL).

The authors stated that the use of multiple agents, including angiotensin-converting enzyme (ACE) inhibitors and ARBs in high-risk patients with diabetes, was higher than anticipated in the primary care setting; however, there may have been a referral bias due to the high motivation of nonsmokers. In addition, lipid control, glycemia, BMI, and statin use were all suboptimal, suggesting that polypharmacy may not have been adequately implemented by PCPs in patients with diabetes who were at high risk for renal disease and cardiovascular events.

Senior PA, Macnair L, Wong T, Jindal K. High rates of ACE-I/ARB use and good blood pressure control in patients referred to community-based diabetic nephropathy prevention clinic. *Diabetes*. 2005;54(suppl 1):A548. Abstract 2278-PO.

### Study Underscores the Fallibility of Serum Creatinine Testing

Patients with diabetes are at increased risk for developing chronic kidney disease (CKD), which left uncontrolled could progress to end-stage renal disease. In addition, renal decline itself is now being considered an independent risk factor for cardiovascular events. Serum creatinine (s-Cr) >150 $\mu$ mol/L has previously been regarded in the clinical setting as the platform at which referral to a nephrologist became protocol; however, recent data suggest s-Cr is not a reliable indicator of kidney function due to its insensitivity and may allow CKD to go unchecked. The modification of diet in renal disease (MDRD) equation has been presented as a more accurate marker of kidney function, used by the National Kidney Foundation (NKF) as the formula for its guidelines. According to the NKF, an estimated glomerular filtration rate (eGFR) 59-30mls/min/m<sup>2</sup> qualifies a patient as having moderate CKD and requiring referral to a nephrologist; an eGFR<30mls/min/m<sup>2</sup> is classified as severe, with kidney replacement as the recommended course.

A study looked at the reliability of these two assessment methods to evaluate kidney function. A total of 288 patients with diabetes were evaluated in a diabetes clinic over a one-month period. Mean age was 59 years, with mean duration of diabetes 12 years. The use of statins, antihypertensives, antiplatelets, anemia, and nephrology visits were recorded.

Of those patients with an eGFR<30mls/min/m<sup>2</sup> (n=11), none had s-Cr<150 $\mu$ mol/L; of those with an eGFR 59-30mls/min/m<sup>2</sup> (n=95), 80 had s-Cr<150 $\mu$ mol/L and 48 had s-Cr<120 $\mu$ mol/L. The authors concluded that s-Cr is an inaccurate measure of kidney function and underestimates the prevalence of CKD. Since this will likely result in fewer nephrology referrals overall, patients whose s-Cr is tested over eGFR to determine the presence of CKD will more often experience adverse outcomes.

Jones CJ, Hughes K, Tan R, Small M, Jones GC. Evaluation of kidney function using estimated glomerular filtration rate: improved detection and treatment of significant chronic kidney disease. *Diabetes*. 2005;54(suppl 1):A550. Abstract 2285-PO.

## Protective Effects of ARB Therapy Shown in Diabetes Risk Populations

Final results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial showed benefit with the angiotensin receptor blocker (ARB) valsartan in preventing the onset of type 2 diabetes in patients at high risk compared to the calcium channel blocker amlodipine. A total of 9,995 VALUE patients who were not diabetic at baseline were followed for an average of 4.2 years and diabetes onset was recorded. Using adverse event reports, new antidiabetic medications, and/or fasting glucose >126 mg/dL, diabetes onset in the valsartan group was 580 (11.5%) vs 718 (14.5%) in the amlodipine group ( $P<0.0001$ ). Stricter criteria showed similar results in proportion.

Patients were stratified for risk of diabetes, and those in the highest tertile were more than six times more likely to develop diabetes than those in the lowest. Valsartan's protective effect increased greatly in the medium ( $P=0.0058$ ) and highest ( $P=0.0007$ ) risk tertiles. The authors concluded that in diabetes prevention, valsartan is superior to amlodipine in high-risk hypertensive patients.

Kjeldsen SE, Julius S, Hua T, Weber MA, for the VALUE Trial Investigators. Effects of valsartan preventing the development of type 2 diabetes in high risk hypertensive patients: analysis from the VALUE trial. American Society of Hypertension Annual Meeting 2005. Late Breaking Clinical Trial #2.

## Hypertension Significantly Reduces Life Expectancy

Hypertension is responsible for a significant proportion of cerebrovascular events and coronary heart disease. Yet, it is a modifiable risk factor and numerous studies have shown that the control of blood pressure (BP) can lead to reductions in cardiovascular disease (CVD) and mortality. Although the effect of hypertension on life expectancy (LE) may be intuitive, few studies have directly addressed this question.

With the objective of determining the impact of increased BP levels at age 50 on total LE and LE with and without CVD, researchers used mortality and 46 years of CVD follow-up data from 3,128 participants of the Framingham Heart Study to construct multistate life tables. The investigators showed that inadequate control of blood pressure in both men and women significantly reduced LE and increased the number of LE with CVD. Overall, data from the study indicate that LE was decreased by 5.1 years (men) and 4.9 years (women) for hypertensive participants. Normotensive participants, regardless of gender, survived >7 years longer without CVD and spent >2 fewer years of life with CVD when compared to hypertensive individuals.

The findings of this study emphasize the importance of adequate blood pressure as a means of prolonging LE directly and indirectly via reduction of hypertension-associated comorbidities.

Franco OH, Peeters A, Bonneux L, de Laet C. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women. Life course analysis. *Hypertension*. 2005;46:1-7.

**U P C O M I N G M E E T I N G S**

As a healthcare professional, you know the rising prevalence of hypertension has reached epidemic proportions in the United States as well as other Western nations. The incidence of myocardial infarction (MI), heart failure (HF), and left ventricular hypertrophy (LVH) also continues to rise despite advances in therapies to lower lipids and blood pressure. These conditions are separately linked not only with chronic cardiovascular disease and other maladies, but with early death as well. The comorbidity, then, of hypertension and these conditions is a strong predictor of a devastating disease-state, signifying an urgent situation for the overall medical community. With its interactive format and faculty of nationally recognized experts, these CME-certified activities are designed to help you overcome these challenges in your practice.

**There is no registration fee for these seminars. However, because of space limitations, we urge you to register in advance.**

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<b>AGENDA</b>	
6:30 – 7:00 PM	<b>Registration</b>
7:00 – 7:05	<b>Opening Remarks</b>
7:05 – 7:50	<b>Didactic Presentation/Q&amp;A</b>
7:50 – 8:35	<b>Case Study/Q&amp;A</b>
8:35 – 8:50	<b>Q&amp;A/Panel Discussion</b>
8:50 – 9:00	<b>Closing Remarks</b>

  

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<b>9/14/05</b> The Westin Princeton at Forrestal Village 201 Village Boulevard Princeton, NJ 08540 <b>Michael A. Weber, MD</b>	<b>9/28/05</b> Hyatt Regency Indianapolis One South Capitol Avenue Indianapolis, IN 46204 <b>Steven M. Haffner, MD</b>
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<b>SATURDAY SEMINARS</b>	
<b>AGENDA</b>	
7:45 – 8:30 AM	<b>Registration</b>
8:30 – 8:40	<b>Opening Remarks</b>
8:40 – 9:35	<b>Didactic Presentation/Q&amp;A</b>
9:35 – 10:30	<b>Case Study 1/Q&amp;A</b>
10:30 – 10:40	<b>Break</b>
10:40 – 11:35	<b>Case Study 2/Q&amp;A</b>
11:35 – 12:30 PM	<b>Case Study 3/Q&amp;A</b>
12:30 – 12:40	<b>Panel Discussion</b>
12:40 – 12:45	<b>Closing Remarks</b>

  

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## CASE REPORT ANSWERS

**1. Charlie B. clearly has uncontrolled diabetes. Which of the following do you recommend? (Choose one or more.)**

**A. Dilated eye examination for diabetic retinopathy**

CORRECT: Current American Diabetes Association (ADA) guidelines recommend an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after diagnosis of type 2 diabetes.<sup>1</sup> One of the main motivations for screening for diabetic retinopathy is the established efficacy of laser photocoagulation surgery in the prevention of visual loss.

**B. Evaluation of urine microalbumin**

INCORRECT: ADA guidelines recommend an annual test for the presence of microalbuminuria in diagnosis starting at diagnosis.<sup>1</sup> However, patient has received this test 6 months prior. The rationale for regular testing is the proven efficacy of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) at delaying the progression to macroalbuminuria.<sup>2,3</sup>

**C. Evaluation for diabetic neuropathy**

INCORRECT: Diabetic neuropathy in type 2 diabetes is related to duration of hyperglycemia and would be unlikely in a patient with diabetes of recent onset. The most effective prevention of diabetic neuropathy is good glycemic control. Although erectile dysfunction as experienced by the patient may be a manifestation of autonomic neuropathy, there are many other possible causes. The evaluation of erectile dysfunction includes a sexual history, genital examination, testing for serum testosterone level and prolactin and thyrotropin levels.

**D. Thyroid-stimulating hormone**

INCORRECT: Measurement of thyroid-stimulating hormone is not indicated in type 2 diabetes

**E. Electrocardiogram**

INCORRECT: There are no cardiac signs or symptoms that would justify performing an electrocardiogram on this patient.

**2. Could the patient's current onset/worsening of diabetes have been prevented using any of the following? (Choose one or more.)**

**A. More effective adherence to a diet and exercise regimen**

CORRECT: The Diabetes Prevention Program demonstrated a 58% reduction in diabetes onset with lifestyle modification versus a control group for patients who had been randomized to intensive nutritional and exercise counseling.<sup>4</sup> Similar results have been obtained in a Finnish study.<sup>5</sup>

**B. Earlier use of antihypertensive therapy**

CORRECT: Although reduction in blood pressure does not in itself reduce the risk of diabetes onset, the ARBs and ACE inhibitors used in the treatment of hypertension appear to reduce the onset of new diabetes. For example, the ALLHAT study showed a 43.2% lower onset of new diabetes with lisinopril compared with chlorthalidone.<sup>6</sup> Further randomized trials are investigating diabetes prevention as a primary endpoint with the use of ARBs and ACE inhibitors.

**C. Aggressive control of lipids**

INCORRECT: Although many patients at risk of developing diabetes will require treatment of dyslipidemia as well, there is no evidence that such treatment can prevent type 2 diabetes.

**D. Use of a thiazolidinedione while still at high-normal fasting glucose**

CORRECT: Several studies have demonstrated that the use of an insulin sensitizer in patients with impaired fasting glucose or impaired glucose tolerance will delay progression to type 2 diabetes.

**3. What should be the main priorities for risk factor reduction?**

**A. Better control of blood pressure**

CORRECT: According to the JNC-7 guidelines, intervention to control blood pressure is recommended for patients with diabetes who have blood pressure >130/80 mm Hg.<sup>7</sup> Based on evidence that ACE inhibitors and ARBs delay progression of microalbuminuria to macroalbuminuria in patients with diabetes and hypertension, the ADA recommends that a drug in one or other of these classes should be selected (unless contraindicated).

**B. Better control of dyslipidemia**

CORRECT: The standard goal for low-density lipoprotein cholesterol (LDL-C) is 130 mg/dL; however, for certain high-risk patients as those with coronary heart disease or diabetes, a lower goal of 100 mg/dL is recommended. In addition, the reduction should be 30%-40% regardless of baseline LDL-C.<sup>1</sup> Charlie B. also has an elevated triglyceride level and low high-density lipoprotein cholesterol (HDL-C); current ADA guidelines recommend lowering triglycerides to <150 mg/dL and raising HDL-C to >40 mg/dL.<sup>1</sup> Although dietary changes may lead to some improvement, combination therapy with statins and fibrates or niacin may be necessary to achieve all lipid targets.

**C. Better control of hyperglycemia with a targeted reduction in HbA<sub>1c</sub>**

CORRECT: Charlie B. has symptomatic diabetes, a diagnosis that is confirmed by his 160 mg/dL fasting plasma glucose (FPG). His current metformin regimen needs to be changed, as the prevention strategy proved unsuccessful. In addition, his diet and sedentary lifestyle need to be addressed.

**4. Which change(s) in treatment would you make?**

**A. A renewed approach to lifestyle modification**

CORRECT: The patient has had little success to date to adhering to guidelines on diet and exercise. Referral for diabetes self-management education is desirable at this point.<sup>1</sup> Appropriate changes to diet and physical activity are an important part of diabetes control as well as in the management of dyslipidemia and hypertension.

**B. Increase metformin to the maximum dose**

INCORRECT: Metformin is contraindicated in patients with renal dysfunction (serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females]).<sup>8</sup> Since the patient is close to this threshold, an escalation in metformin dose may be inadvisable.

**C. The addition of sulfonylurea to metformin**

INCORRECT: see previous explanation.

**D. Replace metformin with a thiazolidinedione**

CORRECT: Both pioglitazone and rosiglitazone increase insulin sensitivity, thereby bringing about a reduction in serum glucose. However, pioglitazone\* appears to have much more favorable effects for dyslipidemic patients; in a recent study, it reduced triglycerides and increased HDL-C.<sup>9</sup>

**E. Begin treatment with an antihypertensive agent**

CORRECT: It is sometimes possible to control mild hypertension by using changes in diet and exercise without any need for pharmacological intervention. However, agents that affect the renin-angiotensin system have additional benefits as they slow the decline in renal function.<sup>1</sup> This is an important consideration for the patient who is bordering on renal insufficiency. Therefore, starting therapy with either an ACE inhibitor or an ARB is a viable option.

**\*Not FDA-approved for this usage.**

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