Hypertension Grand Rounds

Treatment of Cardiovascular and Renal Risk Factors in the Diabetic Hypertensive

James R. Sowers, Steven Haffner

Case
A 38-year-old black woman is seen on referral from a family physician. Her medical records indicate that she has had type 2 diabetes diagnosed 3 years previously. She has been treated for her diabetes with diet and a sulfonylurea, Glucotrol X-L, 10 mg daily. Her last glycohemoglobin 6 months ago was 8.8%. She has had hypertension for ≈10 years and is currently receiving 10 mg amiodipine daily, 25 mg hydrochlorothiazide daily, and 4 mg doxazosin every morning. In her records, her physician notes that her blood pressure (BP) has been relatively well controlled, with BPs generally ≈150/90 mm Hg. She had an EKG 1 year previously, which was remarkable only for left ventricular hypertrophy (LVH) by voltage criteria. Her last total cholesterol was 230 mg/dL with LDL cholesterol of 145 mg/dL. Her records indicated that she was not started on lipid therapy because her LDL was <150 mg/dL. She has a strong family history of diabetes, hypertension, coronary artery disease, stroke, and kidney disease requiring dialysis.

Physical Examination
The patient’s BP was 154/92 mm Hg, with a pulse of 88 bpm. Her weight was 190 lbs (body mass index, 35 kg/m²). Examination of the head, ears, eyes, nose, and throat (HEENT) revealed fundi with background retinopathy (hemorrhages and exudates). Examination of the heart showed that the point of maximum impulse (PMI) was shifted to the anterior auxiliary line and sustained, with an S4 gallop present. Examination of the patient’s abdomen revealed a waist circumference of 38 inches, a slightly enlarged liver, and no abdominal bruits. Examination of the patient's lower extremities showed that the dorsalis pedis and posterior tibial pulses were noticeably decreased in amplitude, and 2+ pretilial pitting edema was present.

Laboratory Values
Laboratory values were as follows: fasting glucose, 140 mg/dL; glycosylated hemoglobin [HbA1c], 8.5%; creatinine, 2.0 mg/dL; urinal albumin, 0.8 mg/dL; total cholesterol, 250 mg/dL (HDL cholesterol, 35 mg/dL; LDL cholesterol, 165 mg/dL; and triglycerides [TGs], 250 mg/dL), and electrolytes serum potassium, 4.7 mmol/L. The EKG showed LVH by voltage criteria.

Discussion
This woman with diabetes, hypertension, LVH, and diabetic nephropathy has a risk for death from myocardial infarction (MI) or stroke that is at least as high as that for persons without diabetes who have already suffered from a MI or stroke1–4 (Figure 1). In addition, the case fatality rate after a MI among patients with diabetes is higher than that for patients without diabetes.4 The risk of atherothrombotic stroke is 2 to 3 times higher in patients with diabetes.3,5,6 Stroke patients with diabetes have a higher death rate and a poorer neurological outcome, with more severe disability.6 There is an increased incidence of congestive heart failure in diabetic persons irrespective of coronary artery disease and hypertension.3,6–8 In the studies of Left Ventricular Dysfunction (SOLVD) Trials, diabetes was found to be an independent risk factor for mortality and morbidity in both symptomatic and asymptomatic heart failure.7 Patients with diabetes, particularly women, have more pronounced heart failure symptoms, use more diuretics, and have a worse prognosis than those without diabetes.8 Diabetes is now the most common cause of end-stage renal disease in the United States.9 Diabetic glomerulopathy is characterized by albuminuria, which is associated with increased coronary artery disease10 and stroke,11,12 as well as renal disease progression.3,11

This patient should be treated more aggressively to control her glycaemia (HbA1c <7%), her LDL cholesterol should be lowered to <100 mg/dL with a statin, and she should have her BP treated to <130/80 mm Hg with a regimen that includes an ACE inhibitor/angiotensin receptor blocker (ARB),1,9,13 as well as diet and exercise14–16 (Figure 2).

In patients with type 2 diabetes, conventional cardiovascular disease (CVD) risk factors are amplified.1,2,17–21 For example, the Multiple Risk Factor Intervention Trial (MRFIT) evaluated the impact of blood cholesterol levels on CVD risk in diabetic and nondiabetic individuals.17 In MRFIT, the higher the cholesterol level, the greater the risk of coronary heart disease (CHD). At any given cholesterol level, the risk was 3- to 4-fold higher in the diabetic patients. In the United Kingdom Prospective Diabetes Study (UKPDS), the major risk factors for CVD in type 2 diabetes were hyperglycemia, hypertension, increased LDL cholesterol, low levels of HDL, and smoking.12,19 Similar CVD risk factors were also observed in a 10-year follow-up of the Prospective Cardiovascular Munster (PROCAM) Study.20,21 Each of these risk factors will be discussed in relation to CVD risk in our diabetic patient and in type 2 diabetes as a whole.
An integral component of management of this patient is the institution of lifestyle changes. A body mass index of 35 kg/m² places this patient in the obesity categorization. Lifestyle changes emphasizing diet and exercise have been shown to prevent the development of type 2 diabetes in persons with impaired glucose tolerance. In addition to improving glycemic control, a diet that is high in fiber and potassium and lower in saturated fats, refined carbohydrates, and salt can improve the lipid profile and significantly lower BP. Clinical trial evidence that rigorous treatment of glycemia, hypertension, and dyslipidemia reduces CVD risk in type 2 diabetes will be addressed.

Hyperglycemia as a CVD Risk Factor and Treatment Benefits

The patient reviewed in this Grand Rounds is at very high risk for all of the cardiovascular complications of diabetes. Better control of glucose, preferably maintaining the HbA1c at <7%, would be expected to reduce the burden of macrovascular (Table 1) and microvascular (Table 2) disease. Metformin cannot be used because of the reduced renal function. Thus, better control of this patient’s glycemia will likely require insulin therapy, possibly along with a thiazolidinedione insulin sensitizer (Table 2). However, use of these medications may compound the overweight problem and exacerbate the edema associated with use of the dihydropyridine calcium channel blocker. Thus, weight reduction and exercise are also important strategies to minimize the requirements for insulin and thiazolidinedione therapy.

Large prospective epidemiologic studies (summarized in Table 1) have shown that in patients with diabetes, the higher the glucose, the greater the incidence of CVD. Collectively, these studies suggest that the risk of a CVD event rises 10% to 30% for every 1% increase in HbA1c. Several studies have shown a trend in reduction of CVD events and significant microvascular disease reduction in type 2 patients with improved glycemic control. The Honolulu Heart Program study showed during 23 years of follow-up that baseline glucose tolerance test results predicted which patients would eventually develop CHD. Persons in this cohort who were not symptomatic but had postload blood glucose levels of ≥224 mg/dL were much more likely to develop CHD, and had twice the risk of CVD death compared with persons with low normal (<150 mg/dL) glucose levels. These findings are consistent with the notion that 50% of newly diagnosed patients with type 2 diabetes have CHD.

A study of insulin-based intensive control of glucose in thin Japanese patients with type 2 diabetes reported a nonsignificant 46% risk reduction for intensively treated patients. In a European study of insulin-based treatment after MI, an HbA1c of 7.1% versus 7.9% after 1 year of therapy was associated with a 29% lower mortality rate. A recent meta-analysis of all glycemic intervention studies in patients with type 1 diabetes showed that intensive therapy with insulin reduced macrovascular events by 28%. These observations helped to shape the recommendation of the American Diabetes Association (ADA) that HbA1c be maintained at <7%.

A cost-effectiveness analysis of the UKPDS and smaller studies has shown societal benefits of more intensive treatment of glycemia, hypertension, and other CVD risks in patients with type 2 diabetes. In the UKPDS, intensive diabetes therapies cost $1000 more per person per year than did conventional intervention, but the resulting reductions in cost of treating complications resulted in a net decrease in expenses of $385 per person per year. In another
report,33 computerized projections showed that comprehensive care in the type 2 diabetic patient is extremely cost-efficient and comparable with the cost-effectiveness of treating patients with diastolic BP >105 mm Hg. Further, the cost-effectiveness of intensive management of type 2 diabetes is greatest for those with higher HbA1c levels.33 In another analysis from a health maintenance organization in California,34 a 36% increase in medical care costs for persons with uncomplicated diabetes was observed as HbA1c levels rose from 6% to 10%. For those with diabetes complicated by hypertension and CVD, the cost of care was 6 times higher at baseline. Even more striking, this high-risk group had a strikingly health care cost reduction over only a 3-year period with a 1% reduction in HbA1c levels. Cost savings of $1200 accrued in patients with uncomplicated diabetes by a reduction in HbA1c levels from 10% to 9%, which rose to $4000 for the same HbA1c level reduction in those whose diabetes was complicated by hypertension and CVD.

In summary, the relationship between glycemia and both microvascular and macrovascular disease is clear from epidemiological data. Although reductions in glycemia have not unequivocally reduced CVD, there is a significant reduction in progression of diabetic renal disease and neuropathy, which are both associated with worsening of hypertension and increasing difficulty in treating this disorder.19

### Treatment of Hypertension in Type 2 Diabetes

The patient presented in this Grand Rounds has not achieved the recommended BP goal of 130/80 mm Hg and needs more aggressive antihypertensive therapy. In diabetic patients there is a graded risk at every level of systolic BP (SBP) or diastolic BP for CVD risk.3,17,27 Because of high CVD and renal disease risk, even at high normal levels of BP, there have been recent recommendations for BP goals of <130/80 to 85 mm Hg by several national organizations (2 or possibly 3) oral drugs

#### Pharmacological Therapy for Hypertension in Diabetic Patients

Randomized prospective clinical trials have shown that rigorous treatment of BP in patients with diabetes with a number of pharmacologic agents reduces macrovascular and microvascular disease (Table 3). The Hypertension Optimal Treatment (HOT) study reported that in the diabetic subgroup (n = 1501), major CVD events were reduced by 51% in those randomized to a diastolic BP goal of <80 mm Hg compared with a goal of <90 mm Hg.37 In the UKPDS, 1148 hypertensive type 2 diabetic patients were randomized to either tight BP control (<150/85 mm Hg) or less-tight BP control (<180/105 mm Hg). Tight control was associated with a reduction in diabetes-related endpoints by 24%, in deaths related to diabetes by 37%, in strokes by 44%, and in microvascular endpoints by 37% after a median follow-up of

### Table 1. Relationship Between Glycemia and Risk of CVD in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Age</th>
<th>Follow-Ups, y</th>
<th>Glycemic Control</th>
<th>Outcome</th>
<th>Rate, %</th>
<th>Relative Risk</th>
<th>Relative Risk/HbA1c Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersson, 1995</td>
<td>411</td>
<td>66</td>
<td>7.4</td>
<td>SMBG ≥7.8 mmol/L (140.4 mg/dL) vs &lt;7.8 mmol/L</td>
<td>Death</td>
<td>4.4 vs 3.2</td>
<td>1.4</td>
<td>N/A</td>
</tr>
<tr>
<td>Gall, 1995</td>
<td>328</td>
<td>56</td>
<td>5.3</td>
<td>HbA1c ≥7.8 vs &lt;7.8</td>
<td>CV Death</td>
<td>10.4 vs 4.6</td>
<td>2.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Kuusisto, 1997</td>
<td>1059</td>
<td>58</td>
<td>7.2</td>
<td>HbA1c ≥10.7 vs &lt;10.7</td>
<td>CHD Death</td>
<td>N/A</td>
<td>1.4</td>
<td>N/A</td>
</tr>
<tr>
<td>Wei, 1998</td>
<td>4875</td>
<td>52</td>
<td>7.5</td>
<td>FPG 8–11.5 mmol/L (144–207 mg/dL) vs &lt;6 mmol/L</td>
<td>CV Death</td>
<td>6.3 vs 2.8</td>
<td>2.9</td>
<td>N/A</td>
</tr>
<tr>
<td>UKPDS, 1998</td>
<td>3055</td>
<td>52</td>
<td>7.9</td>
<td>HbA1c &gt;7.5 vs &lt;6.2</td>
<td>Fasting MI</td>
<td>N/A</td>
<td>1.72</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any MI/angina</td>
<td>1.52</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke Death</td>
<td>N/A</td>
<td>1.1</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG MI/angina</td>
<td>30.8 vs 20.3</td>
<td>1.5</td>
<td>1.17</td>
</tr>
</tbody>
</table>

FPG indicates fasting plasma glucose; CV, cardiovascular; IHD, ischemic heart disease; and SMBG, self-monitoring of blood glucose.
Average BP over 9 years was 144/82 mm Hg and 154/87 mm Hg in the tight and less-tight BP control groups, respectively, for a BP difference of 10/5 mm Hg. In a placebo-controlled trial of treatment of isolated systolic hypertension, the Systolic Hypertension in Europe (Syst-Eur) trial, 38,492 patients with diabetes were reported in a post hoc analysis to have significant reductions in CVD mortality, all CVD events, and stroke, with the mean SBP reduced from 175 to 153 mm Hg. These trials suggest that more rigorous BP control is particularly advantageous in diabetics.

Renin-Angiotensin System and Antihypertensive Therapy

There is accumulative evidence that pharmacologic therapy that interrupts the renin-angiotensin system may afford special benefits in reducing CVD and renal disease in diabetic patients with hypertension. 39–45 In a post hoc subgroup analysis of the Captopril Prevention Project (CAPP) the diabetic patients treated with captopril fared significantly better compared with conventional therapy (β-blockers and diuretics) for the primary endpoints and for MI, all cardiac events, and total mortality. 39 These relative beneficial effects of ACE inhibitor therapy were particularly striking in those at highest risk, with highest median fasting glucose, highest BP, more elevated serum cholesterol, or more depressed HDL cholesterol. This is in contrast to the UKPDS, 17 in which there was comparable CVD benefits for type 2 diabetic patients who were randomized to captopril or atenolol, perhaps reflecting a lower CVD risk in the newly diagnosed diabetic patients in the UKPDS.

In a substudy of the Heart Outcomes and Prevention Study (HOPE), the MICRO-HOPE, 40 of the relative risk reduction in the 3577 patients who had diabetes and 1 other CVD risk factor, there was a risk reduction of 25% for combined CVD events, 37% for CVD mortality, 22% for MI, and 33% for stroke (Figure 3). All-cause mortality was reduced by 24%, and albuminuria/overt nephropathy was also decreased in those who were randomized to ramipril treatment. In addition, in the ramipril treatment group, there was a 34% reduction in new onset diabetes. 40 This exceeded the 15% reduction seen with captopril

**TABLE 3. Clinical Trials of Blood Pressure Lowering in Diabetic Patients**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No.</th>
<th>Duration, y</th>
<th>Mean BP</th>
<th>Initial Therapy</th>
<th>Outcome</th>
<th>Risk Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP, 1996</td>
<td>583</td>
<td>5</td>
<td>155/72*</td>
<td>143/68*</td>
<td>Stroke</td>
<td>22 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVD</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chlorthalidone</td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>Syst-Eur, 1999</td>
<td>492</td>
<td>2</td>
<td>162/82</td>
<td>153/78</td>
<td>Stroke</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nitrendipine</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>HOT, 1998</td>
<td>1501</td>
<td>3</td>
<td>144/85*</td>
<td>140/81*</td>
<td>CV events</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Felodipine</td>
<td>MI</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
<td>30 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CV mortality</td>
<td>67</td>
</tr>
<tr>
<td>UKPDS, 1999</td>
<td>1148</td>
<td>8.4</td>
<td>154/87</td>
<td>144/82</td>
<td>Captopril or atenolol</td>
<td>Diabetes-related endpoints:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Strokes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Microvascular</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; NS, not significant.

*BP in diabetic+nondiabetic population, because BP not reported for diabetic patients alone.

8.4 years. 19 Average BP over 9 years was 144/82 mm Hg and 154/87 mm Hg in the tight and less-tight BP control groups, respectively, for a BP difference of 10/5 mm Hg. In a placebo-controlled trial of treatment of isolated systolic hypertension, the Systolic Hypertension in Europe (Syst-Eur) trial, 38,492 patients with diabetes were reported in a post hoc analysis to have significant reductions in CVD mortality, all CVD events, and stroke, with the mean SBP reduced from 175 to 153 mm Hg. These trials suggest that more rigorous BP control is particularly advantageous in diabetics.

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diabetes in the ARB-treated group, reminiscent of what had already been observed with ACE inhibitor therapy. Thus, an ACE inhibitor, or possibly an ARB, is an initial antihypertensive agent of choice in this woman with diabetes, hypertension, LVH, and diabetic nephropathy, because these agents have CVD and renal benefits that appear to extend beyond their beneficial effects on BP reduction. Nevertheless, most persons with diabetes will likely require ≥3 medications to reach the recommended BP goal of 130/80–85 mm Hg.

**Treatment of Lipids in Diabetic Patients**

The patient presented in our Grand Rounds has a typical dyslipidemia for persons with type 2 diabetes with low HDL cholesterol and elevated TGs and likely increased small, dense LDL cholesterol particles. In vivo studies of lipoprotein metabolism have shown that insulin-resistant states and dyslipidemia for persons with type 2 diabetes with low HDL cholesterol and elevated TGs and likely increased small, dense LDL cholesterol particles. Indeed, increased production of both TGs and apoB is typical for type 2 diabetes. Increased lipolysis of insulin-resistant visceral fat and increased fatty acid flux to the liver appears to drive TG synthesis. Reduced activity of the major enzyme involved in TG removal, lipoprotein lipase (an insulin-responsive enzyme), also contributes to the elevated TG in type 2 diabetes. Low HDL levels are also related to reduced insulin sensitivity. In patients with type 2 diabetes, increased secretion of apoB-containing lipoproteins appears to result in increased cholesterol ester transfer protein-mediated transfer of HDL cholesterol esters to these lipoproteins, resulting in reduction in HDL. Increased hepatic lipase, and the resulting increase in HDL catabolism, may also contribute to low levels of HDL. Correcting hyperglycemia helps lower TG levels but has little effect on HDL.

Subgroup analysis of several primary and secondary prevention studies show very high rates of CVD events and mortality in patients with type 2 diabetes, as well as substantial benefits of treatment with statins. Table 4.}

<table>
<thead>
<tr>
<th>Event Rates in Diabetic Patients in Statin Trials</th>
<th>Event Rate</th>
<th>Event Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>AFCAPS 155</td>
<td>6/71 = 8.4% = 1.6%/y</td>
</tr>
<tr>
<td>High LDL-C</td>
<td>4S 202</td>
<td>44/97 = 45% = 8.4%/y</td>
</tr>
<tr>
<td>High LDL-C</td>
<td>CARE 602</td>
<td>112/304 = 37% = 7.4%/y</td>
</tr>
<tr>
<td>High LDL-C</td>
<td>CARE*</td>
<td>3.9%/y</td>
</tr>
<tr>
<td>High LDL-C</td>
<td>LIPID 782</td>
<td>88/396 = 23% = 3.8%/y</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High LDL-C</td>
<td>HPS 5986</td>
<td>24% reduction</td>
</tr>
</tbody>
</table>

NFMI indicates nonfatal myocardial infarction.

*Data from CARE are corrected assuming that the proportion of events attributable to revascularizations in diabetic patients equals that in nondiabetic patients. CARE and 4S data for diabetic patients have been published separately.
and revascularization. In the overall populations, subjects had a reduction even when their baseline LDL cholesterol levels were <100 mg/dL. The incidence of CVD events declined from 18.5% to 14%, for an overall decline of 24%. Some of the beneficial effects of statins in diabetics may involve pleiotropic effects of statins, including reduced oxidative stress, inflammation, and coagulability, as well as improved endothelial function.51

This patient has a lipid pattern consisting of low HDL cholesterol and hypertriglyceridemia and presumably increased numbers of small dense LDL particles.16 Given that the diabetic dyslipidemic profile is more atherogenic,46 diabetic patients have a CVD risk equivalent to that of a history of MI,1,12 and benefits of statin therapy are proven in women and diabetic patients,47–50 statin therapy is indicated in this woman (Table 5).

Aspirin Therapy
Patients with diabetes, especially those with albuminuria, have increased inflammation and enhanced oxidative stress, enhanced platelet aggregation, and hypercoagulability.4,52–54 (Table 6). Patients with diabetes and hypertension are at markedly increased risk of stroke.54 Rigorous treatment of hypertension,52 lipids,47–51 and use of aspirin therapy56–58 may substantially reduce the risk. As suggested by the results of the UKPDS,55 the American Heart Association, and the ADA,56,57 adult persons with diabetes with any evidence of CVD (most patients with type 2 diabetes) should receive aspirin therapy.56,57 However, as estimated by data from the Atherosclerosis Risk in Communities (ARIC) Study58 and from extensive chart reviews in 2 large urban medical centers,59 only 50% of eligible diabetic patients are treated with aspirin. The patient reviewed in this report should be placed on aspirin therapy unless absolutely contraindicated; aspirin therapy has shown to reduce CVD events in patients with type 2 diabetes.13,52–56

Thus, the high-risk diabetic patient presented in this Grand Rounds, as is the case in the majority of such patients,59 needs more comprehensive CVD risk reduction treatment strategies. Optimal therapy in diabetic hypertensive patients, such as our case study, includes treatment with an aspirin, treatment with an HMG-CoA reductase inhibitor, aggressive control of glycermia (HbAlc <7%), and lowering of BP to <130/80 mm Hg with a regimen that interrupts the renin-angiotensin system. Whether additional strategies such as addition of nicotinic acid and/or a fibrate to address low HDL and high TGs, and platelet antagonists to further reduce platelet aggregation are beneficial remains to be determined in appropriate clinical trials.

Summary
In summary, considerable gains have been made in the past several years regarding the treatment of CVD and renal disease risk factors in patients with diabetes and hypertension. However, future research needs to be directed to a better understanding of the pathophysiological mechanisms underlying the high incidence of strokes, MI, heart failure, peripheral vascular disease, and end-stage renal disease in this high-risk group of patients. More research needs to be directed toward better strategies to prevent the development of type 2 diabetes, as well as cardiovascular and renal complications associated with this disease.

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References


\textbf{Key Words:} diabetes ■ hyperglycemia ■ lipids ■ angiotensin-converting enzyme inhibitors ■ aspirin

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