

■ clinical contributions

Evidence-Based Clinical Vignettes
from the Care Management Institute:

Diabetes Mellitus

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Introduction

Patients with diabetes mellitus comprise 7% of Kaiser Permanente (KP) nationwide membership.^{1:p21} However, because complications accompany the disease, patients with diabetes account for a disproportionately increased share of medical expenditures. In the KP Northern California Region, patients with diabetes use 2.4 times more medical resources than patients without diabetes.² Cardiovascular complications of diabetes are particularly excessive and devastating. In the KP Northwest Region, macrovascular complications account for 62% to 89%

Historically, treatment of diabetes emphasized control of blood glucose level. However, recent studies have shown that glucose control alone does not have a statistically significant effect on preventing cardiovascular disease (CVD), although the trend for successful prevention of CVD is in a positive direction.^{5,6}

This article, part of a series highlighting key aspects of guidelines and care programs from the KP Care Management Institute (CMI), is an overview of part of the recently completed *Evidence-based Guidelines and Technical Review for the Management of Diabetes Mellitus*.⁷ Members of the committee that assembled these guidelines are listed in Table 1. One section of the guidelines is devoted to CVD prevention and discusses the evidence supporting seven interventions proven to decrease macrovascular complications of diabetes. The clinical practice guidelines are available through the CMI product line at 510-271-6426, CMIproducts@kp.org, or <http://pkc.kp.org>.

recalled that his father was diagnosed with diabetes at age 52 years. His father's diagnosis was quickly followed by onset of hypertension, a heart attack, congestive heart failure, and, finally, death from a stroke (at age 58 years). Equally disconcerting to Dan was the fact that three of his uncles had diabetes and that, despite good control of their blood glucose levels, all three died of similar complications before age 60 years.

Dan's doctor told him that his blood sugar was 300 mg/dL (16.65 mmol/L) and that he was overweight at 240 lb (108 kg). Dan also learned his blood pressure was elevated at 150/90 mm Hg, his LDL cholesterol level was high at 160 mg/dL (4.14 mmol/L), and his HDL cholesterol level was low at 35 mg/dL (0.91 mmol/L). In addition, although he tried many times to quit, Dan still smoked. Dan's doctor told him that he had a high risk of having a heart attack, stroke, cardiac surgery, or hospitalization in the next ten years.

The doctor said other things, but Dan couldn't remember anything else. A feeling of hopelessness overwhelmed him. He felt that he would inevitably follow in his father's footsteps. What Dan did not yet know was that if he used an appropriate diet, exercise, and several commonly used medications, he

for 62% to 89% of the cost associated with inpatient treatment of diabetes-related complications.³ KP members with diabetes are admitted to the hospital for myocardial infarction at a rate of 18.3 admissions per 1000 members^{1:p21} compared with a rate of 6.6 admissions per 1000 members without diabetes.^{4:p2} This difference between members with diabetes and members without diabetes has increased in the past two years.^{1:p21}

Case Study: Dan's Devastating News

During what he thought was to be a routine office visit, Dan learned he had diabetes. Dan was instantly devastated—after all, he was only 55 years old—but then

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could take control of his diabetes and would probably proceed down a markedly altered path from that of his father.

Calculating Dan's Risk for CVD Events: "High Risk" as Defined Using The Framingham and HOPE Data

Which patients with diabetes have the highest risk for heart disease? The CMI diabetes guidelines recognize that not every type of treatment for CVD reduction can be given to all patients with diabetes; treatment risks, side effects, compliance with medical follow-up and medication regimen, and resource limitations preclude such uniform treatment. However, assessing CVD risk in each patient with diabetes and targeting for treatment those patients at "high risk" (these patients stand to benefit the most from preventive therapy) constitutes a logical, practical approach to population-based diabetes care.

The Southern California Permanente Medical Group guidelines use the classic Framingham formula to calculate risk of a CVD event (eg, heart attack, stroke, or hospitalization).⁸ At the time and place of the office visit, most KP clinicians already have the data needed to determine this risk (Table 2). These data are used in a formula to calculate risk (expressed as a percentage) of a CVD event occurring during the next ten years. Different methods are available for accessing tools to calculate this risk. One such method is to use the Intranet at the Web site <http://kpnet.kp.org/california/scpmg/CPG/images/Dyslipidemia.pdf>, where the formula to calculate this risk is available (Figure 1).⁹

The CMI diabetes guidelines define "high cardiovascular risk" as $\geq 20\%$ ten-year risk of having a CVD event.^{7,p53} Alternatively, high risk may be defined by the criteria used in the HOPE study:¹⁰ patients with known CVD or patients with diabetes aged ≥ 55 years who have one of the following additional CVD risk factors: hypertension; total cholesterol level of >200 mg/dL (>5.17 mmol/L) or LDL cholesterol >130 mg/dL (3.36 mmol/L); HDL cholesterol level <35 mg/dL (<0.91 mmol/L); or being a smoker.

To calculate Dan's ten-year risk for CVD by using the table shown in Figure 1, first scan the top rows of the table (choose the table for males) to find Dan's age (55 years), LDL cholesterol level (160 mg/dL [4.14 mmol/L]), and HDL cholesterol level (35 mg/dL [0.91 mmol/L]). Next, using the risk factors in the left-hand column, find the cell that reflects a hypertensive smoker with diabetes; this cell is found at the bottom of that HDL column. The table shows that Dan's risk of having a CVD event in the next ten years is 36%. Dan would have reason to be depressed about such news if it were not for the powerful treatments is available that may literally make a life-or-death difference to him.

Preventing CVD is as Simple as AABCC'S

A convenient way to recall seven types of CVD prevention treatment is to use a memory cue, the AABCCs (Table 3): **a**spirin; **a**ngiotensin-converting enzyme inhibitors (ACE-I); **b**lood pressure level; **b**eta-adrenergic blocking drugs (beta blockers); treatment for **c**holesterol and dyslipidemia; **g**lucose control with metformin; and **s**moking cessation.

Table 2. Major risk factors for cardiovascular disease (CVD)

Age
Diabetes
Hypertension
Smoking
LDL cholesterol level
HDL cholesterol level

A: Aspirin

The CMI diabetes guidelines state that patients with diabetes and a $\geq 10\%$ ten-year risk of CVD events should be treated with ≥ 75 mg/dL of aspirin.⁷ For patients at lower CVD risk, the CMI diabetes guidelines workgroup decided that the potential risks for aspirin-induced bleeding outweighed the proven benefit of aspirin therapy for CVD.

Key support for this conclusion is provided by a meta-analysis¹¹ of "high-risk" patients with diabetes (most of whom have established CVD) treated with aspirin vs placebo: That analysis showed a decline of 16% in CVD events in the treated group (absolute risk reduction [ARR]¹² = 2%, number needed to treat [NNT]¹² = 50). The appropriate age to start aspirin therapy is not established; however, the consensus recommendation of the guidelines workgroup is to start aspirin therapy in patients with diabetes excluding patients with low CVD risk ($<10\%$).

A: ACE-I

The CMI diabetes guidelines state that ACE inhibitors should be prescribed to patients with diabetes aged ≥ 55 years who either have one or more additional factors predisposing to cardiovascular conditions^b or have a history of CVD (ie, coronary artery disease, stroke, or peripheral vascular disease). The single most convincing piece of evidence for use of ACE inhibitors in this group is the HOPE study,¹⁰ which evaluated more than 1800 patients

Table 3. Seven CVD prevention strategies from the CMI diabetes guidelines⁷

A: Aspirin
A: Angiotensin-converting enzyme inhibitor (ACE-I)
B: Blood pressure level
B: Beta blocker
C: Cholesterol and other lipid optimization
C: Glucose control specifically with metformin (for type 2 diabetes)
S: Smoking cessation

with diabetes who were treated for nearly five years with an ACE inhibitor or placebo. The group treated with ACE inhibitors had 22% fewer heart attacks (ARR = 2.7%, NNT = 37), 33% fewer strokes (ARR = 1.9%, NNT = 53), 37% fewer deaths from CVD (ARR = 3.5%, NNT = 29), and a 25% overall mortality rate (ARR = 3.2%, NNT = 32) compared with the placebo group.¹⁰

B: Blood Pressure Control

The CMI diabetes guidelines recommend initiating antihypertensive therapy in patients with diabetes who have systolic blood pressure level ≥ 140 mm Hg, diastolic blood pressure level $\geq 85-90$ mm Hg, or both.⁷ The target blood pressure level is 130/80 mm Hg. ACE inhibitors are the recommended first-line antihypertensive therapy, but other antihypertensive medication may be needed for optimal control. A simple way to remember the types of blood pressure treatment documented as effective in CVD prevention is another ABC memory guide: **A**CE-I, **B**eta blocker, and **H**ydrochlorothiazide (HCTZ).

One large study, the United Kingdom Prospective Diabetes Study (UKPDS),¹³ showed that people with diabetes who were treated with either an ACE inhibitor or beta blocker had a 44%

a ten-year CVD event risk of 20% or higher. The guidelines recommend an LDL cholesterol treatment goal of less than 100 mg/dL in CVD patients and 100 to 130 mg/dL (2.59-3.36 mmol/L) in primary prevention of CVD. The most supportive data come from the Heart Protection Study (HPS), which treated almost 6000 patients with diabetes between ages 40 and 80 years for five years.¹⁷ Allowing for noncompliance, the program found that use of 40 mg/dL simvastatin produced a reduction of about 33% in major vascular events among patients with diabetes (ARR and NNT not determined from data provided). For patients with diabetes who did not

have established CVD at entry into the study, these results represent avoidance of about seven major cardiovascular events per 100 patients treated for five years.¹⁸

Although not reported for the subset of patients with diabetes, the Heart Protection Study showed no statistically significant excess liver disease or rhabdomyolysis in the treated group compared with the control group.¹⁹ Moreover, in regard to secondary prevention, the Scandinavian Simvastatin Survival Study trial found that patients with diabetes who were treated with statins for secondary prevention of CVD events had a 42% reduced risk of major coronary events (ARR = 13.8%, NNT = 7), a finding

that confirmed the benefit found in the Heart Protection Study.²⁰

C: Glucose Control Using Metformin

The CMI diabetes guidelines recommend metformin (Glucophage, Bristol Myers-Squibb, Princeton, New Jersey) for use as the first line drug in obese, middle-aged patients with type 2 diabetes.⁷ The best evidence supporting this recommendation is derived from the UKPDS study of type 2 diabetes,²¹ which showed that patients with diabetes who were treated with metformin had a 36% lower mortality rate from all causes (ARR = 7.1%, NNT¹² = 14) than did patients with diabetes treated con-

ventionally. In addition, patients with diabetes who were treated with metformin had a 32% risk reduction (ARR = 13.5% NNT¹² = 7-8) of diabetes-related endpoints (ie, sudden death; hyperglycemia; hypoglycemia; fatal or nonfatal myocardial infarction; angina; congestive heart failure; stroke; renal failure; amputation; vitreous hemorrhage; retinopathy; blindness in one eye; or cataract extraction), and had fewer strokes (ARR = 2.2%, NNT¹² = 48),²¹ and fewer MIs (ARR = 7%, NNT = 16).

S: Smoking Cessation

The CMI Diabetes Guidelines workgroup did not formally review the literature on smoking cessation

WOMEN																																					
AGE:	30-34												35-39						40-44																		
LDL:	100-129			130-159			160-189			190-219			100-129			130-159			160-189			190-219			100-129			130-159			160-189			190-219			
HDL:	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	
No Risk Factors	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	
Hypertension (HTN)	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Diabetes (DM) ^a	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Tobacco (TBCO)	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
HTN + DM ^a	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
TBCO + HTN	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
TBCO + DM ^a	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
HTN + DM + TBCO ^a	2	2	3	6	3	4	5	8	3	4	6	9	4	5	7	11	5	6	9	12	7	8	10	13	18	9	11	15	20	9	11	14	19	11	14	17	23

WOMEN																																					
AGE:	45-49												50-54						55-59																		
LDL:	100-129			130-159			160-189			190-219			100-129			130-159			160-189			190-219			100-129			130-159			160-189			190-219			
HDL:	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	
No Risk Factors	2	2	4	6	2	3	5	7	3	4	6	8	4	5	6	10	3	3	5	7	3	4	6	9	4	5	6	9	13	3	4	6	9	4	5	7	9
Hypertension (HTN)	4	5	6	10	5	6	8	12	6	7	10	14	6	8	11	16	5	6	9	12	6	8	11	15	7	9	12	17	9	11	14	19	6	8	10	15	
Diabetes (DM) ^a	5	6	8	12	6	7	10	14	7	9	12	16	8	10	13	19	6	8	11	15	8	10	13	18	9	11	15	20	11	13	17	23	8	10	13	17	
Tobacco (TBCO)	4	5	6	10	5	6	8	12	6	7	10	14	6	8	11	16	5	6	9	12	6	8	11	15	7	9	12	17	9	11	14	19	6	8	10	15	
HTN + DM ^a	8	10	13	18	10	12	16	21	12	14	18	24	13	16	20	26	11	13	17	22	13	15	19	25	15	17	22	28	17	20	24	31	13	15	19	25	
TBCO + HTN	7	8	11	15	8	10	13	18	10	12	15	21	11	13	17	23	9	11	14	19	11	13	16	22	12	15	19	24	14	17	21	27	11	13	16	22	
TBCO + DM ^a	8	10	13	18	10	12	16	21	12	14	18	24	13	16	20	26	11	13	17	22	13	15	19	25	15	18	22	28	17	20	24	31	13	15	19	25	
HTN + DM + TBCO ^a	13	16	20	26	16	18	23	29	18	21	26	33	20	23	28	35	17	20	24	31	19	23	28	34	22	25	30	38	24	28	33	40	20	23	27	34	

WOMEN																																				
AGE:	60-64												65-69						70-74																	
LDL:	100-129			130-159			160-189			190-219			100-129			130-159			160-189			190-219			100-129			130-159			160-189			190-219		
HDL:	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25	60	48	35	25
No Risk Factors	3	5	7	10	5	6	9	12	6	8	10	15	7	9	12	17	4	5	7	11	5	7	9	13	7	8	11	16	8	9	12	18	4	5	7	11
Hypertension (HTN)	7	8	11	16	9	11	14	19	10	12	16	22	12	14	18	24	7	9	12	17	9	11	15	20	11	12	17	23	12	15	19	25	8	9	12	17
Diabetes (DM) ^a	8	10	14	19	11	13	17	22	12	15	19	25	14	17	21	28	9	11	15	20	11	14	18	23	13	16	20	26	15	18	22	29	9	11	15	20
Tobacco (TBCO)	7	8	11	16	9	11	14	19	10	12	16	22	12	14	18	24	7	9	12	17	9	11	15	20	11	13	17	23	12	15	19	25	8	9	12	17
HTN + DM ^a	14	16	21	27	17	20	24	31	19	22	27	34	21	24	30	37	15	17	22	28	18	21	25	32	20	23	28	35	22	26	31	38	15	18	22	29
TBCO + HTN	11	14	18	23	14	17	21	27	16	19	24	30	18	21	26	33	12	15	19	24	15	18	22	28	17	20	24	31	19	22	27	34	13	15	19	25
TBCO + DM ^a	14	16	21	27	17	20	24	31	19	22	27	34	21	24	30	37	15	17	22	28	18	21	25	32	20	23	28	35	22	26	31	38	15	18	22	29
HTN + DM + TBCO ^a	21	24	29	36	24	28	33	40	27	31	36	43	29	33	39	46	22	25	30	37	25	29	34	41	28	32	37	45	31	34	40	47	23	26	31	38

General notes:

1. The CAD Risk and Recommendations for Dyslipidemia Drug Treatment tables use the Framingham equations (1991) to estimate the ten-year risk of a CAD event in people who do not have atherosclerotic disease at baseline.
2. In deriving the treatment recommendations, weights were applied to predicted events to compensate for the longer life expectancy in younger age groups. The CAD event risk (%) in each cell is not weighted. For information on assumptions used in the model for the CAD Risk and Recommendations for Dyslipidemia Drug Treatment, go to the Clinical Practice Guidelines Intranet Web site at: <http://kpnet.kp.org/california/scpmg/CPG>.

in patients with diabetes; instead, the committee accepted the conclusions in the British Medical Journal's Clinical Evidence:²² "People with diabetes are likely to benefit from smoking cessation at least as much as people who do not have diabetes but have other risk factors for cardiovascular events." Although little new or diabetes-specific data on smoking cessation exist, many data conclude that the subgroup with diabetes is likely to benefit from smoking cessation and that this group should therefore be advised to stop smoking.

Implementing Treatment Protective Against CVD: Impact on Dan's CVD Risk

On the basis of the large studies cited here, the additive relative risk reduction for a CVD event exceeds 50% for aspirin, ACE inhibitors, statins, metformin, and smoking cessation. However, not all benefits are certain to accrue by simple addition. Nonetheless, some evidence exists that the benefits may be cumulative. For example, in regard to the combined effect of taking ACE inhibitors, the HOPE study showed that benefits of this therapy occurred in patients who were already taking aspirin, lipid-lowering drugs, and beta blockers.²³ Therefore, a reasonable plan would be to tell Dan that he will probably reduce his risk substantially by starting the recommended treatment.

... patients with diabetes at high risk for CVD should receive evidence-based forms of intervention proven to reduce CVD risk ...

What Dan's Doctor Should Recommend

A: Aspirin

Dan is at "high CVD risk" because he has a 36% risk of having a CVD event in the next ten years. Starting 81 mg/dL or 325 mg/dL of aspirin is recommended.

A: ACE-I

Dan meets the HOPE criteria for ACE inhibitor use: He is a 55-year-old hypertensive smoker with diabetes and an LDL cholesterol level >130 mg/dL (>3.36 mmol/L) and HDL cholesterol level of 35 mg/dL (0.91 mmol/L). The recommendation is to start lisinopril at 10 to 20 mg daily, and to check Dan's potassium and creatinine levels in two weeks.

B: Blood Pressure

Dan's systolic blood pressure level was 150 mm Hg. Use of an ACE inhibitor is already recommended; however, because Dan's systolic blood pressure is >15 mm Hg above the target level, one could consider simultaneously starting hydrochlorothiazide at 12.5 mg to 25 mg daily. Dan's blood pressure should be checked after three weeks, and the medication dose should be titrated to achieve the target blood pressure level, 130/80 mm Hg.

B: Beta-Blocker

Dan does not have known CVD and thus does not meet the guideline's criteria for treatment. How-

ever, because many hypertensive patients with diabetes eventually need three antihypertensive agents, use of a beta blocker (ie, atenolol, 25-50 mg daily) would be reasonable if other antihypertension treatment fails to achieve the target pressure level of 130/80 mm Hg.

C: Cholesterol Treatment

Dan's baseline LDL is >150 mg/dL and his ten-year risk for CVD is >20% indicating initiation of lipid-lowering therapy. The recommended action is to start drug therapy with 40 mg lovastatin daily, confirm normal kidney and liver function when starting the medication (to assure safety), and check lipid panel results and alanine aminotransferase (ALT) level after two months.

C: Glucose Control with Metformin

Dan meets the criteria of being a middle-aged, obese patient with type 2 diabetes. The recommendation is therefore to prescribe

500 mg/day metformin for glycemic control initially and then titrate the dosage to achieve a usual glucose target.

S: Smoking Cessation

Dan should be advised to stop smoking. Use of a KP regional smoking cessation program is suggested.

When Dan and his physician had a talk, the doctor noted Dan's disheartened look and asked about the cause. Dan admitted he was depressed because he felt that he was inevitably progressing to a heart attack, stroke, or early death. Dan's doctor presented to Dan facts that encouraged him to actively change his path. Using these facts, Dan should be able to reduce his risk of myocardial infarction and stroke by stopping smoking, improving his diet, exercising, and taking a few pills each day. Dan became energized; knowing that he could take achievable steps to prevent a death similar to his father's was "just what the doctor ordered." Dan knew it would not be easy

Aspirin	Adult dose of aspirin is 81-325 mg/dL; do not use in patients with low (<10%) ten-year CVD risk.
ACE-I	Use in patients with CVD or microalbuminuria or who are aged ≥55 years and have either hypertension, LDL cholesterol level >130 mg/dL (3.36 mmol/L), HDL cholesterol level <35 mg/dL (0.91 mmol/L), or who smoke. <i>Target therapy is lisinopril 10-20 mg/dL.</i>
Blood pressure	Start therapy if blood pressure level is >140/90 mm Hg; target level, 130/80 mm Hg; <i>use ACE-I, beta-blocker, HCTZ, or combination of these agents. Many patients will need two or three types of drugs. If systolic blood pressure is >145 mm Hg, consider starting drug therapy with two medications simultaneously.</i>
Beta-blocker	Use to treat CVD or to control blood pressure. <i>Atenolol 25-50 mg/dL is appropriate dose.</i>
Cholesterol	Treat if ten-year CVD risk is ≥20% or baseline LDL is >150 mg/dL; target LDL cholesterol level <100-130 mg/dL (<2.59-3.36 mmol/L). <i>Lovastatin 40 mg/dL is appropriate dose for patients with normal creatinine level.</i>
Glucose (metformin)	Metformin is the preferred glucose control agent for treating middle-aged, obese patients with type 2 diabetes.
Smoking cessation	Advise smokers to stop smoking.

CVD = cardiovascular disease, HCTZ = hydrochlorothiazide, SBP = systolic blood pressure, ACE-I = angiotensin-converting enzyme inhibitor. *Italicized comments not formally included in CMI Diabetes Guideline but added by one author (RJD) for convenience of the practitioner.*

to change his path, but he now had the hope that by getting involved and taking charge of his health-related behavior, he could change his own future.

Table 4 presents a practical summary of the CMI diabetes guidelines for CVD prevention.

Summary

Providing population-based care to patients with diabetes requires stratification of patients according to their risk for CVD. On the basis of this risk profile, patients with diabetes at high risk for CVD should receive evidence-based forms of intervention proven to reduce CVD risk and, in some cases, to decrease mortality. Although not included in the CMI diabetes guidelines for CVD prevention, specific medications and dosages are suggested. ❖

^a Here and throughout, unless otherwise referenced, AAR and NNT calculated by author JB.

^b Total cholesterol level >200 mg/dL (>5.17 mmol/L) (or LDL cholesterol level \geq 130 mg/dL [\geq 3.36 mmol/L]), HDL cholesterol level <35 mg/dL (<0.91 mmol/L).

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