■■ **clinical medicine**

Clinical Evidence Review: Best Practices

Diabetes Mellitus Update

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Introduction

Patients with diabetes mellitus comprise over 10% of Kaiser Permanente (KP) nationwide membership.[1] 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% of the cost associated with inpatient treatment of diabetes-related complications.

Historically, treatment of diabetes emphasized control of blood glucose level. However, 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.[3,4] In addition, there is strong clinical evidence that the use of a combination of three medications—aspirin, ACE-inhibitors, and statins—can reduce the incidence of cardiovascular disease by 75%.[5]

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 2006 KP National Adult Diabetes Guidelines.[6] 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 at http://cl.kp.org/pkc/national/cmi/programs/diabetes/guideline/index.html.

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 recalled that his father was diagnosed with diabetes at age 52. 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 discomforting 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. 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

Table 1. 2006 CMI Adult Diabetes Guideline Development Team
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> **In the KP Northern California Region, patients with diabetes use 2.4 times more medical resources than patients without diabetes.[2]**

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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 foot- steps. What Dan did not yet know was that if he used an appropriate diet, exercise, and several commonly used medications, he could take control of his diabetes and would probably proceed down a markedly altered path from that of his father.

Figure 1. 10-Year CAD Risk (%) and Recommendations for Dyslipidemia Drug Treatment
(For people WITHOUT known atherosclerosis or Chronic Kidney Disease Stages 3-5[a])

HOW TO USE THE DRUG TREATMENT TABLES:
- Select the table matching the person's gender.
- Find the column corresponding to the person's age, TC level, and HDL-C level.
- Find the row that matches the person's non-lipid risk factors, e.g., NONE, Hypertension (HTN), Diabetes (DM), Tobacco (TBCO).
- The number in the intersecting "cell" is the person's estimated risk (%) of a CAD event in the next 10 years.
- The color in the "cell" indicates the drug treatment recommendation and goals.
- CAD risk is estimated using TC and HDL-C. However, treatment thresholds and goals are based on LDL-C and non-HDL cholesterol. Non-HDL cholesterol = TC minus HDL-C.

DYSLIPIDEMIA DRUG TREATMENT RECOMMENDATIONS:*
- Treatment STRONGLY recommended when 10-year CAD risk ≥25%, regardless of baseline LDL-C[b]
- Treatment recommended for people with DIABETES ≥40 years old, regardless of baseline LDL-C [b]
- Treatment RECOMMENDED if baseline LDL-C ≥130 mg/dL
- Treatment recommended IF positive FHx of early atherosclerosis and baseline LDL-C ≥130 mg/dL[c]
- Drug Treatment NOT recommended

*Treatment is recommended for all people with LDL-C ≥220 mg/dL, regardless of CAD risk.

Aspirin treatment, 81-325 mg daily, is recommended for people who are at high enough risk to warrant statin treatment. Discuss aspirin treatment with people with 10-year CAD risk ≥10% who are not otherwise recommended for statin treatment.

DYSLIPIDEMIA DRUG TREATMENT GOALS:
- Use statin treatment, regardless of baseline LDL-C.
- The goal is LDL-C <100 mg/dL. After LDL-C is at goal, an optional goal is non-HDL cholesterol <130 mg/dL.
- The goal is LDL-C <130 mg/dL. After LDL-C is at goal, an optional goal is non-HDL cholesterol <160 mg/dL.

MEN *

AGE:	30-34																35-39																40-44															
TC:	160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319			
HDL-C:	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39
No Risk Factors	<1	<1	1	3	<1	1	2	4	1	2	2	5	1	2	3	6	<1	1	2	4	1	2	3	6	2	3	4	7	2	4	5	9	2	2	3	6	2	3	5	8	3	4	6	11	4	6	7	13
Hypertension (HTN)	1	2	2	5	2	2	3	7	2	3	4	7	3	4	6	10	1	2	3	7	3	4	6	10	4	5	7	12	5	7	9	14	3	4	6	11	4	6	8	13	5	8	10	16	7	9	12	19
Diabetes (DM)[b]	<1	1	2	4	1	2	3	5	2	3	4	7	2	3	5	9	1	2	3	6	2	3	5	8	3	4	6	10	4	5	7	12	2	4	5	9	3	5	7	12	4	6	9	14	6	8	10	17
Tobacco (TBCO)	1	2	3	5	2	3	4	7	2	3	5	8	3	4	6	10	2	3	4	8	3	4	6	10	4	5	7	12	5	7	9	15	3	5	6	11	4	6	8	14	6	8	10	16	7	10	12	19
HTN + DM[b]	2	3	4	7	2	4	5	9	3	5	7	11	4	6	8	13	3	4	6	10	4	6	8	13	5	8	10	16	7	9	12	18	4	6	9	14	6	9	11	18	8	11	13	21	9	13	16	24
TBCO + HTN	2	3	5	8	3	5	6	11	4	6	8	13	5	7	10	16	4	5	7	12	5	7	10	15	7	9	12	18	8	11	14	21	6	8	10	16	7	10	13	20	9	13	16	24	11	15	18	27
TBCO + DM[b]	2	3	4	7	3	4	5	9	3	5	7	12	4	6	8	14	3	4	6	11	4	6	8	14	5	8	10	16	7	9	12	19	5	7	9	14	6	9	11	18	8	11	14	21	10	13	16	24
HTN + DM[b] + TBCO	3	5	7	12	5	7	9	15	6	9	11	18	7	10	13	20	5	8	10	16	7	10	13	20	9	12	16	23	11	15	18	26	8	11	14	21	10	14	17	25	13	17	20	29	15	19	23	32

AGE:	45-49																50-54																55-59															
TC:	160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319			
HDL-C:	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39
No Risk Factors	2	4	5	9	3	5	7	11	4	6	8	14	5	8	10	16	3	5	7	11	5	7	9	15	6	8	11	17	7	10	13	20	5	7	9	14	6	9	11	18	8	11	14	21	9	13	16	24
Hypertension (HTN)	4	6	8	14	6	8	11	17	8	10	13	20	9	12	16	23	6	8	11	17	8	11	14	21	10	13	17	25	12	16	19	28	8	11	14	21	10	14	17	25	13	16	20	29	15	19	23	32
Diabetes (DM)[b]	4	5	7	12	5	7	9	15	6	9	11	18	8	11	14	21	5	7	9	15	7	9	12	19	9	12	15	23	11	14	18	26	7	9	12	19	9	12	15	23	11	14	18	26	13	17	21	29
Tobacco (TBCO)	4	6	9	14	6	9	11	18	8	11	14	21	9	13	16	24	6	9	11	18	8	11	14	22	10	14	17	25	12	16	20	28	8	11	14	21	10	14	17	26	13	17	21	29	15	19	23	33
HTN + DM[b]	6	9	11	18	8	11	14	22	10	14	17	26	12	16	20	29	8	12	15	22	11	15	18	26	13	17	21	30	16	20	24	34	11	14	18	26	14	18	22	31	16	21	25	35	19	24	28	38
TBCO + HTN	8	11	14	21	10	14	17	25	12	16	20	29	15	19	23	32	10	14	17	25	13	17	21	30	16	20	24	34	18	23	27	37	13	17	21	29	16	21	25	34	19	24	28	38	22	27	32	42
TBCO + DM[b]	7	9	12	18	9	12	15	22	11	14	18	26	13	17	20	29	9	12	15	22	11	15	18	27	14	18	22	31	16	21	25	34	11	15	18	27	14	18	22	31	17	21	26	35	20	24	29	39
HTN + DM[b] + TBCO	11	14	18	26	14	18	22	30	16	21	25	34	19	24	28	38	14	18	22	31	17	22	26	35	20	25	30	39	23	28	33	43	17	21	26	35	21	26	30	40	24	29	34	44	27	33	38	48

AGE:	60-64																65-69																70-74															
TC:	160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319			
HDL-C:	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39
No Risk Factors	6	8	11	17	8	11	14	21	10	13	17	25	12	16	19	28	7	10	13	20	10	13	16	24	12	16	19	28	14	18	22	31	9	12	15	23	12	15	19	28	14	18	22	31	17	21	25	35
Hypertension (HTN)	10	13	17	24	13	17	20	29	15	20	24	33	18	22	27	36	12	16	19	28	15	19	24	33	18	23	27	37	21	26	30	40	14	18	22	31	18	22	27	36	21	26	31	40	24	29	34	44
Diabetes (DM)[b]	8	11	14	22	11	14	18	26	13	17	21	30	16	20	24	33	10	14	17	25	13	17	21	30	16	20	24	34	18	23	28	37	12	16	20	29	16	20	24	33	19	23	28	37	21	26	31	41
Tobacco (TBCO)	10	14	17	25	13	17	21	29	16	20	24	33	18	23	27	37	12	16	20	28	15	20	24	33	18	23	28	37	21	26	31	41	15	19	23	32	18	23	27	37	21	26	31	41	24	30	34	44
HTN + DM[b]	13	17	21	30	17	21	25	35	20	25	29	39	23	28	32	42	16	20	24	34	20	24	29	39	23	28	33	43	26	31	36	46	18	23	28	37	22	28	32	42	26	32	36	46	29	35	40	50
TBCO + HTN	16	20	24	33	19	24	29	38	22	28	32	42	26	31	36	46	18	23	28	37	22	28	32	42	26	31	36	46	29	35	40	50	21	26	31	41	25	31	36	46	29	35	40	50	33	38	43	53
TBCO + DM[b]	14	18	22	30	17	22	26	35	20	25	30	39	23	28	33	43	16	21	25	34	20	25	29	39	23	29	33	43	26	32	37	47	19	24	28	38	23	28	33	43	26	32	37	47	30	35	40	50
HTN + DM[b] + TBCO	20	25	30	39	24	30	34	44	28	33	38	48	31	37	42	52	23	29	33	43	28	33	38	48	31	37	42	52	35	41	46	55	26	32	37	47	31	37	42	52	35	41	46	55	39	44	49	59

[a] Known atherosclerosis = documented CAD, carotid (>50% stenosis) or peripheral artery disease, abdominal aortic aneurysm, or atherosclerotic TIA/CVA. Chronic Kidney Disease Stages 3-5 = National Kidney Foundation (NKF) Stages 3-5, defined as Glomerular Filtration Rate (GFR) <60 ml/mon per 1.73 m², persisting at least 3 months. See Dyslipidemia Management in Adults Guideline for detailed description.

[b] The Heart Protection Study showed that people with diabetes ≥40 years old without CAD are at high risk for CAD and derive a large benefit from statin treatment, regardless of baseline LDL-C. A 10-year CAD risk ≥25% is roughly equivalent to the risk of people with known CAD. Therefore, for people with diabetes ≥40 years old, and for people with 10-year CAD risk ≥25%, the recommendations are: use statin treatment, regardless of baseline LDL-C; the goal is LDL-C <100 mg/dL; after LDL-C is at a goal, an optional goal is non-HDL <130 mg/dL. Clinical judgment is advised when considering lipid-lowering medications in people with diabetes at very low 10-year CAD risk (<7-10%).

[c] Positive FHx of early atherosclerosis = family history of CAD or peripheral or carotid artery disease in a first degree relative <55 years old (male relative) or <65 years old (female relative).

General notes:
1. The 10-Year CAD Risk (%) and Recommendations for Dyslipidemia Drug Treatment tables use the Framingham equations (1991) to estimate the 10-year CAD risk in people without known atherosclerosis or chronic kidney 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.

* Chart for women available on the Intranet at http://cl.kp.org/pkc/scal/cpg/cpg/html/SCPMG_DyslipidemiaCADRisk Table2005.pdf.

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).[7] 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://cl.kp.org/pkc/scal/cpg/cpg/html/SCPMG_DyslipidemiaCADRiskTable2005.pdf where the formula to calculate this risk is available.[8] Alternatively, high risk may be defined by the criteria used in the HOPE study: 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 mgdL [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 available that may literally make a life-or-death difference to him. Preventing CVD is as simple as AABBCC (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; glu**C**ose control with metformin; and **S**moking cessation.

A: Aspirin

The CMI diabetes guidelines state that patients with diabetes age 40 years and older should be treated with at least 81 mg/day of aspirin unless contraindicated[6] 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-analysis[10] 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]a 12 = 2%, number needed to treat [NNT]12 = 50).

A: ACE-I

The CMI diabetes guidelines state that ACE-I should be prescribed to patients with diabetes aged >55 years who either have one or more additional factors predisposing to cardiovascular conditions 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-I in this group is the HOPE study,[9] which evaluated more than 1800 patients with diabetes who were treated for nearly five years with an ACE-I or placebo. The group treated with ACE-I 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.[9]

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 ≥85-90 mm Hg, or both.[6] The target blood pressure level is 130/80 mm Hg. ACE-I, diuretics, or combination therapy of diuretics/

> **The target blood pressure level is 130/80 mm Hg.**

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

Age
Diabetes
Hypertension
Smoking
LDL cholesterol
HDLcholesterol

Table 3. Seven CVD prevention strategies from the CMI diabetes guideline[7]

A: **A**spirin
A: **A**ngiotensin-converting enzyme (ACE-I) inhibitor
B: **B**lood pressure control
B: **B**eta blocker
C: **C**holesterol and other lipid optimization
C: Glu**C**ose control specifically with metformin (for type 2 diabetes)
S: **S**moking cessation

ACE-I are the recommended first-line antihypertensive therapy, but additional antihypertensive medication may be needed for optimal control. One large study, the United Kingdom Prospective Diabetes Study (UKPDS),[12] showed that people with diabetes who were treated with either an ACE-I or beta blocker had a 44% decline in incidence of stroke (ARR = 3.7%, NNT = 27) and in incidence of myocardial infarction (ARR = 7%, NNT = 14) as well as a 24% decline in any diabetes endpoint (ie, stroke, myocardial infarction, sudden death, angina, heart failure, renal failure, amputation, eye disease, or peripheral vascular disease) (ARR = 1.65%, NNT = 60). This study also showed that 29% of the patients needed three or more medications to lower their blood pressure.[12] Use of thiazide diuretic agents produced a 34% decline in CVD events (ARR = 10.1%, NNT12 = 10) compared to placebo in the subpopulation of patients with diabetes described in the large Systolic Hypertension in the Elderly Population (SHEP) study.[13]

B: Beta Blocker

The CMI diabetes guidelines list use of beta blockers as recommended for patients with diabetes and a history of myocardial infarction (MI) and as an option for secondary prevention of CVD in patients with diabetes without previous MI.[6] The best evidence of benefit is shown for patients after myocardial infarction: in the Bezafibrate Infarction Prevention study,[14] subgroup analyses of patients with diabetes receiving beta blockers during the study period showed that these patients had 44% fewer myocardial infarctions (ARR = 6.2%, NNT = 16) than did patients with diabetes who did not receive beta blockers. These study findings were supported in a retrospective review.[15]

> **The guidelines recommend an LDL cholesterol treatment goal of less than 100 mg/dL in patients age over 40 with diabetes.**

C: Cholesterol

The CMI diabetes guidelines recommend treating patients with diabetes and dyslipidemia for secondary prevention of cardiovascular events.[6] It is recommended that statin therapy be prescribed for all patients age 40 to 80 years with diabetes and TC ≥ 135, regardless of LDL level. The guidelines recommend an LDL cholesterol treatment goal of less than 100 mg/dL in patients age over 40 with diabetes. 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.[16] 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.[17] 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.[18] 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.[19]

C: Glucose Control Using Metformin

The CMI diabetes guidelines recommend metformin for use as the first line drug in obese, middle-aged patients with type 2 diabetes.[6] The best evidence supporting this recommendation is derived from the UKPDS study of type 2 diabetes,[20] 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 conventionally. 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),[20] and fewer MIs (ARR = 7%, NNT = 16).

S: Smoking Cessation

The CMI Diabetes Guidelines workgroup did not formally review the literature on smoking cessation in patients with diabetes; instead, the committee accepted the conclusions in the British Medical Journal's Clinical Evidence:[11] *"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-I, 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-Is, the HOPE study showed that benefits of this therapy occurred in patients who were already taking aspirin, lipid-lowering drugs, and beta blockers.[21] Therefore, a reasonable plan would be to tell Dan that he will probably reduce his risk substantially by starting the recommended treatment.

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-I 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-I 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. However, 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 40-80 mg lovastatin or 40 mg simvastatin 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 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 prac-

> **Dan became energized; knowing that he could take achievable steps to prevent a death similar to his father's …**

Table 4. Practical summary of CMI diabetes guideline for preventing CVD	
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. Target therapy is lisinopril 10-20 mg/dL.
Blood pressure	Start therapy if blood pressure level is >140/90 mmHg; target BP is ≤130/80 mmHg; diuretics or ACE-I are preferred first line agents; use a combination of ACE-I, beta-blocker, diuretics if a single drug is not sufficient to control HTN. When BP is more than 20/10 mmHg to 30/10 mmHg above goal, initiate combination therapy.
Beta-blocker	Use to treat CVD or to control blood pressure. Atenolol 25-50 mg/dL is appropriate dose.
Cholesterol	Treat all diabetes patients age 40 to 80 years old with a statin, regardless of baseline LDL. Target LDL is <100 for patients over age 40 with diabetes.
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.

tical summary of the CMI diabetes guidelines for CVD prevention.

Summary

Patients with diabetes are at high risk for CVD and should be considered for evidence-based forms of intervention proven to reduce CVD risk and to decrease mortality. All patients over age 55 years with one additional risk factor should be prescribed an ACE inhibitor. All patients with diabetes over age 40 should be prescribed a statin and should be treated with 81 mg daily aspirin unless contraindicated. Proper glucose control, blood pressure control, treatment with a beta-blocker (if appropriate), and smoking cessation counseling will prevent or reduce progression of macrovascular and microvascular complications. ❖

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