Should All Diabetic Patients Be Treated With a Statin?

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The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% (171 million) in the year 2000, and the projected number could rise to 4.4% (366 million) in 2030 (1). This rapid rise is mainly attributable to the increase of diabetes. The continuing escalation of obesity and the metabolic syndrome contribute to the upsurge in frequency of diabetes (2,3).

Interestingly, the appreciation in the number of people >65 years of age was found to be the most important demographic change to diabetes prevalence around the world, indicating that the "diabetes epidemic" will continue even if levels of obesity remain constant. Therefore, it is likely that future diabetes preponderance is underestimated, given the growing frequency of obesity (1). Because the vast majority of diabetic patients have type 2 diabetes and almost all the studies were performed in such subjects, in this article, "type 2 diabetes" will be referred to as "diabetes."

DIABETES AS A MAJOR RISK FACTOR FOR CARDIOVASCULAR DISEASE

— Cardiovascular disease (CVD) is one of the foremost causes of mortality and is a major contributor to morbidity for individuals with diabetes. In addition, diabetes is an independent risk factor for macrovascular disease, as are the common coexisting conditions (hypertension and dyslipidemia). The U.K. Prospective Diabetes Study (UKPDS) evaluated baseline risk factors for coronary artery disease in patients with newly diagnosed diabetes without evidence of vascular disease. When comparing the relative contribution of the three modifiable coexisting conditions (dyslipidemia, hypertension, and hyperglycemia) with development of future coronary heart disease (CHD), the estimated hazard ratio (HR) for the upper third, relative to the lower third, for LDL cholesterol, systolic blood pressure, and A1C were 2.26, 1.82, and 1.52, respectively (4). This finding supports the notion that dyslipidemia, and specifically LDL cholesterol, are major contributors to the increased CHD risk in patients with diabetes (4,5). Hyperglycemia occurs at a far later stage in the sequence of events from insulin resistance to frank diabetes, whereas lipoprotein abnormalities are manifested during the pre-diabetic stage and contribute substantially to the increased risk of macrovascular disease. The most common pattern of dyslipidemia in diabetic patients is elevated triglyceride levels and decreased HDL cholesterol levels. Although the mean concentration of LDL cholesterol in patients with diabetes is not significantly different from that in individuals without diabetes, qualitative changes in LDL cholesterol may be present. Patients with diabetes tend to have a higher proportion of LDL particles that are smaller and denser, are more susceptible to oxidation, and may thereby increase the risk of cardiovascular events (6,7). The Framingham cohort (8), and more recent data, have established the notion that diabetes is associated with a two- to fourfold increased risk of both CHD and stroke (9–11). Furthermore, diabetic patients who develop cardiovascular complications do not fare as well as nondiabetic patients, namely the case-fatality rates for myocardial infarction (MI) and stroke are also higher among diabetic patients, emphasizing the important need for primary prevention of cardiovascular complications in these individuals. The realization that diabetes is considered a major risk for cardiovascular events evolved to the concept regarding diabetes as a "CHD-risk equivalent." This concept was first introduced in the 2001 American National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines (12), based on studies showing that the absolute risk for first major coronary events for diabetic individuals approximates that for recurrent events in nondiabetic individuals with clinical CHD (12,13). This hypothesis was reiterated in the 2004 NCEP report, and current treatment recommendations consider patients with diabetes to be CHD-risk equivalents and have established more aggressive treatment goals for LDL cholesterol, as well as for blood pressure lowering (14–17). However, other studies suggested that although diabetic patients are at increased risk for CHD morbidity and mortality, the risk may not be as high as previously perceived, and also question whether diabetic patients without vascular disease should be categorized as being at similar risk.

DIABETES IS A CHD-RISK EQUIVALENT

— The seminal article by Haffner et al. (13) is the basis for this premise. This observational Finnish study examined the 7-year incidence of cardiovascular events among 890 patients with diabetes who had no history of MI, compared with 69 patients with previous MI. The risk of death from CHD was not significantly different between the two groups, with an adjusted HR of 1.2. The main flaw of this study was the lack of power to detect differences between the two groups because of the small sample size, leading to wide CIs around the risk ratios. In an effort to correct this weakness, follow-up of this cohort was prolonged for up to 18 years (18). Diabetic patients without prior MI had an HR of 0.9 for the risk of CHD mortality compared with nondiabetic patients with prior MI infarction. Furthermore, with respect to other definitions of CHD, the prognosis for patients with diabetes with-

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The publication of this supplement was made possible in part by unrestricted educational grants from Eli Lilly, Ethicon Endo-Surgery, Generex Biotechnology, Hoffmann-La Roche, Johnson & Johnson, LifeScan, Medtronic, MSD, Novo Nordisk, Pfizer, sanofi-aventis, and WorldWIDE.
DOI: 10.2337/dc09-S344

out prior CHD was actually worse than that for nondiabetic patients with prior CHD, particularly for women. Similar results were found in the Renfrew and Paisley Survey, a prospective cohort study of 7,052 men and 8,354 women, who were followed up for 25 years (19). Diabetes without previous CHD was found to carry a lifetime fatality risk from vascular disease equal to that of CHD alone. Women were found to be at particular risk. The adjusted HR for CHD mortality in men with diabetes only, compared with men who had CHD, was 1.17. The corresponding HR for women was 1.97. In the Nurse's Health Study, in a cohort of 121,700 women followed up for 20 years, the age-adjusted relative risk of fatal CHD was almost similar between women with a history of diabetes and no CHD and those with a history of CHD and no diabetes at baseline (8.7 and 10.6, respectively) (20). In the Women's Pooling Project, a prospective study that combined data from nine long-term epidemiological studies, 27,269 women were followed up for an average of 8.3 years (10). Diabetic women without CVD were found to have a fatal stroke risk similar to that of nondiabetic females who had a history of prior stroke and a similar risk factor profile (HR 1.29).

DIABETES IS NOT A CHD-RISK EQUIVALENT

— In cross-sectional and cohort studies from Scotland, patients with diabetes were found to be at lower risk of cardiovascular outcomes compared with patients with established CHD (21). In the cross-sectional study (n = 1,155), the adjusted risk ratio for death from all-cause mortality was 2.27 for patients with a previous MI compared with diabetic patients without CHD. In the cohort study (n = 3,477), the diabetic group was at a lower risk for all-cause and cardiovascular mortality, compared with those who had diabetes but no CHD. However, the reduced risk of diabetic patients without CHD seemed to occur mainly in the early period of follow-up, with the gradients of the curves converging after ~3 years (21). In the Atherosclerosis Risk in Communities (ARIC) study, a population-based cohort from four U.S. communities (n = 13,790) with over 11 years of follow-up, diabetic patients without MI had less danger of CHD events and mortality from CVD, compared with nondiabetic patients with a prior MI. However, the possibility for stroke was similar in these groups. After adjustment for multiple baseline risk factors, patients with a history of MI without diabetes at baseline had a 1.9 times greater likelihood of fatal CHD or nonfatal MI, compared with diabetic patients without a prior MI. The nondiabetic patients with MI also had a 1.8 times higher risk of CVD mortality than diabetic patients without MI. In the Prospective Cardiovascular Munster (PROCAM) study (n = 5,389), only 26.5% of men with diabetes were estimated as having a 10-year coronary event risk at or above the threshold of 20%, which is regarded as being equivalent to that of established CHD. The positive predictive value of a high-risk estimate was only 35% in diabetic men. In the Physician's Health Study, a prospective cohort analysis of 91,285 U.S. male physicians, CHD was a stronger predictor of death from CHD than diabetes (22). The risk of CHD mortality was 3.3% among men with diabetes and without CHD and 5.6% among men with CHD and without diabetes. For all-cause mortality, the magnitude of excess vulnerability presented by diabetes was similar to that of a history of CHD. Similar results were found in the Multiple Risk Factor Intervention Trial (MRFIT) (9). The adjusted HR for all-cause mortality for individuals with MI only, compared with diabetes only, was 0.97, but the pattern of demise was different: higher coronary mortality and lower mortality from noncardiovascular causes in individuals with MI only, compared with individuals with diabetes only.

CALCULATING THE RISK OF DIABETIC PATIENTS

— Different risk calculators vary in their attitude toward diabetes as a CHD risk factor. The Framingham risk calculator uses age, sex, blood pressure, cholesterol (total and HDL), and smoking for calculating the risk, with diabetes considered a CHD-risk equivalent, requiring no further risk calculation (12). The European Systematic Coronary Risk Evaluation (SCORE) calculator uses a similar approach. Patients with diabetes are automatically assigned to the highest risk category, and further hazard calculation is unnecessary (23). Other risk calculators treat diabetes the same as other danger factors and include this condition in the probability equations. An example for such an approach is the PROCAM risk calculator. Other risk calculators were specifically designed for patients with diabetes; the UKPDS risk engine uses glycemia, systolic blood pressure, lipid levels, age, sex, ethnic group, smoking status, and time since diagnosis of diabetes to form a diabetes-specific risk assessment (24). Other calculators combine a general and a diabetes-specific approach. Recently, a modification of the Framingham calculator was proposed for women, which included A1C in the risk calculation if the patient was diabetic.

CHOLESTEROL REDUCTION AND CARDIOVASCULAR RISK REDUCTION IN DIABETIC PATIENTS

— The vast majority of clinical trials examining cholesterol reduction as a means to reduce cardiovascular risk were performed using HMG-CoA reductase inhibitors (statins). Only three trials recruited diabetic patients exclusively, but some other trials included sufficient diabetic patients to facilitate prespecified or post hoc analyses of the effect of statins in these patients.

SECONDARY PREVENTION AND MIXED SECONDARY AND PRIMARY PREVENTION TRIAL

— In a post hoc analysis of the Scandinavian Simvastatin Survival Study (4S), a significant reduction in major coronary events and revascularization was observed in simvastatin-treated diabetic patients (25) (Table 1). Total and coronary mortality were also reduced, but not significantly, because of the small sample size. Notably, risk reduction for major coronary events was greater in diabetic (42%) than in nondiabetic patients (32%). In the Cholesterol and Recurrent Events (CARE) trial, pravastatin treatment, compared with placebo, reduced by 25% the relative risk of coronary events for both diabetic and nondiabetic patients (26). In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, treatment with pravastatin was associated with a reduction of 19% in major CHD (albeit not statistically significant) (27). A possible explanation for the nonsignificant reduction may be the lower baseline risk: diabetic patients treated with placebo in the LIPID trial had a 15.9% chance of fatal CHD and nonfatal MI compared with a likelihood of >20% in CARE and ~35% in 4S. The Heart Protection Study (HPS), the largest statin trial, comprised almost 6,000 diabetic patients (28). For the first occurrence of major vascular events among participants with diabetes, there was a statistically significant 22% reduction in the event rate, which was similar to that among the other high-risk individu-

Table 1—*Cholesterol reduction and cardiovascular risk reduction in diabetic patients*

Study (reference)	Number of patients with diabetes	Drug and dose	Mean baseline LDL cholesterol (mg/dl)	Mean achieved LDL cholesterol (mg/dl)	% Reduction in major adverse coronary events*	*P*
Secondary prevention and mixed trials						
4S (25)	483	Simvastatin 20–40 mg	189	117	42	0.001
CARE (26)	586	Pravastatin 40 mg	136	96	25	0.05
LIPID (27)	782	Pravastatin 40 mg	150†	112†	19	NS
HPS (28)	5,936	Simvastatin 40 mg	124	89	22	<0.0001
ASPEN (29)	2,410	Atorvastatin 10 mg	113	79	10	NS
Diabetes and Dialysis (30)	1,255	Atorvastatin 20 mg	123	72	8	NS
Primary prevention trials						
ASCOT (31)	2,532	Atorvastatin 10 mg	132†	81†	36	0.0005
CARDS (32)	2,838	Atorvastatin 10 mg	117	81	37	0.001
Intensive versus less intensive therapy						
PROVE-IT (34)	734	Atorvastatin 80 mg vs. pravastatin 40 mg	106†	62 vs. 95†‡	17	NS
TNT (35)	1,231	Atorvastatin 80 mg vs. atorvastatin 10 mg	99	73 vs. 99‡	29	<0.0001
A to Z (36)	1,059	Simvastatin 40/80 mg vs. simvastatin 0/20 mg	111†	66 vs. 81†‡	14	NS

*According to study definition. †Value for the entire study population. ‡Intensive versus moderate therapy.

als studied. The Atorvastatin Study for Prevention of Coronary Heart Disease End Points (ASPEN) trial examined the effect of 10 mg atorvastatin versus placebo on major cardiovascular events in 2,410 subjects with diabetes (29). This trial was originally designed as a secondary prevention trial for individuals with CHD. However, the protocol was amended within 2 years of initiation of the study to enable enrollment of subjects without prior CHD. Subsequent treatment guidelines necessitated all secondary prevention subjects, and primary prevention subjects who developed a primary CVD end point during the trial, to discontinue the study medication and commence active therapy. In this trial, there was no difference in major cardiovascular events between the atorvastatin and placebo groups. In the Diabetes and Dialysis Study, 1,255 patients with diabetes receiving hemodialysis (30% of whom had CHD), were randomly assigned to receive 20 mg atorvastatin per day or placebo (30). Atorvastatin had no significant effect on the composite primary end point of cardiovascular death, nonfatal MI, and stroke. These results were observed despite a high incidence rate of major cardiovascular events, which was the highest in all long-term prospective statin therapy trials. It is noteworthy that the subgroup analyses showed no difference in outcomes for baseline LDL cholesterol level, or presence or absence of CVD. A possible explanation for the lack of benefit from statin therapy in this trial may be due to the type of patients studied. In patients on dialysis, other pathogenetic factors may be more prominent in contributing to cardiovascular risk. It is of interest that, in patients with end-stage renal disease, there is a kind of "reverse epidemiology," with inverse associations between blood cholesterol (as well as other risk factors including hypertension and obesity) and all-cause or cardiovascular mortality (31).

PRIMARY PREVENTION TRIALS — The West of Scotland Coronary Prevention Study and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) comprised only a small number of diabetic patients (1 and 2% of the patients studied, respectively), precluding a meaningful subanalysis of this patient population.

In the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA), 24% of the 19,342 hypertensive patients enrolled had diabetes (32). The proportional effect of atorvastatin on the primary end point of nonfatal MI and fatal CHD did not differ significantly in any prespecified subgroup from that noted overall, although the benefit was not significant in patients with diabetes. However, the absolute number of events among patients with diabetes was small, so the study may have had inadequate power, especially due to the shortened follow-up period (the study was stopped prematurely after a median of 3.3 years' follow-up because of the obvious benefit of atorvastatin). Another issue was the high rate of statin use among patients with diabetes assigned to placebo: 14% compared with 8% in individuals without diabetes. The Collaborative Atorvastatin Diabetes Study (CARDS) is the only diabetes-specific primary prevention trial performed (33). In this trial, 2,838 diabetic patients without CHD, but with at least one other risk factor (hypertension, retinopathy, albuminuria, or smoking), were randomized to 10 mg atorvastatin daily, or placebo. The primary end point was the time to first occurrence of acute CHD events, coronary revascularization, or stroke. The trial was terminated 2 years earlier than expected because the prespecified stopping rule for efficacy had been met. There was a significant relative risk reduction of 37%, with 37 major vas-

cular events prevented per 1,000 people treated for 4 years. Overall mortality was also reduced with atorvastatin, although just failing to reach statistical significance.

INTENSIVE VERSUS MODERATE LIPID LOWERING WITH STATINS

— The PROVE-IT study compared 80 mg atorvastatin to 40 mg pravastatin (LDL cholesterol level achieved, 62 vs. 95 mg/dl, respectively) in patients with acute coronary syndrome (34); 18% of the patients enrolled had diabetes. The benefit of high-dose atorvastatin on the primary composite end point of death from any all-cause mortality, MI, unstable angina, revascularization, and stroke was consistent among the prespecified subgroups, including diabetic patients. The Treating-to-New-Targets (TNT) study compared 80 mg with 10 mg atorvastatin (LDL cholesterol level achieved, 72 vs. 99 mg/dl, respectively), in patients with stable CHD. Of the 10,001 patients enrolled in this study, 5,584 had metabolic syndrome and 1,231 had diabetes (35). High-dose (compared with low-dose) atorvastatin reduced the risk of the primary end point (time to first major cardiovascular event) in diabetic patients, with a relative risk reduction similar to that observed in nondiabetic patients. In the A to Z Trial, which compared early intensive versus a delayed conservative simvastatin treatment in patients with acute coronary syndromes (LDL cholesterol level achieved 63 vs. 77 mg/dl, respectively), 24% of patients had diabetes (36). In this study, the intensive strategy did not significantly reduce the risk for the composite end point of cardiovascular death, nonfatal MI, readmission for acute coronary syndrome, and stroke, and the diabetic subgroup was no exception.

SHOULD ALL DIABETIC PATIENTS BE TREATED WITH A STATIN?

— It has been shown in different populations that a positive log-linear relation exists between blood LDL cholesterol and the risk of CHD, and this association persists well below the range of typical cholesterol levels (37–39).

A large body of data has provided the evidence that LDL lowering with statins, in a variety of populations at risk for CVD, including patients with diabetes, reduced the relative risk for cardiovascular events (39,40). However, it is important to emphasize that treatment decisions should be based not on the reduction in relative risk, but on the reduction of *absolute risk*.

Therefore, in patients with a high absolute cardiovascular risk, even a modest reduction in relative risk provides substantial clinical benefits. In addition, other parameters should also be considered, namely life expectancy, concomitant diseases, and quality of life.

To address the controversy as to whether diabetic patients without vascular disease should be treated in a manner similar to patients with established CHD, the absolute risk for developing CVD in diabetic patients should be clarified. Are risks similar in all diabetic patients? Can we consider all diabetic patients to be CHD-risk equivalents? Is intensive treatment in diabetic patients without CHD more beneficial than moderate treatment?

CARDIOVASCULAR RISK ASSESSMENT OF DIABETIC PATIENTS: IMPLICATIONS IN PRACTICE GUIDELINES

— The NCEP ATP III guidelines recognized the fact that not all diabetic patients are alike (12). The authors chose to consider all diabetic patients to be in the highest-risk category, because of the notion that most seemingly low-risk diabetic patients are younger and do not manifest multiple major risk factors. However, if their risk is projected to age 65 years, the majority will attain a risk of 20%. For example, in the Third National Health and Nutrition Examination Survey (NHANES III), individuals aged 50 years, with both diabetes and metabolic syndrome, had the highest prevalence of CHD (19.2%), compared with individuals with neither condition. Among people with diabetes, the prevalence of metabolic syndrome was extremely high (86%). In the small subset of diabetic patients who did not meet the criteria for metabolic syndrome, the incidence of CHD was only 7.5%, which was comparable to that of individuals with neither diabetes nor metabolic syndrome (8.7%). Furthermore, diabetic patients have an increased case-fatality rate with an MI, and their overall prognosis for survival is far worse once they develop CHD than it is for CHD patients without diabetes, making primary prevention of cardiovascular events extremely important in this patient population. Therefore, an LDL cholesterol goal of <100 mg/dl was set for all patients with diabetes. It is stated that if a patient with diabetes and no CVD is considered to be at lower risk, because of young age or lack of other risk factors, an LDL-lowering drug should not be started if the LDL cholesterol level is <130 mg/dl, depending on clinical judgment.

In the 2004 NCEP report (12), updating the ATP III guidelines, the view of diabetes as a high-risk state was unchanged, and an LDL cholesterol goal of <70 mg/dl was considered optional. The European guidelines took a similar approach, stating that "patients . . . who have diabetes . . . have already declared themselves to be at markedly increased risk" without a need for further risk stratification (23). An LDL cholesterol goal of <100 mg/dl was set, with a goal of <80 mg/dl if feasible. A recent scientific statement by the American Heart Association and the American Diabetes Association took a more cautious approach (41). In individuals with diabetes who are over the age of 40 years, without overt CVD, but with one or more major CVD risk factor (hypertension, low HDL cholesterol levels, smoking, and family history of premature CHD), the primary goal is an LDL cholesterol level <100 mg/dl. If LDL-lowering drugs are used, a reduction of at least 30–40% in LDL cholesterol levels should be obtained. If baseline LDL cholesterol is <100 mg/dl, statin therapy should be initiated on the basis of risk factor assessment and clinical judgment. In individuals with diabetes who are under the age of 40 years, without overt CVD, but who are estimated to be at increased risk of CVD, either by clinical judgment or by risk calculator, the LDL cholesterol goal is <100 mg/dl, and LDL-lowering drugs should be considered if lifestyle changes do not achieve the goal. The Canadian guidelines use a similar approach, stating that most adults with diabetes should be considered at high risk for vascular disease. The exceptions are younger patients with shorter duration of disease and without diabetic complications (including established CVD) and without other CVD risk factors. A computerized risk engine (e.g., UKPDS risk engine, Cardiovascular Life Expectancy Model) can be used to estimate vascular risk (24).

LDL cholesterol lowering with statins has been previously shown to be beneficial with a substantial risk reduction of major vascular events in a wide spectrum of high-risk participants, irrespective of baseline lipid profile or other characteristics, including diabetes. However, a small number of trials recruited diabetic patients exclusively, and other trials did not

enroll a sufficient number of diabetic patients to facilitate prespecified or post hoc analyses of the effect of statins in these patients. In addition, there was scant information about the separate effects of statins on cardiovascular complications and whether the benefits of statin therapy are worthwhile in people with diabetes without a history of clinically manifested vascular disease. A recent meta-analysis addressed these issues and examined the efficacy of statin therapy in 18,686 people with diabetes in 14 randomized trials (39). During a mean follow-up of 4.3 years, statin therapy significantly reduced the risk of all-cause and vascular mortality, major vascular events, MI, coronary revascularization, and stroke. A salient point is that the proportional effect of statin therapy in diabetic patients was similar, irrespective of whether there was a prior history of vascular disease and other baseline characteristics, namely sex, age, hypertension, pretreatment LDL cholesterol levels, other lipid levels, BMI, smoking, and estimated glomerular filtration rate. The authors suggested that the use of standard doses of statins that reduced LDL cholesterol by almost 40% would prevent approximately one-third of patients from experiencing a major vascular event. Moreover, a greater decline in LDL cholesterol levels is expected to further decrease cardiovascular risk, since the benefits were almost linearly related to the absolute reduction in LDL cholesterol, with no threshold below which there was no further benefit. Not surprisingly, evaluation of the outcome of diabetic patients in the placebo arm of this meta-analysis revealed that those with a history of vascular disease had the worst outcome (31.6% risk for major vascular events during 4.3 years of follow-up). The risk for developing a major vascular event was higher in patients with vascular disease without diabetes, compared with diabetic patients without vascular disease (23.5 and 11.8%, respectively), the lowest risk being in patients without diabetes and no vascular disease (8.3%). This indicates that the notion that diabetes is a CHD-risk equivalent cannot be applied to all diabetic patients. The relative risk reduction of major vascular events per millimole per liter reduction in LDL cholesterol in participants with and without diabetes, and with or without a history of vascular disease, was analogous. Despite the fact that the absolute risk of patients with diabetes without vascular disease was lower than nondiabetic patients with vascular disease, the average risk over a 10-year period in those with diabetes, but without vascular disease, would exceed the U.K. National Institute for Health and Clinical Excellence (NICE) threshold of 20% risk at which level these guidelines recommend statin therapy (39).

Although it is recognized that not all patients with diabetes are at risk, which is equivalent to patients who had developed cardiovascular complications, it is our recommendation that all patients with diabetes should be prescribed statin therapy to achieve a reduction in LDL cholesterol by at least 30–40%, to a target goal of <100 mg/dl (2.60 mmol/l). This approach is supported by evidence showing that all diabetic patients are in the highest risk category, and the majority of those considered at lower risk, mostly younger individuals, will attain a risk of 20% over a 20-year period. This seemingly aggressive approach is also justified because primary prevention of cardiovascular complications in diabetic patients is essential because of the high case-fatality rates among individuals who develop cardiovascular complications. Furthermore, this approach simplifies treatment guidelines and potentially will increase treatment rates in this high-risk group. It is important to emphasize that data obtained from a large number of clinical trials have shown that statin-based therapy is relatively safe. Moreover, recent data have shown that some generic statins are cost-effective, and it is expected that within the next few years, more statins will be available in the generic form, which will reduce cost and increase cost-effectiveness.

Acknowledgments— This study was supported by the Talpiot Medical Leadership Program Award, Sheba Medical Center, Tel Hashomer, Israel, and the Sami and Angela Shamoon Vascular Biology Research Fund (to Y.K.).

No potential conflicts of interest relevant to this article were reported.

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