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FPIN's Clinical Inquiries

Statin Therapy in Patients with Type 2 Diabetes

Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (http://www.cebm.net/levels_of_evidence.asp).

This series of Clinical Inquiries is coordinated for American Family Physician by John Epling, M.D., State University of New York Upstate Medical University, Syracuse, N.Y. The complete database of evidence-based questions and answers is copyrighted by FPIN. If you are interested in submitting questions to be answered or writing answers for this series, go to http://www.fpin.org or contact questions@fpin.org.

Clinical Question

Should statin therapy be offered to all patients with type 2 diabetes?

Evidence-Based Answer

Based on current evidence, statin therapy should be offered to all patients with type 2 diabetes who are known to have coronary artery disease.1,2 [Strength of recommendation: A]

For patients older than 40 years with type 2 diabetes who are not known to have cardiovascular disease, statins are recommended if other cardiovascular risk factors are present, regardless of the initial low-density lipoprotein (LDL) level, if the patient has failed to reach the target LDL goal of less than 100 mg per dL (2.6 mmol per L) by lifestyle modification for primary prevention.1-3 [Strength of recommendation: A]

There is no clear evidence to support routine use of statins in patients with type 2 diabetes who are younger than 40 years, who have no cardiovascular risk factors, and who have an LDL level lower than 130 mg per dL (3.4 mmol per L), although that has been suggested by some expert groups. [Strength of recommendation: C]

Evidence Summary

A recent systematic review and meta-analysis1 identified 14 randomized controlled trials of primary and secondary prevention of type 2 diabetes. Six studied primary prevention and eight

studied secondary prevention (i.e., prevention in patients with known heart disease). All but one study in each group used statins. Lipid-lowering agents were more effective than placebo for secondary prevention of any cardiovascular event (absolute risk reduction [ARR]: 7%; 95% confidence interval [CI]: 3 to 12%; number needed to treat [NNT]: 14 for 4.9 years of treatment) (Table 11). This review1 included trials whose participants had diverse pretreatment LDL cholesterol levels. Lipid-lowering medications reduced the risk of any cardiovascular event in patients with diabetes who did not have known heart disease (ARR: 3%; 95% CI: 1 to 4%; NNT: 35 for 4.3 years of treatment).

TABLe 1

Meta-analysis of Six Trials of Statins for Primary Prevention

Trials	CHD event rate, control group, (n/n)	CHD event rate, intervention group, (n/n)	ARR for CHD event (%[95% CI])	NNT
Primary Prevention				
AFCAPS/TexCAPS	6/71	4/84	4 (-4 to 12)	27.1
HHS	8/76	2/59	7 (-1 to 15)	14.0
HPS	367/1,976	276/2,006	5 (3 to 7)	20.8
PROSPER	28/205	32/191	-3 (-10 to 4)	-32.3
ASCOT-LLA	46/1,274	38/1,258	1 (-1 to 2)	169.5
Pooled*			3 (1 to 4)	34.5†
Secondary Prevention				
4S	44/97	24/105	23 (10 to 35)	4.4
CARE	112/304	81/282	8 (1 to 16)	12.3
HPS	381/1,009	325/972	4 (0 to 9)	23.1
LIPID	88/386	76/396	4 (-2 to 9)	27.7
LIPS	31/82	26/120	16 (3 to 29)	6.2
Post-CABG	14/53	9/63	12 (-3 to 27)	8.2
PROSPER	31/115	38/112	-7 (-19 to 5)	-14.3
VA-HIT	116/318	88/309	8 (1 to 15)	12.5
Pooled*			7 (3 to 12)	13.8†

CHD = coronary heart disease; ARR = absolute risk reduction; CI=confidence interval; NNT = number needed to treat; AFCAPS/TexCAPS = Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study; HHS = Helsinki Heart Study; HPS = Heart Protection Study; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm; 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events trial; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease trial; LIPS = Lescol Intervention Prevention Study; Post-CABG= Post-Coronary Artery Bypass Graft trial; VA-HIT = Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial.

*-Pooled estimates generated by using meta-analysis; for primary prevention, there was no heterogeneity between studies, so a fixed-effects model was used; for secondary prevention, there was a substantial between-study heterogeneity (P = .026), so a random-effects model was used.

†-For primary prevention, the NNT for benefit is for 4.3 years; for secondary prevention, the NNT for benefit is for 4.9 years.

Adapted with permission from Vijan S, Hayward RA, for the American College of Physicians. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. Ann Intern Med 2004;140:654.

For primary and secondary prevention, most of the patients came from the Heart Protection Study (HPS).2 HPS was the only individual trial that showed a statistically significant benefit for primary prevention. HPS was a large randomized, placebo-controlled trial of 5,963 patients with type 2 diabetes. Patients ranged in age from 40 to 80 years, had a total cholesterol of at least 135 mg per dL (3.5 mmol per L), and were treated with simvastatin (Zocor) or placebo for an average of 4.8 years (primary prevention was ARR: 5%; 95% CI: 3 to 7%; secondary prevention was ARR: 4%; 95% CI: zero to 9%). HPS found similar relative benefit among those whose pretreatment LDL cholesterol level was below 116 mg per dL (3.0 mmol per L) to those with a higher LDL level.2 The Prospective Study of Pravastatin in the Elderly at Risk trial found a trend toward harm regarding primary and secondary prevention, but it was not statistically significant in either case.3 The meta-analysis did not report the impact of statin therapy on all-cause mortality and cardiovascular mortality because the information was not included in the original study.

The Collaborative Atorvastatin Diabetes Study (CARDS)4 is a recent multicenter, randomized, placebo-controlled trial on the primary prevention of cardiovascular disease in patients with type 2 diabetes that was not included in the above meta-analysis. This study randomized patients with type 2 diabetes who were 40 to 75 years of age with at least one other additional cardiac risk factor (e.g., hypertension, retinopathy, albuminuria, current smoking) and an entry LDL cholesterol level lower than 160 mg per dL (4.1 mmol per L) to either atorvastatin (Lipitor) 10 mg once daily or placebo. The mean LDL cholesterol level was 117 mg per dL (3.0 mmol per L) in the placebo and treatment groups. After a median duration of 3.9 years, ARR = 3.7% of the first occurrence of a major cardiovascular event in the treatment group (NNT: 31 for four years, P = .001).

Recommendations from Others

The American Diabetes Association (ADA) recommends that lipid-lowering therapy be initiated with lifestyle intervention in patients with type 2 diabetes and clinical coronary artery disease. The primary goal for all patients with diabetes is an LDL cholesterol level lower than 100 mg per dL. Furthermore, the ADA recommends that for patients older than 40 years with diabetes, a total cholesterol greater than 135 mg per dL, and without overt cardiovascular disease, statin therapy should be offered to achieve an LDL level reduction of 30 to 40 percent regardless of

baseline LDL levels. For patients younger than 40 years without overt cardiovascular disease but with additional cardiac risk factors, the addition of pharmacologic therapy to ongoing lifestyle modification to reach a target goal of an LDL cholesterol level lower than 100 mg per dL is recommended.5

A recent evidence-based guideline6 from the American College of Physicians recommends that lipid-lowering therapy should be used for all patients with type 2 diabetes and known coronary artery disease. It also recommends that statins should be used for primary prevention against macrovascular complications in all patients with type 2 diabetes and other cardiovascular risk factors.

The National Cholesterol Education Project (NCEP) Adult Treatment Panel III guideline7 recommends that patients with diabetes and cardiovascular disease should initiate statin therapy regardless of baseline LDL cholesterol levels. For patients in this high-risk group, statins are a therapeutic option to achieve a low LDL cholesterol level (i.e., lower than 70 mg per dL [1.8 mmol per L]).7 This recommendation is endorsed by the ADA.7 However, for patients with diabetes who have no known cardiovascular disease and an LDL cholesterol level lower than 116 mg per dL, NCEP recommends that initiation of a lipid-lowering medication should be an option based on the clinical judgment of the physician.7

Clinical Commentary

Evidence from recent clinical trials has given physicians a new opportunity to reduce cardiovascular morbidity and mortality in patients with type 2 diabetes. For patients with type 2 diabetes, there is compelling evidence for aggressive lipid lowering in addition to tight blood pressure and glycemic control with statin therapy. A recent cost-effectiveness study based on a cardiovascular disease life-expectancy model with the assumed benefit of statin therapy from the Scandinavian Simvastatin Survival Study8 suggests that among men and women with diabetes but no cardiovascular disease, lipid therapy with a statin is likely to be as cost-effective as treating individuals with cardiovascular disease who do not have diabetes. The study estimated the cost ranges from $5,063 to $23,792 per year of life saved.9 Although more evidence is needed to support a universal recommendation of statin therapy for all patients with type 2 diabetes and without clinical cardiovascular disease, it is clear that most patients with diabetes probably benefit to some extent from lipid-lowering therapy.

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