**National Quality Forum—Evidence (subcriterion 1a)**

**Measure Title**: Adherence to Statins for Individuals with Diabetes Mellitus

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** Not applicable

**Date of Submission**: 1/31/2014

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| **Instructions**  *For composite performance measures:*  *A separate evidence form is required for each component measure unless several components were studied together.*  *If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.*   * Respond to all questions as instructed with answers immediately following the question. All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of *supplemental* materials may be submitted, but there is no guarantee it will be reviewed. * If you are unable to check a box, please highlight or shade the box for your response. * Maximum of 10 pages (*includes questions/instructions*; minimum font size 11 pt; do not change margins). ***Contact NQF staff if more pages are needed.*** * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

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| **Note: The information provided in this form is intended to aid the Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**  **Subcriterion 1a.** **Evidence to Support the Measure Focus**  The measure focus is a health outcome or is evidence-based, demonstrated as follows:   * Health outcome:[**3**](#Note3) a rationale supports the relationship of the health outcome to processes or structures of care. * Intermediate clinical outcome, Process,[**4**](#Note4) or Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence[**5**](#Note5)that the measure focus leads to a desired health outcome. * Patient experience with care: evidence that the measured aspects of care are those valued by patients and for which the patient is the best and/or only source of information OR that patient experience with care is correlated with desired outcomes. * Efficiency:[**6**](#Note6) evidence for the quality component as noted above.   **Notes**  **3.** Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.  **4.** Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement.  **5.** The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions](http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm) and [methods](http://www.uspreventiveservicestaskforce.org/methods.htm), or Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org/publications/index.htm).  **6.** Measures of efficiency combine the concepts of resource use and quality (NQF’s [Measurement Framework: Evaluating Efficiency Across Episodes of Care](http://www.qualityforum.org/Publications/2010/01/Measurement_Framework__Evaluating_Efficiency_Across_Patient-Focused_Episodes_of_Care.aspx); [AQA Principles of Efficiency Measures](http://www.aqaalliance.org/files/PrinciplesofEfficiencyMeasurementApril2006.doc)). |

**1a.1.This is a measure of**:

Outcome

☐ Health outcome: Click here to name the health outcome

*Health outcome includes patient-reported outcomes (PRO, i.e., HRQoL/functional status, symptom/burden, experience with care, health-related behaviors)*

X Process: Adherence to chronic medications

☐ Structure: **Click here to name the structure**

☐ Other: Click here to name what is being measured

**HEALTH OUTCOME PERFORMANCE MEASURE** *If not a health outcome, skip to* [*1a.3*](#Section1a3)

**1a.2.** **Briefly state or diagram the linkage between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.**

**1a.2.1.** **State the rationale supporting the relationship between the health outcome (or PRO) and at least one healthcare structure, process, intervention, or service**.

*Note: For health outcome performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.*

**intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measure**

**1a.3.****Briefly state or diagram the linkages between structure, process, intermediate outcome, and health outcomes**. **Include all the steps between the measure focus and the health outcome.**

The measure focus is on adherence to statins among patients with diabetes mellitus.[[1]](#footnote-1) Good adherence, defined as a PDC of 0.8 or higher, to statins is expected to lead to a reduction in adverse patient outcomes and other outcomes as follows:

Links of Process 🡪 Health Outcome

Improved communication and education regarding adherence to statins 🡪

Higher rates of good adherence to statins among persons with diabetes 🡪

Lower blood cholesterol levels 🡪

Fewer cardiovascular events 🡪

Lower hospitalization rates, lower healthcare costs, and lower mortality rates

Summary

The desired outcome for this measure is better adherence to statins among individuals with diabetes mellitus. Better adherence should result in a higher likelihood of blood cholesterol levels remaining in the normal range, resulting in fewer cardiovascular events and thus, fewer hospitalizations, lower costs, and fewer deaths.

**1a.3.1.** **What is the source of the systematic review of the body of evidence that supports the performance measure?**

X Clinical Practice Guideline recommendation – ***complete sections*** [***1a.4***](#Section1a4)***, and*** [***1a.7***](#Section1a7)

☐ US Preventive Services Task Force Recommendation – ***complete sections*** [***1a.5***](#Section1a5) ***and*** [***1a.7***](#Section1a7)

X Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*) – ***complete sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)

X Other – ***complete section*** [***1a.8***](#Section1a8)

*Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.*

**1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION**

**1a.4.1.** **Guideline citation** (*including date*) and **URL for guideline** (*if available online*):

American Diabetes Association (ADA). (2013). Standards of Medical Care in Diabetes—2013. *Diabetes Care, 36*(Supplement 1), S11-S66.

<http://care.diabetesjournals.org/content/36/Supplement_1/S11.full>

Handelsman, Y., Mechanick, J., Blonde, L., Grunberger, G., Bloomgarden, Z., Bray, G., . . . Wyne, K. (2011). American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan. *Endocrine Practice, 17*(Suppl 2), 1-53.

[https://www.aace.com/files/dm-guidelines-ccp.pdf](https://pghconnect.rand.org/owa/,DanaInfo=randmail.rand.org,SSL+redir.aspx?C=921725b5ff224de4ab73986a03f26b72&URL=https%3a%2f%2fwww.aace.com%2ffiles%2fdm-guidelines-ccp.pdf)

Stone, N. J., Robinson, J., Lichtenstein, A. H., Merz, C. N. B., Blum, C. B., Eckel, R. H., . . . Wilson, P. W. F. (2013). 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. Advance online publication. doi:10.1016/j.jacc.2013.11.002.

<http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a>

**1a.4.2.** **Identify guideline recommendation number and/or page number** and **quote verbatim, the specific guideline recommendation**.

The measure is supported by recommendations in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (Stone et al., 2013), American Diabetes Association’s "Standards of Medical Care in Diabetes—2013" ([American Diabetes Association, 2013](#_ENREF_1)) and in the "Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan" by the American Association of Clinical Endocrinologists (Handelsman et al., 2011). Although the guidelines do not address the topic of medication adherence directly, recommendations regarding the use of a medication imply that the patient is taking the medication regularly.

**2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults guideline recommendations concerning " Primary Prevention in Individuals With Diabetes Mellitus and LDL–C 70-189 mg/dL" (Stone et al., 2013):**

(page 23)

1. Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. (Class I; A-Strong)

2. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. (Class IIa; E-Expert Opinion)

3. In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. (Class IIa; E-Expert Opinion)

**2013 American Diabetes Association guideline recommendations concerning "Dyslipidemia/lipid management" (**[**American Diabetes Association, 2013**](#_ENREF_1)**):**

(page S31) Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients:

* with overt CVD. (A)
* without CVD who are over the age of 40 years and have one or more other CVD risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (A)

(page S31) For lower-risk patients than the above (e.g., without overt CVD and under the age of 40 years), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains above 100 mg/dL or in those with multiple CVD risk factors. (C)

(page S34) In patients with known CVD, consider ACE inhibitor therapy (C) and use aspirin and statin therapy (A) (if not contraindicated) to reduce the risk of cardiovascular events. In patients with a prior MI, β-blockers should be continued for at least 2 years after the event. (B)

**American Association of Clinical Endocrinologists (AACE) guideline recommendations (Handelsman et al., 2011) about "Dyslipidemia" in section 3.Q11.3. on page 13:**

R41. All patients with DM should be screened for dyslipidemia (**Grade A; BEL 1**). Therapeutic recommendations should include therapeutic lifestyle changes and, as needed, consultation with a registered dietitian and/or CDE (**Grade A; BEL 1**). Pharmacologic therapy is used to achieve targets unresponsive to therapeutic lifestyle changes alone. LDL-C is the primary target for therapy. Statins are the treatment of choice in the absence of contraindications. Combinations of statins (**Grade A; BEL 1**) with bile acid sequestrants, niacin, and/or cholesterol absorption inhibitors should be considered in situations of inadequate goal attainment. These agents may be used instead of statins in cases of statin-related adverse events or intolerance (**Grade A; BEL 2**). In patients with LDL-C at goal, but with triglyceride concentrations of 200 mg/dL or higher or low HDL-C (<35 mg/dL), treatment protocols including the use of fibrates or niacin are used to achieve non–HDL-C goal (<100 mg/dL when at highest risk; <130 mg/dL when at high risk) (**Grade A; BEL 1**). Apolipoprotein B targets are less than 80 mg/dL in patients with CVD and less than 90 mg/dL in patients without CVD.

**1a.4.3.** **Grade assigned to the quoted recommendation with definition of the grade:**

The following is a complete set of definitions that apply to the grades used for the recommendations in 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults guideline recommendations concerning "Primary Prevention in Individuals With Diabetes Mellitus and LDL–C 70-189 mg/dL" (Stone et al., 2013) listed in Section 1a.4.2. above:

Size of Treatment Effect:

Class I = Benefit >>> Risk. Procedure/Treatment SHOULD be performed/administered.

Class IIa = Benefit >> Risk. Additional studies with focused objectives needed. IT IS REASONABLE to perform procedure/administer treatment.

Class IIb = Benefit ≥ Risk. Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/Treatment MAY BE CONSIDERED.

Class III No Benefit = Procedure/Test is not helpful. Treatment has no proven benefit.

Class III Harm = Procedure/Test entails excess cost without benefit or is harmful. Treatment is harmful to patients.

Certainty (Precision) of Treatment Effect:

Level A = Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses.

Level B = Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.

Level C = Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care.

For each recommendation in the "Standards of Medical Care in Diabetes--2013" by the American Diabetes Association (American Diabetes Association, 2013), the level of evidence is defined as follows:

A level of evidence of "A" for the ADA recommendations is defined as:

* Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including:
  + Evidence from a well-conducted multicenter trial
  + Evidence from a meta-analysis that incorporated quality ratings in the analysis
* Compelling nonexperimental evidence, i.e., “all or none” rule developed by the Centre for Evidence-Based Medicine at the University of Oxford
* Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:
  + Evidence from a well-conducted trial at one or more institutions
  + Evidence from a meta-analysis that incorporated quality ratings in the analysis

A level of evidence of “B” for the ADA recommendations is defined as:

* Supportive evidence from well-conducted cohort studies
  + Evidence from a well-conducted prospective cohort study or registry
  + Evidence from a well-conducted meta-analysis of cohort studies
* Supportive evidence from a well-conducted case-control study

A level of evidence of “C” for the ADA recommendations is defined as:

* Supportive evidence from poorly controlled or uncontrolled studies
  + Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
  + Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)
  + Evidence from case series or case reports
* Conflicting evidence with the weight of evidence supporting the recommendation

A level of evidence of "E" for the ADA recommendations is defined as:

* Expert consensus or clinical experience

For each recommendation in the "Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan " by the American Association of Clinical Endocrinologists (Handelsman et al., 2011), the level of evidence is defined as follows:

"Recommendations (labeled “R”) are based on importance and evidence (Grades A, B, and C) or expert opinion when there is a lack of conclusive clinical evidence (Grade D). The best evidence level (BEL), which corresponds to the best conclusive evidence found in the Appendix to follow, accompanies the recommendation grade in this Executive Summary; definitions of evidence levels are provided in…Table 1. There are 4 intuitive levels of evidence: 1 = strong, 2 = intermediate, 3 = weak, and 4 = no evidence…."

The footnote in Table 2 (identified as Table 3 in the guidelines) describes how the various factors are used to grade the recommendation.

**Table 1. 2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step I: Evidence Rating a**

|  |  |
| --- | --- |
| **Numerical descriptor (evidence level)b** | **Semantic descriptor (reference methodology)** |
| 1 | Meta-analysis of randomized controlled trials (MRCT) |
| 1 | Randomized controlled trials (RCT) |
| 2 | Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT) |
| 2 | Nonrandomized controlled trial (NRCT) |
| 2 | Prospective cohort study (PCS) |
| 2 | Retrospective case-control study (RCCS) |
| 3 | Cross-sectional study (CSS) |
| 3 | Surveillance study (registries, surveys, epidemiologic study, retrospective chart  review, mathematical modeling of database) (SS) |
| 3 | Consecutive case series (CCS) |
| 3 | Single case reports (SCR) |
| 4 | No evidence (theory, opinion, consensus, review, or preclinical study) (NE) |

a Table from Handelsman et al. (2011)

b 1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; and 4 = no evidence

**Table 2. 2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step III: Grading of Recommendations; How Different Evidence Levels Can Be Mapped to the Same Recommendation Grade** a,b

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Best evidence level (BEL)** | **Subjective factor impact** | **Two-thirds consensus** | **Mapping** | **Recommendation grade** |
| 1 | None | Yes | Direct | A |
| 2 | Positive | Yes | Adjust up | A |
|  |  |  |  |  |
| 2 | None | Yes | Direct | B |
| 1 | Negative | Yes | Adjust down | B |
| 3 | Positive | Yes | Adjust up | B |
|  |  |  |  |  |
| 3 | None | Yes | Direct | C |
| 2 | Negative | Yes | Adjust down | C |
| 4 | Positive | Yes | Adjust up | C |
|  |  |  |  |  |
| 4 | None | Yes | Direct | D |
| 3 | Negative | Yes | Adjust down | D |
|  |  |  |  |  |
| 1, 2, 3, 4 | NA | No | Adjust down | D |

a Starting with the left column, best evidence levels (BELs), subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact (“none”), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up (“positive” impact) or down (“negative” impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. NA, not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).

b Table from Handelsman et al. (2011).

**1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

All grades for the ACC/AHA Guideline (Stone et al., 2013), for the ADA guideline (American Diabetes Association, 2013) and for the AACE guideline (Handelsman et al., 2011) are defined under 1a.4.3.

**1a.4.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.4.1*)**:**

The citation and URL for the methodology for grading recommendations presented in the "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults " (Stone et al., 2013) are listed in Section 1a.4.1., above.

The citation and URL for the methodology for grading recommendations presented in the "Standards of Medical Care in Diabetes-2013" (American Diabetes Association, 2013) are listed in Section 1a.4.1., above.

The citation and URL for the methodology for grading the AACE recommendations are as follows:

Mechanick, J., Camacho, P., Cobin, R., Garber, A., Garber, J., Gharib, H., . . .Trence, D. (2010). American Association of Clinical Endocrinologists Protocol for Standardized Production of Clinical Practice Guidelines—2010 update. *Endocrine Practice. 16*, 270-283.

<https://www.aace.com/files/gl-standards.pdf>

**1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?**

☐ Yes **→ *complete section*** [***1a.7***](#Section1a7)

XNo **→ *report on another systematic review of the evidence in sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)***; if another review does not exist, provide what is known from the guideline review of evidence in*** [***1a.7***](#Section1a7)

**1a.5.** **UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

**1a.5.1.** **Recommendation citation** (*including date*) and **URL for recommendation** (*if available online*):

**1a.5.2.** **Identify recommendation number and/or page number** and **quote verbatim, the specific recommendation**.

**1a.5.3.** **Grade assigned to the quoted recommendation with definition of the grade**:

**1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: the* *grading system for the evidence should be reported in section 1a.7.*)

**1a.5.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.5.1*)**:**

**1a.6. OTHER SYSTEMATIC REVIEW OF THE BODY OF EVIDENCE**

**1a.6.1.** **Citation** (*including date*) and **URL** (*if available online*):

Cholesterol Treatment Trialists’ (CTT) Collaboration. (2010). Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *The* *Lancet, 376*, 1670-1681. doi: 10.1016/S0140-6736(10)61350-5

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2810%2961350-5/fulltext

**1a.6.2.** **Citation and** **URL for methodology for evidence review and grading** (*if different from 1a.6.1*)**:**

Cholesterol Treatment Trialists’ (CTT) Collaboration. (1995). Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. *American Journal of Cardiology, 75*(16), 1130-1134.

<http://www.sciencedirect.com/science/article/pii/S0002914999807449>

**1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE supporting the measure**

**1a.7.1.** **What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?**

The authors examined risks of cause-specific mortality, major coronary events, coronary revascularization, strokes, and new cancer diagnoses associated with more intensive versus standard statin regimens. Two meta-analyses were conducted, one that compared more versus less intensive statin therapy based on 5 randomized controlled trials, and another that compared statin therapy versus control based on 21 randomized controlled trials.

**1a.7.2.** **Grade assigned for the quality of the quoted evidence with definition of the grade**:

There was no grade assigned for the quality of quoted evidence.

**1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.**

Because there was no grade assigned for the quality of quoted evidence, this information is not available.

**1a.7.4.** **What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range**: 1988-2008

**QUANTITY AND QUALITY OF BODY OF EVIDENCE**

**1a.7.5.****How many and what type of study designs are included in the body of evidence**? (*e.g., 3 randomized controlled trials and 1 observational study*)

All 26 studies included in the meta-analysis were randomized controlled trials. Three of the trials were limited to diabetic patients exclusively, although every trial included some diabetic patients.

**1a.7.6.** **What is the overall quality of evidence across studies in the body of evidence**? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)

PROPORTION OF PATIENTS WITH DIABETES

In the 26 trials, the proportion of patients with diabetes ranged from 0.4% ([Ridker et al., 2008](#_ENREF_3_5)) to 100% ([Colhoun et al., 2004](#_ENREF_3_1); [Knopp, d’Emden, Smilde, & Pocock, 2006](#_ENREF_3_3); [Wanner et al., 2005](#_ENREF_3_7)). In total, 32,210 (19%) of the 169,138 patients in all 26 trials combined had a diabetes diagnosis.

DEMOGRAPHICS AND MEDICAL HISTORY OF STUDY SAMPLES

The proportion of women in each study ranged from 0% ([Shepherd et al., 1995](#_ENREF_3_6)) to 68% ([Nakamura et al., 2006](#_ENREF_3_4)). Almost 27% (N=45,495) of all patients in the studies were women. Twelve of the 26 studies examined only patients with prior coronary heart disease (CHD) and another 5 study samples included a small percentage of patients (≤5%) with prior CHD.

MEASURES OF ADHERENCE

Levels of patient adherence to statins in the 26 trials are not reported in the meta-analysis (CTTC, 2010). Instead, patients are assigned by their study group in the meta-analysis; this would mean they were assigned to the "more" or "less" group in the trials of more versus less intensive statin therapy, or to the "treatment" or "control" group in the trials of statin versus control).

MEAN AGE AND SIZE OF STUDY SAMPLES

In the 26 trials, the mean age of participants ranged from 49 to 75 years. The total number of trial participants in the 26 trials ranged from 1,255 patients ([Wanner et al., 2005](#_ENREF_3_7)) to 20,536 patients ([Heart Protection Study Collaborative Group, 2002](#_ENREF_3_2)).

TYPES OF ADVERSE EVENTS

The following types of adverse events were included in the 26 studies:

* Major vascular events: 26 studies
* Major coronary events: 26 studies
* Coronary revascularization: 26 studies
* Stroke: 24 studies
* Cancer: 26 studies

LIMITATIONS

Although randomized controlled trials are typically seen as the gold standard of evidence, the lack of inclusion of other types of studies in this review may make its conclusions somewhat less generalizable. The tight control and close monitoring of a randomized controlled trial may not translate into actual clinical practice. For example, patients enrolled in a randomized controlled trial may take their statin medications at a rate higher than that of patients outside of a clinical trial.

Citations for 1a.7.6.

Colhoun, H. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., W Neil, H. A., Livingstone, S. J., . . . Fuller, J. H. (2004). Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *The Lancet, 364*(9435), 685-696.

Heart Protection Study Collaborative Group. (2002). Medical Research Council (MRC)/ British Heart Foundation (BHF) Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. The *Lancet, 360*(9326), 7-22.

Knopp, R. H., d’Emden, M., Smilde, J. G., & Pocock, S. J. (2006). Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). *Diabetes Care, 29*(7), 1478-1485.

Nakamura, H., Arakawa, K., Itakura, H., Kitabatake, A., Goto, Y., Toyota, T., . . . Ohashi, Y. (2006). Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *The Lancet, 368*(9542), 1155-1163.

Ridker, P. M., Danielson, E., Fonseca, F., Genest, J., Gotto Jr, A. M., Kastelein, J., . . . Glynn, R. J. (2008). Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New England Journal of Medicine, 359*(21), 2195-2207.

Shepherd, J., Cobbe, S. M., Ford, I., Isles, C. G., Lorimer, A. R., Macfarlane, P. W., . . . Packard, C. J. (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine, 333*(20), 1301-1308.

Wanner, C., Krane, V., März, W., Olschewski, M., Mann, J. F., Ruf, G., & Ritz, E. (2005). Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *New England Journal of Medicine, 353*(3), 238-248.

**ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE**

**1a.7.7.** **What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence**? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*)

To estimate the efficacy of intensive lowering of LDL cholesterol with statin therapy, this meta-analysis (CTTC, 2010) combined individual participant data from 26 trials. The average risk reduction and the average risk reduction per 1.0 mmol/L LDL cholesterol reduction were calculated for multiple adverse outcomes. Based on the results from the meta-analysis, the authors concluded, "Across all 26 trials, all-cause mortality was reduced by 10% per 1.0 mmol/L LDL reduction (RR 0.90, 95% CI 0.87–0.93; p<0.0001), largely reflecting significant reductions in deaths due to coronary heart disease (RR 0.80, 99% CI 0.74–0.87; p<0·0001) and other cardiac causes (RR 0.89, 99% CI 0.81–0.98; p=0.002), with no significant effect on deaths due to stroke (RR 0.96, 95% CI 0.84–1.09; p=0.5) or other vascular causes (RR 0.98, 99% CI 0.81–1.18; p=0.8)."

**1a.7.8.** **What harms were studied and how do they affect the net benefit (benefits over harms)?**

To address the possibility that intensive lowering of LDL cholesterol may result in adverse health effects, pre-specified outcomes of the trials were analyzed in the meta-analysis; these included incident cases of cancer, and non-vascular causes of death (i.e., cancer, respiratory, trauma, and other) (CTTC, 2010). Based on the meta-analysis of the 26 trials, the authors concluded, "No significant effects were observed on deaths due to cancer or other non-vascular causes (RR 0.97, 95% CI 0.92–1.03; p=0.3) or on cancer incidence (RR 1.00, 95% CI 0.96–1.04; p=0.9), even at low LDL cholesterol concentrations."

**UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE**

**1a.7.9.** **If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review**.

**1a.8 OTHER SOURCE OF EVIDENCE**

*If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.*

In this section, we summarize the findings of three recent studies on the relationship between adherence of patients with diabetes to statins and patient outcomes and resource use.

**1a.8.1** **What process was used to identify the evidence?**

Three studies were identified using hand searches of reference lists of relevant clinical practice guidelines and other relevant articles and Web of Science citation searches of key articles. The abstracts and/or full-text articles from both types of searches were reviewed to identify those studies that addressed the relationship between adherence to statins among patients with diabetes mellitus and patient outcomes and/or resource utilization. The three selected studies met the following criteria: the study measured adherence to statins among patients with diabetes mellitus; the study reported patient outcomes, hospitalization rates, and/or resource use in subgroups defined by adherence levels; and the study was published in the last 10 years.

**1a.8.2.** **Provide the citation and summary for each piece of evidence.**

Consistency and Magnitude of Evidence

Three studies of adherence to statins among patients with diabetes mellitus focused on outcomes. In a study by Ho et al. (2006), nonadherence to statins was associated with increased risk for all-cause hospitalization (OR, 1.39, 95% CI 1.18-1.63) and all-cause mortality (OR, 2.07, 95% CI 1.54-2.80). In another study, a 10% increase in CMG for statins was significantly associated with an increase of 4.9 mg/dL in LDL cholesterol levels ([Pladevall et al., 2004](#_ENREF_38)). A PDC of ≥80% for statins was associated with a lower risk for major coronary events in patients with prior CHD (AOR 0.84, 95% CI 0.74-0.95) ([Ruokoniemi et al., 2011](#_ENREF_44)).

Detailed Results of Studies

[Ho et al. (2006](#_ENREF_27)): In this retrospective cohort study of 11,532 patients with diabetes mellitus being seen in a managed care organization (mean age 62-66 years), medication nonadherence to statins was found to be associated with adverse outcomes. Patients enrolled in the diabetes registry as of September 2002 through the end of 2003 were included, and patient adherence based on automated pharmacy records was assessed during 2003. Outcomes were assessed from January 2004 through April 2005. Patient medication adherence was defined as a minimum of 240 days (80%) and a maximum of 365 days (100%). Nonadherence for statins was associated with increased risk for all-cause hospitalization (OR, 1.39; 95% CI 1.18-1.63) and all-cause mortality (OR 2.07; 95% CI 1.54-2.80).

[Pladevall et al. (2004](#_ENREF_38)): In this retrospective study of 677 patients aged 18 and older (mean age 64 years), nonadherent patients experienced more adverse outcomes than adherent patients. Patients with a diagnosis of diabetes, hypertension, and dyslipidemia during the period of 1999 to 2001 and at least one prescription drug claim for an antidiabetic, lipid-lowering, or antihypertensive drug in those years were included. Health plan, administrative, and clinical data were used to identify patients. Nonadherence was measured for three classes of drugs: metformin, statins, and ACE inhibitors. Patients were classified as nonadherent when the percentage of the continuous measure of medication gaps (CMG) was 20% or higher. The nonadherence rate was 36% for statins. Average levels of outcomes were significantly higher in nonadherent patients compared to adherent patients. A 10% increase in CMG for statins was significantly associated with an increase of 4.9 mg/dL in LDL cholesterol.

[Ruokoniemi et al. (2011](#_ENREF_44)): In this case-control study of 3,513 major coronary event (MCE) cases (mean age 62-66 years), good statin adherence was associated with a reduced incidence of MCE. Data were obtained from health databases about diabetic patients aged 45 to 75 who initiated statin therapy between 1995 and 2007. Adherence was defined as a PDC of 80%. Of the 60,677 patients included in the cohort, 2,031 patients with MCE without prior cardiovascular heart disease were matched with 15,886 controls. Patients with good adherence had a reduced incidence of MCEs, both in those with prior CHD (AOR 0.84, 95% CI 0.74-0.95) and those without prior CHD (AOR 0.86; 95% CI 0.78-0.95). When considering age, good adherence to statins among those with prior CHD was associated with a lower risk for MCEs only in patients aged 65 and older (AOR 0.79; 95% CI 0.65-0.95). When PDC was divided into three groups (<40%, 40-79%, and ≥80%), MCE incidence decreased as PDC increased. For each 10% unit increase in PDC, the incidence of MCEs decreased by 3% in both risk groups (with and without prior CHD) (AOR 0.97 per 10% units).

Summary of Recently Published Studies

Regarding the certainty or confidence in the estimates of benefits and harms to patients across studies in the body of evidence resulting from study factors, (a) study design/flaws, (b) directness/indirectness of the evidence to this measure, and (c) impression/wide confidence intervals due to few patients or events are addressed below.

Study Design/Flaws

We identified three recent studies that measured the association between adherence to statins among patients with diabetes mellitus to patient outcomes. The results of these studies are summarized above under "Detailed Results of Studies." The methodological quality of the body of evidence in this section was judged from the published articles about these studies. Of the three studies described above, two are retrospective cohort studies based on claims data ([Pladevall et al., 2004](#_ENREF_38)), or automated pharmacy data ([Ho et al., 2006](#_ENREF_27)); and the other is a case-control study using claims data ([Ruokoniemi et al., 2011](#_ENREF_44)). None of the studies was a randomized controlled trial; however, all of them controlled for confounders in estimating the association between adherence and patient outcomes or resource use. Different settings were represented by the studies: members of a managed care organization ([Ho et al., 2006](#_ENREF_27)); and an integrated delivery group ([Pladevall et al., 2004](#_ENREF_38)).

Directness of the Evidence

Measures of adherence and adherence thresholds used in the three studies were the percentage (or proportion) of days covered (PDC) with an 80% threshold ([Ho et al., 2006](#_ENREF_27); [Ruokoniemi et al., 2011](#_ENREF_44)), and a continuous measure of medication gaps (CMG) using a mean value ([Pladevall et al., 2004](#_ENREF_38)). All three studies restricted the study sample to patients with diabetes mellitus. In addition, the studies reported outcomes for adherent and nonadherent patients, using the adherence measures and thresholds listed in this paragraph. The three studies of statins focused on a variety of outcomes: all-cause hospitalization and all-cause mortality (Ho et al., 2006); LDL cholesterol levels ([Pladevall et al., 2004](#_ENREF_38)); and major coronary events ([Ruokoniemi et al., 2011](#_ENREF_44)). The evidence from these studies is directly relevant to the focus of the measure and target population. The focus of the three studies and of the measure is on adherence of adult patients with diabetes mellitus to statins.

Age Distributions of Study Samples

The target population of the proposed measure is all persons 18 years of age and older. In the three studies from the literature, all patients were 18 years of age and older. The mean ages of subgroups in the three studies were 65 years (Ho et al., 2006); 64 years (Pladevall et al., 2004) and 63 years ([Ruokoniemi et al., 2011](#_ENREF_44)).

Possible Imprecision

In the two studies, the sample sizes for patients with diabetes who were taking statins ranged from 677 ([Pladevall et al., 2004](#_ENREF_38)) to 23,603 ([Ruokoniemi et al., 2011](#_ENREF_44)).

Citations for Other Sources of Evidence

Ho, P., Rumsfeld, J., Masoudi, F., McClure, D., Plomondon, M., Steiner, J., & Magid, D. (2006). Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Archives of Internal Medicine, 166*, 1836-1841.

Pladevall, M., Williams, L., Potts, L., Divine, G., Xi, H., & Lafata, J. (2004). Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. *Diabetes Care, 27*(12), 2800-2906.

Ruokoniemi, P., Korhonen, M., Hellin-Salmivaara, J., Lavikainen, P., Jula, A., Junnila, S., . . . Huupponen, R. (2011). Statin adherence and the risk of major coronary events in patients with diabetes: A nested case–control study. *British Journal of Pharmacology, 71*(5), 766-776.

1. The measure applies only to patients with type 2 diabetes. Therefore, the content of the form also focuses on patients with type 2 diabetes. [↑](#footnote-ref-1)