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

**Measure Title**: Adherence to ACEIs/ARBs 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 ACEIs/ARBs among patients with diabetes mellitus.[[1]](#footnote-1) Good adherence, defined as a PDC of 0.8 or higher, to these medications 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 ACEIs/ARBs 🡪

Higher rates of good adherence to ACEIs/ARBs among persons with diabetes 🡪

Lower blood pressure 🡪

Fewer cardiovascular events 🡪

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

Summary

The desired outcomes for this measure are better adherence to ACEIs/ARBs among individuals with diabetes mellitus. Better adherence should result in a higher likelihood of blood pressure 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)

☐ 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>

James, P. A., Oparil, S., Carter, B. L., Cushman, W. C., Dennison-Himmelfarb, C., Handler, J., . . . Ortiz, E. (2013). 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). *Journal of the American Medical Association.* doi: 10.1001/jama.2013.284427

URL: [http://jama.jamanetwork.com/article.aspx?articleid=1791497](https://pghconnect.rand.org/owa/,DanaInfo=randmail.rand.org,SSL+redir.aspx?C=b7dac7637a5a43a8ba3093fb5cdeb9eb&URL=http%3a%2f%2fjama.jamanetwork.com%2farticle.aspx%3farticleid%3d1791497)

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)

**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 American Diabetes Association’s "Standards of Medical Care in Diabetes—2013" ([American Diabetes Association, 2013](#_ENREF_1)), 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), and in the 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) (James et al., 2014). Although the guidelines do not address the topic of adherence to ACEIs/ARBs directly, recommendations regarding the use of a medication imply that the patient is taking the medication regularly. The ADA guideline offers recommendations regarding use of ACEIs/ARBs on pages S29 and S34. The AACE guideline offers recommendations regarding use of ACEIs/ARBs on page 13. The JNC 8 guideline offers recommendations regarding use of ACEIs/ARBs on page E5.

**2013 American Diabetes Association guideline recommendations concerning "Hypertension/blood pressure control":**

(page S29) Patients [with diabetes] with confirmed blood pressure ≥140/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. (B)

(page S29) Pharmacological therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted. (C)

(page S34) In patients with [diabetes and] 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)

(page S34) In the treatment of the nonpregnant patient [with diabetes] with modestly elevated (30–299 mg/day) (C) or higher levels (≥300 mg/day) of urinary albumin excretion (A), either ACE inhibitors or ARBs are recommended.

**American Association of Clinical Endocrinologists (AACE) guideline recommendations (Handelsman et al., 2011) about "Hypertension" in section 3.Q11.2. on page 13:**

R40. Therapeutic recommendations for hypertension should include lifestyle modification to include DASH diet (Dietary Approaches to Stop Hypertension), in particular reduced salt intake, physical activity, and, as needed, consultation with a registered dietician and/or CDE (**Grade A; BEL 1**). Pharmacologic therapy is used to achieve targets unresponsive to therapeutic lifestyle changes alone. Initially, antihypertensive agents are selected on the basis of their ability to reduce blood pressure and to prevent or slow the progression of nephropathy and retinopathy; angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are considered the preferred choice in patients with DM (**Grade D; BEL 4**). The use of combination therapy is likely required to achieve blood pressure targets, including calcium channel antagonists, diuretics, combined a/b-adrenergic blockers, and newer-generation b-adrenergic blockers in addition to agents that block the renin-angiotensin system (**Grade A; BEL 1**).

**2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) (James et al.. 2013)**

(page E5)

Recommendation 5: In the population aged ≥18years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140mm Hg or DBP ≥90mmHg and treat to a goal SBP <140mmHg and goal DBP <90mmHg. (Expert Opinion –Grade E)

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

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).

For each recommendation in the: 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)" (James et al., 2013), the strength of recommendation is defined as follows:

* A: Strong Recommendation. There is high certainty based on evidence that the net benefit is substantial.
* B: Moderate Recommendation. There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.
* C: Weak Recommendation. There is at least moderate certainty based on evidence that there is a small net benefit.
* D: Recommendation against. There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.
* E: Expert Opinion (“There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.”) Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
* N: No Recommendation for or against (“There is insufficient evidence or evidence is unclear or conflicting.”) Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the committee thought no recommendation should be made. Further research is recommended in this area.

**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 ADA guideline (American Diabetes Association, 2013), for the AACE guideline (Handelsman et al., 2011), and for the JNC 8 Guideline for Management of High Blood Pressure (James et al., 2013) are defined under 1a.4.3.

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

Methodology for Development of the American Diabetes Association Guideline

The citation and URL for the methodology for grading recommendations (American Diabetes Association, 2013) are listed in Section 1a.4.1., above.

Methodology for Development of the American Association of Clinical Endocrinologists Guideline

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>

Methodology for Development of the JNC 8 Guideline for Management of High Blood Pressure

The citation and URL for the methodology for grading recommendations (James et al., 2013) are listed in Section 1a.4.1. above.

**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)?**

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

☐No **→ *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*):

Blood Pressure Lowering Treatment Trialists' Collaboration. (2005). Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Archives of Internal Medicine, 165*(12), 1410-1419.

<http://archinte.jamanetwork.com/article.aspx?articleid=486624>

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

The citation and URL for the methodology used in the evidence review (Blood Pressure Lowering Treatment Trialists' Collaboration, 2005) are the same as those provided in 1a.6.1.

**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 review addresses the effects of blood pressure-lowering medications on cardiovascular events in patients with and without diabetes mellitus. The authors completed separate reviews for trials that compared treatment with medications to controls, and trials that compared treatment with different medications. Section 1a.7 is completed based on the four trials of ACE inhibitors compared to placebo, as reported by the Blood Pressure Lowering Treatment Trialists' Collaboration (2005).

**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**: 1991-1999 (no date range provided for 2 of the 4 studies on ACE inhibitors)

**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 27 studies included in the systematic review were randomized controlled trials. Of these 27, 4 studies compared ACE inhibitors to a placebo treatment.

**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 four trials, the proportion of patients with diabetes ranged from 9% ([MacMahon et al., 2000](#_ENREF_2_2)) to 38% ([The Heart Outcomes Prevention Evaluation Study Investigators, 2000](#_ENREF_2_5)). In total, 4,389 of the 15,862 patients (28%) in the three studies providing counts of patients had diabetes.

DEMOGRAPHICS AND MEDICAL HISTORY OF STUDY SAMPLES

The proportion of women in each study ranged from 11% ([Teo et al., 2000](#_ENREF_2_4)) to 30% ([PROGRESS Collaborative Group, 2001](#_ENREF_2_3)). About 28% of all patients (N=4,382) in the three studies providing counts of patients were women. The studies included patients with prior coronary heart disease (CHD) ([Teo et al., 2000](#_ENREF_2_4)); CHD or cardiovascular disease (CVD) ([MacMahon et al., 2000](#_ENREF_2_2)); CHD, CVD, or diabetes mellitus plus CVD risk factors ([The Heart Outcomes Prevention Evaluation Study Investigators, 2000](#_ENREF_2_5)); or cerebrovascular disease ([PROGRESS Collaborative Group, 2001](#_ENREF_2_3)).

MEASURES OF ADHERENCE

Levels of patient adherence to ACEIs in the four trials are not reported in the meta-analysis ([Blood Pressure Lowering Treatment Trialists' Collaboration, 2005](#_ENREF_2_1)). Instead, patients are assigned in the meta-analysis by their study group in the trial; this would mean they were assigned to the "ACE inhibitor" or "placebo" group.

MEAN AGE AND SIZE OF STUDY SAMPLES

In the four studies included in this section, the mean age ranged from 61 to 66 years. In the studies, the total sample sizes for patients ranged from 460 patients ([Teo et al., 2000](#_ENREF_2_4)) to 9,297 patients ([The Heart Outcomes Prevention Evaluation Study Investigators, 2000](#_ENREF_2_5)).

TYPES OF ADVERSE EVENTS

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

* nonfatal stroke or death from cerebrovascular disease
* nonfatal myocardial infarction or deaths from CHD, including sudden deaths
* heart failure causing death or requiring hospitalization
* total major cardiovascular events (stroke, CHD events, heart failure, and other cardiovascular death)
* total cardiovascular deaths
* total mortality

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 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 ACEIs at a rate higher than that of the general population.

Citations for 1a.7.6.

Blood Pressure Lowering Treatment Trialists' Collaboration. (2005). Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Archives of Internal Medicine, 165*(12), 1410-1419.

MacMahon, S., Sharpe, N., Gamble, G., Clague, A., Mhurchu, C. N., Clark, T., . . . White, H. (2000). Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. *Journal of the American College of Cardiology, 36*(2), 438-443.

PROGRESS Collaborative Group. (2001). Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *The* *Lancet, 358*(9287), 1033-1041.

Teo, K. K., Burton, J. R., Buller, C. E., Plante, S., Catellier, D., Tymchak, W., . . . Montague, T. J. (2000). Long-Term Effects of Cholesterol Lowering and Angiotensin-Converting Enzyme Inhibition on Coronary Atherosclerosis: the Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation, 102*(15), 1748-1754.

The Heart Outcomes Prevention Evaluation Study Investigators. (2000). Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *The New England Journal of Medicine, 342*(3), 145-153.

**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*)

Among patients with diabetes in the four studies combined, the risk of stroke was significantly lower for those taking ACE inhibitors compared to those in the control groups (RR 0.69, 95% CI 0.55-0.86). The relative risks for other outcomes were lower, but not statistically significant (coronary heart disease: RR 0.91, 95% CI 0.62-1.34; heart failure (RR 0.88, 95% CI 0.67-1.16). The authors ([Blood Pressure Lowering Treatment Trialists' Collaboration, 2005](#_ENREF_2_1)) concluded, "...the short- to-medium- term effects on major cardiovascular events of the BP-lowering regimens studied were broadly comparable for patients with and without diabetes."

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

Several outcomes are mentioned in the article by the Blood Pressure Lowering Treatment Trialists' Collaboration (2005) as possible effects of the regimens studied, including "renal outcomes, the risk of new diabetes, or the progression of existing diabetes." Although these specific outcomes were not analyzed in this meta-analysis, the authors’ state, "These outcomes are a planned focus of future overviews using individual participant data from all contributing studies."

**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.*

Not applicable.

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

Not applicable.

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

Not applicable.

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)