



Effective Health Care Hypertension Management in Patients with Diabetes Mellitus

Results of Topic Selection Process & Next Steps

The nominator, a physician from a community hospital, is interested in a new evidence review on hypertension management in patients with comorbid diabetes mellitus to inform clinical practice. Because there are limited studies addressing this topic that have been published since the most recent systematic review in 2017, a new AHRQ review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Number and Name: 0784 Hypertension Management in Patients with Diabetes Mellitus

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

Hypertension and diabetes mellitus (DM) are two of the most common chronic medical conditions in the United States. According to the Centers for Disease Control and Prevention (CDC), as of 2016, 75 million American adults suffered from high blood pressure,¹ and over 30 million have a form of diabetes.² Nearly two-in-three people with diabetes have high blood pressure or take medication to manage their blood pressure.³ Older adults are at a higher risk of adverse events from blood pressure lowering, including cognitive impairment, falls, and fractures.⁴ The use of polypharmacy to manage multiple chronic conditions (including hypertension and diabetes) is also common among older adults and increases the risk of fall injury, hyperkalemia and hypokalemia, heart failure and blood pressure exacerbation.⁵

The American College of Physicians/American Academy of Family Physicians provides a strong recommendation to treat all older adults to a systolic blood pressure (SBP) target of 150 mmHg for most adults and a weak recommendation to treat older adults with cardiovascular risk factors, including those with diabetes, to a lower SBP threshold of 140 mmHg. Guidelines by the American College of Cardiology (ACC), American Heart Association (AHA) and others however recommend lower treatment targets (<130 mmHg) for those with hypertension and diabetes. Given these conflicting recommendations, there continues to be discussion on the best treatment target for older adults with diabetes.

Nominator and Stakeholder Engagement

We engaged with the nominator regarding the originally nominated topic, and refined the key questions and scope accordingly.

Key Questions and PICOs

The key question for this nomination is:

1. In adults over 60 years old with comorbid diabetes mellitus and hypertension, treatment to what blood pressure threshold improves outcomes?

To define the inclusion criteria for the key questions, we specify the population, interventions, comparators, and outcomes (PICOs) of interest (Table 1).

Table 1. Key Questions and PICOs

Key Questions	In adults over 60 years old with comorbid diabetes mellitus (DM) and hypertension (HTN), pharmacologic treatment to what blood pressure threshold improves HTN and DM-related outcomes?
Population	Adults over 60 years old with HTN and DM
Interventions	Pharmacologic treatment for hypertension
Comparators	No treatment, other active treatment
Outcomes	Blood pressure, CVD-related morbidity and mortality, DM-related morbidity and mortality, adverse events

Abbreviations: CVD=Cardiovascular Disease; DM=Diabetes Mellitus; HTN=Hypertension

Methods

We assessed nomination 0784 Hypertension Management in Patients with Diabetes for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established

selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from February 2017 to October 2018, based on the end date of the most recent search of our identified systematic reviews. See Appendix C for the PubMed search strategy and link to the ClinicalTrials.gov search.

Because a large number of articles were identified (n=514), we reviewed a random sample of 200 titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This is an appropriate and important topic. Hypertension and diabetes are two of the most prevalent and high cost chronic conditions in the United States. The CDC estimates that \$48.6 billion per year is lost to the cost of health care services, medications, and missed work due to high blood pressure.¹

Desirability of New Review/Duplication

A new evidence review would not be duplicative of an existing evidence review, as there are multiple, recent reviews that address this question to various degrees of specificity that come to different conclusions.

In 2016, a review by the Veterans Affairs Evidence-based Synthesis Program (VA ESP) was published examining higher versus lower thresholds in addition to more versus less intensive hypertension management in older adults. This review conducted a sub-analysis of patients by comorbidity burden, which included diabetes.⁶ This review found that diabetic patients were “at least as likely to benefit from blood pressure-lowering treatment,” as other older adults. In 2016, another review⁷ was published on the effects of antihypertensive treatment to different blood pressure thresholds in patients with diabetes. This review concluded that antihypertensive treatment to 140 mm Hg decreased mortality and cardiovascular morbidity risk; however, treatment to lower thresholds was associated to an increased risk of cardiovascular death. A 2017 review⁸ on higher versus lower thresholds and more versus less intensive hypertensive management for adults (mean age: 63) included diabetes in its meta-regression analyses and found that diabetes was not significantly associated with treatment effect. A 2018 review⁹ by the American College of Cardiology examined the effect of antihypertension management to <130 mmHg versus higher targets, conducted a sensitivity analysis for studies that did and did not include patients with diabetes, and found that the greatest effects were seen for those with diabetes.

Given the diverse approaches in assessing blood pressure targets for older patients with hypertension and diabetes, and the differing conclusions of these reviews, a new AHRQ review would not be duplicative.

See Table 2, Duplication column.

Impact

The VA ESP review formed the basis of the joint American College of Physician (ACP) and American Academy of Family Physician (AAFP) guidelines.¹⁰ Based on high quality evidence, they recommend treating all older adults to a systolic blood pressure target of 150 mmHg. Based on low quality evidence, these guidelines recommend treating hypertension in older adults with cardiovascular risk factors to lower targets (<140 mmHg)¹⁰ Joint guidelines by the American College of Cardiology (ACC), American Heart Association (AHA) and others however recommend lower treatment targets (<130 mmHg) for those with hypertension and diabetes.¹¹ Given this disagreement among professional societies, a new AHRQ review may have a large impact.

Feasibility

A new evidence review is not feasible. From our review of a selection of 200 random studies, we identified two studies that indirectly addressed the key question, for a projected total of 5 studies.

One study¹² was a subgroup analysis of participants in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) trial. Patients with diabetes and additional cardiovascular (CVD) risk factors received hypertension treatment to intensive (<120 mmHg) or standard (<140 mmHg) blood pressure targets. These patients were then compared to a cohort of patients with CVD risk factors but no diabetes from the Systolic Blood Pressure Intervention Trial (SPRINT), to see if the presence of a diabetes diagnosis affected outcomes. This analysis

found that intensive BP control reduced the risk of a composite measure of cardiovascular disease death, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or heart failure by 21% among patients with diabetes. There were no differences in effects seen among patients with diabetes from the ACCORD-BP trial versus their counterparts in the SPRINT trial. Of note, this analysis included participants as young as 40 years old.

A second study¹³ examined patients (mean age= 62.8 years) who had undergone a 4-week treatment with telmisartan/amlodipine (TA) combination for essential hypertension and did not respond to the treatment. After the four weeks, patients were randomly assigned to continue receiving TA, or receive TA + hydrochlorothiazide (TAH) for an additional eight weeks. In the TAH group (more intensive), patients without diabetes had better blood pressure control at 2 and 8 weeks than those with diabetes. In the TA group (less intensive), patients without diabetes had greater BP control at 8 weeks only.

We identified no ongoing clinical trials that will compare blood pressure thresholds or more versus less intensive treatment for hypertension and diabetes.

See Table 2, Feasibility column.

Table 2. Key Questions and Results for Duplication and Feasibility

Key Question	Duplication (9/2015-9/2018)	Feasibility (2/2017-10/2018)
KQ 1: In adults over 60 with comorbid diabetes mellitus (DM) and hypertension (HTN), pharmacologic treatment to what blood pressure threshold improves HTN and DM-related outcomes?	Total number of identified systematic reviews: 1 <ul style="list-style-type: none"> • VA ESP: 1⁶ • Other: 3⁷⁻⁹ 	<u>Size/scope of review</u> Relevant Studies Identified: 2 <ul style="list-style-type: none"> • Post hoc analysis 1¹² • RCT: 1¹³ Projected Total: 5 <u>Clinicaltrials.gov</u> None identified

Abbreviations: KQ=Key Question; VA ESP=Veterans Affairs Evidence-based Synthesis Program

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would not be duplicative of an existing product. We identified 4 reviews published in the last 2 years which came to different conclusions on the effects of lower blood pressure targets on mortality and cardiovascular risk in patients with hypertension and diabetes.
- Impact: Professional societies disagree on the best blood pressure target for patients with hypertension and diabetes, based on the differing conclusions of these systematic reviews. A new AHRQ review therefore may have a high impact.
- Feasibility: A new review is not feasible. We identified two studies that indirectly addressed the key question, for a projected total of 5 studies.

References

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Appendix A. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this nomination represents a health care intervention in the United States.
1b. Is the nomination a request for a systematic review?	Yes, this nomination is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes, this nomination is focused on effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, this nomination is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant disease burden for a large proportion of the population.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic is of high interest to the public.
2c. Represents important uncertainty for decision makers	Yes this topic represents important uncertainty for health care systems, providers, and patients.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination takes into consideration both clinical benefits and harms.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this topic represents high costs due to high prevalence for patients, health care systems, and payers.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A review on this topic would not be duplicative of an existing topic. We identified 4 systematic reviews ⁶⁻⁹ published in the last 2 years that came to different conclusions on the benefits and harms of lower versus higher blood pressure targets for patients with hypertension and diabetes. Given the diverse approaches taken by reviews in assessing this question, and the different conclusions of these reviews, a new AHRQ review would not be duplicative.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	The standard of care is unclear. Guidelines from the ACP/AAFP ¹⁰ and the ACC/AHA ¹¹ disagree on the ideal blood pressure target for patients with diabetes and hypertension, with the ACC/AHA recommending lower targets than ACP/AAFP.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation due to the disagreement among professional societies.
5. Primary Research	

Selection Criteria	Assessment
<p>5. Effectively utilizes existing research and knowledge by considering:</p> <ul style="list-style-type: none"> - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies) 	<p>A new review is not feasible.</p> <p><i>Size/scope of review:</i> We identified one post hoc subgroup analysis not specific to older adults¹² and one RCT that did not focus on blood pressure thresholds¹³ that indirectly addressed the key question, for a projected total of 5 studies.</p> <p><i>ClinicalTrials.gov.</i> We identified no ongoing clinical trials that will compare blood pressure thresholds or more versus less intensive treatment for hypertension and diabetes.</p>

Abbreviations: AAFP=American Academy of Family Physicians; ACC= American College of Cardiology; ACP=American College of Physicians; AHA= American Heart Association; AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question

Appendix B. Search for Evidence Reviews (Duplication)

Listed below are the sources searched, hierarchically

Primary Search
AHRQ: Evidence reports and technology assessments https://effectivehealthcare.ahrq.gov/ ; https://www.ahrq.gov/research/findings/ta/index.html ; https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program https://www.hsr.d.research.va.gov/publications/esp/
Cochrane Systematic Reviews http://www.cochranelibrary.com/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/

Appendix C. Search Strategy & Results (Feasibility)

PubMed

Date Searched: October 9, 2018

Searched by: Information Specialist

Search	Query
#14	Search (("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive)) AND (((((((((((randomized controlled trial [pt] AND Clinical Trial[ptyp])) OR (controlled clinical trial [pt] AND Clinical Trial[ptyp])) OR (randomized [tiab] AND Clinical Trial[ptyp])) OR (placebo [tiab] AND Clinical Trial[ptyp])) OR (drug therapy [sh] AND Clinical Trial[ptyp])) OR (randomly [tiab] AND Clinical Trial[ptyp])) OR (trial [tiab] AND Clinical Trial[ptyp])) OR (groups [tiab] AND Clinical Trial[ptyp])) AND Clinical Trial[ptyp])) NOT ((animals [mh] NOT humans [mh]) AND Clinical Trial[ptyp])) AND Clinical Trial[ptyp]) Filters: Clinical Trial; Publication date from 2017/02/01 to 2018/10/09
#13	Search (("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive)) AND (((((((((((randomized controlled trial [pt] AND Clinical Trial[ptyp])) OR (controlled clinical trial [pt] AND Clinical Trial[ptyp])) OR (randomized [tiab] AND Clinical Trial[ptyp])) OR (placebo [tiab] AND Clinical Trial[ptyp])) OR (drug therapy [sh] AND Clinical Trial[ptyp])) OR (randomly [tiab] AND Clinical Trial[ptyp])) OR (trial [tiab] AND Clinical Trial[ptyp])) OR (groups [tiab] AND Clinical Trial[ptyp])) AND Clinical Trial[ptyp])) NOT ((animals [mh] NOT humans [mh]) AND Clinical Trial[ptyp])) AND Clinical Trial[ptyp]) Filters: Clinical Trial
#12	Search (((((((((((randomized controlled trial [pt] AND Clinical Trial[ptyp])) OR (controlled clinical trial [pt] AND Clinical Trial[ptyp])) OR (randomized [tiab] AND Clinical Trial[ptyp])) OR (placebo [tiab] AND Clinical Trial[ptyp])) OR (drug therapy [sh] AND Clinical Trial[ptyp])) OR (randomly [tiab] AND Clinical Trial[ptyp])) OR (trial [tiab] AND Clinical Trial[ptyp])) OR (groups [tiab] AND Clinical Trial[ptyp])) AND Clinical Trial[ptyp])) NOT ((animals [mh] NOT humans [mh]) AND Clinical Trial[ptyp])) Filters: Clinical Trial
#11	Search animals [mh] NOT humans [mh] Filters: Clinical Trial
#10	Search (((((((((((randomized controlled trial [pt] AND Clinical Trial[ptyp])) OR (controlled clinical trial [pt] AND Clinical Trial[ptyp])) OR (randomized [tiab] AND Clinical Trial[ptyp])) OR (placebo [tiab] AND Clinical Trial[ptyp])) OR (drug therapy [sh] AND Clinical Trial[ptyp])) OR (randomly [tiab] AND Clinical Trial[ptyp])) OR (trial [tiab] AND Clinical Trial[ptyp])) OR (groups [tiab] AND Clinical Trial[ptyp])) AND Clinical Trial[ptyp])) Filters: Clinical Trial
#9	Search groups [tiab] Filters: Clinical Trial
#8	Search trial [tiab] Filters: Clinical Trial
#7	Search randomly [tiab] Filters: Clinical Trial
#6	Search drug therapy [sh] Filters: Clinical Trial
#5	Search placebo [tiab] Filters: Clinical Trial
#4	Search randomized [tiab] Filters: Clinical Trial
#3	Search controlled clinical trial [pt] Filters: Clinical Trial
#2	Search randomized controlled trial [pt] Filters: Clinical Trial
#1	Search "blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive

ClinicalTrials.gov Search:

https://clinicaltrials.gov/ct2/results?cond=diabetes+OR+diabetic+OR+T1DM+OR+T2DM&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=antihypertensive+OR+an

[ti-hypertensive+OR+%22blood+pressure+lowering%22+OR+%22blood-pressure+lowering%22&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd e=10%2F15%2F2021&prcd s=&prcd e=&sfpd s=&sfpd e=&lupd s=&lupd e=&sort=](#)