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The Other Side of the Story: A Discontinuation Trial of Antihypertensive Treatment:

Invited Commentary on: Effects of Discontinuation of Antihypertensive Treatment in Elderly people on cognitive functioning (DANTE) a randomized controlled trial

Michelle C. Odden, PhD

School of Biological and Population Health Sciences, College of Public Health and Human Sciences, Oregon State University, 141B Milam Hall, Corvallis, OR, 97331, Ph: 541-737-3184, Fax: 541-737-6914, Michelle.Odden@oregonstate.edu

The overwhelming majority of research and guidelines have focused on the initiation and intensification of medication. Not surprisingly, the burden of medication use in older adults is high; nearly 40% of adults aged 65 years and older and 50% of those aged 80 years and older are on five or more prescription medications.¹ The use of cardioprotective medications, including antihypertensives and statins, is greatest among those aged 80 years and older.¹ There currently are no U.S. guidelines for the discontinuation of blood pressure lowering medications, although the 2014 guideline from the panel members appointed to the Eighth Joint National Committee (JNC 8) recommend a higher systolic blood pressure treatment target among adults aged 60 years and older.² Presumably, this would result in the discontinuation of antihypertensive medications in some older adults, but the consequences of this discontinuation and whether age 60 years and older is the right population, have been controversial.³ A group from Canada recently released a guideline for frail older adults recommending a target systolic blood pressure of 140–160 mmHg, and 160–190 mmHg in those with limited life expectancy;⁴ although they also note the guideline was based on consensus expert opinion due to the limited available evidence in these populations.

Antihypertensive medications are generally safe and have prevented millions of cardiovascular events and untimely deaths, although they are not without harm. The question remains, whether there is some population at some time in whom the harms outweighs the benefits. We are most comfortable considering discontinuation in the setting of end of life care. For example, we might consider a 75-year old patient who is dying of pancreatic cancer and is in the last two weeks of her life. Blood pressure lowering is unlikely to be helpful in this patient, and may cause dizziness and increase the risk of falls. In this example, the choice seems clear. However, when did the scale shift from net benefit to net harm? Was it one month before death? Upon diagnosis of cancer? When the patient turned 70 years old? This crucial question remains unanswered.

A paucity of literature has reviewed the discontinuation of therapies in a population who is aging, but not yet dying. We can take lessons from the field of cancer screening; there has been extensive research on the relative benefits and harms of mammography and prostate specific antigen screening in older women and men.⁵ The key in evaluation of the net benefit is the inclusion of unintended clinical consequences of treatment (surgical complications,

urinary incontinence, etc.) as well as patient-centered outcomes (pain, test anxiety, quality of life, etc.).

The world of preventive medication use remains less well explored. Some research exists on cessation of medication intended primarily for short term use; including benzodiazepines, antiplatelet agents, and proton pump inhibitors.⁶ Decision-making becomes murkier when a therapy is prescribed for a condition that is expected to be life long, such as hypertension or dyslipidemia. In these cases, we are in uncharted territory. How can health care providers discuss goals of care and the possibility of discontinuation of a medication, when we haven't studied these questions?

In this issue of JAMA Internal Medicine, Moonen *et al.* present a study to chart these new waters. They evaluate whether discontinuation of antihypertensive medication improves cognitive, psychological, and general daily functioning in a population of adults with mild cognitive deficits. Their study was motivated by the evidence demonstrating an association between lower blood pressure and greater decline in cognitive function, as well as the hypothesis that increasing blood pressure would help maintain better perfusion of the brain. The results of the study were null. In their study population, discontinuation of antihypertensive medication did not improve function at 4-months follow-up.

Substantively, the value of the present study is modest. Without a clear beneficial effect, the clinician is left wondering if this should impact their practice. It is notable that there were also no adverse effects of discontinuation, so perhaps discontinuation would have no net effect on the balance of benefit and harms. However, the study was only for 4 months, so it is also possible that longer follow-up is necessary to observe benefit; or conversely, that longer follow-up would put the patient at risk of subsequent cardiovascular events.

Methodologically, the value of the present study is enormous. The discontinuation study design represents a paradigm shift in the way we conduct randomized controlled trials (RCTs) of antihypertensive therapy. Additionally, this design could be extended to examine other typically lifelong medications. The authors did an exemplary job of designing the right study at the right time to advance the evidence base. Following are four key features that will be important for any discontinuation study.

First, the DANTE study focused on patient-centered outcomes. We can no longer build evidence bases with only 'hard' outcomes, such as death or myocardial infarction. No one would disagree that these are important outcomes, but older adults have told us repeatedly that there is more to life than just living. Cognitive function, physical functioning, emotional well-being, and social connectivity give a more complete picture of the quality of life. We need to consider the broad spectrum of health when evaluating both initiation and discontinuation of medication use to optimize health and well-being.

Second, there is strong scientific rationale motivating the research question. There is conflicting evidence on the impact of antihypertensive therapy on cognitive function in older adults. The authors point to systematic reviews of observational studies that demonstrate that lower blood pressure is associated with an *increased* risk of cognitive decline, and inconclusive evidence from randomized controlled trials. Additionally, there is biologic

plausibility behind the relationship of interest. The authors note evidence that impaired cerebral blood flow and hypoperfusion could contribute to cognitive decline. Finally, there have been analogous findings between lower blood pressure and other adverse outcomes, including depression and physical function.

Third, the authors chose a study population that has been underrepresented in previous RCTs. Few studies have included older adults, and frequently older adults with cognitive impairment or in poor health are excluded from RCTs. Functional status may modify the effect of blood pressure on outcomes;⁷ therefore, we cannot extrapolate findings from younger and healthier populations to older, sicker populations. Yet the benefits of discontinuation may be greatest in such populations.

Fourth, the study took measures to minimize any potential patient harm associated with discontinuation. There was intensive monitoring of blood pressure levels and multiple safety checkpoints. The short follow-up time was ethically-motivated in an attempt to reduce any harm on cardiovascular risk. Short term follow-up studies of discontinuation should be conducted first to demonstrate safety, analogous to the progression of evidence for medication initiation RCTs.

In summary, the DANTE trial represents an innovative approach to the RCT design. We've made great strides in building the evidence base for initiating and intensifying antihypertensive therapy, but we have neglected to study the effects of continuing and discontinuing therapy in older adults. This study is the first step forward in answering these important scientific questions.

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References

1. Charlesworth CJ, Smit E, Lee DS, Alramadhan F, Odden MC. Polypharmacy Among Adults Aged 65 Years and Older in the United States: 1988–2010. *J Gerontol A Biol Sci Med Sci*. Mar 1.2015
2. James PA, Oparil S, Carter BL, et al. 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). *Jama*. Feb 5; 2014 311(5):507–520. [PubMed: 24352797]
3. Wright JT Jr, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. *Ann Intern Med*. Apr 1; 2014 160(7):499–503. [PubMed: 24424788]
4. Mallery LH, Allen M, Fleming I, et al. Promoting higher blood pressure targets for frail older adults: a consensus guideline from Canada. *Cleve Clin J Med*. Jul; 2014 81(7):427–437. [PubMed: 24987044]
5. Walter LC, Schonberg MA. Screening mammography in older women: a review. *Jama*. Apr 2; 2014 311(13):1336–1347. [PubMed: 24691609]
6. Ostini R, Jackson C, Hegney D, Tett SE. How is medication prescribing ceased? A systematic review. *Medical care*. Jan; 2011 49(1):24–36. [PubMed: 20966784]
7. Odden MC, Beilby PR, Peralta CA. Blood Pressure in Older Adults: the Importance of Frailty. *Current hypertension reports*. Jul.2015 17(7):564.