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Title	Physician follow-up and long-term use of evidence-based medication in hypertension patients discharged from an emergency department: a prospective cohort study
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Reviewer 1	Dr. Lee Green
Institution	University of Alberta, Family Medicine, Edmonton, Alta.
General comments (author response in bold)	The authors report a retrospective cohort study of intensification of antihypertensive therapy with known outcome-improving drugs (which they term evidence-based medications, or EBMs) according to followup after ED visits for poorly controlled hypertension. The introduction summarizes the relevant literature briefly but sufficiently, and establishes the place of this study in that literature. The study design and methods are well explained, and replicable. The patient populations chosen are justified sufficiently. The proxy outcome measure is likewise explained well. Thank you! Two points on medication need to be addressed. 1. First, and most importantly, they include only HCTZ among diuretics. However, HCTZ not the only evidence-based diuretic for HTN. Most of the actual outcome evidence is for chlorthalidone, and there is some evidence that HCTZ underperforms in comparison. This was an oversight on our part. chlorthalidone represents < 10% of thiazide diuretics prescribed in Ontario. We have added it and rerun the analyses, which did not change. **Thank you for catching this.** 2. Second, the dihydropyridine CCBs should be specified as long-acting. **This was a typo – it has been added. Thank you!** The analysis plan and statistical modeling are clearly explained and well chosen. **Thank you.** The interpretation is well presented. Limitations are addressed, and potential threats to validity are well handled. **Thank you!** Tables and graphs are appropriate and useful. Figures 3 and 4 in particular are helpful. **That is nice to hear!**
Reviewer 2	Dr. Wilson Pace
Institution	University of Colorado, Family Medicine, Denver, Colo.
General comments (author response in bold)	,This manuscript explores the impact of rapid follow up versus more delayed follow up to no follow up of a visit to the emergency department resulting in a new diagnosis of hypertension on medication usage one year later. It also explores similar outcomes for patients with an existing diagnosis of hypertension (HTN) who are on one or no anti-hypertensive medications at the time of an emergency department visit that included a diagnosis of hypertension. The analysis is based on claims data linked to physician and location data. The data set is very complete for the data that is available. The data sets that are available for the analysis are appropriately linked and provide an interesting spectrum of data for the analysis. The background information of the increasing use of emergency departments (ED) for high blood pressure visits is interesting. Thank you. 1. The immediate question that comes to mind is how do people know to visit an ED for an asymptomatic condition without somehow taking their blood pressure? **As noted above, in the response to the EIC's questions (#1), we know that in all-comers to the ED who are given a primary ED diagnosis of hypertension, about half come secondary to an abnormally high reading (on a home BP cuff, pharmacy cuff, or at a doctor's office or some kind of clinic). Many have symptoms that prompted them to take the measurement in the first place. Most of the rest do have symptoms (listed above). Since home blood pressure monitoring in individuals without a diagnosis of HTN would seem unusual the cohort of individuals making these visits would seem to be an atypical group to start with. In practice, I find that some of these patients use the cuff of their spouse (or parent), or use a pharmacy cuff or are sent in from a doctor's office or clinic (e.g. family doctor, or a pre-op appointment). Often they believe the number is life-threatening. Or they come in due to vague symptoms, often a mild headache or feeling 'dizzy'. This is a typical**

	ED hypertension cohort. The inception cohort of individuals with "newly" diagnosed HTN during a single ED visit is a typical starting point for observational studies. 2. For the second cohort of individuals, with what might be characterized as non-aggressively treated HTN or a group of patients with poor medication compliance for an existing condition, the outcome of starting a new medication a year later is harder to comprehend as a universally appropriate. **Since the median BP of these patients is 181/97, the majority do need some intervention to get them to the goal BP (according to CHEP) of 140/90. Both the CHEP (Canadian) guidelines and the ESC hypertension guidelines specificially encourage additional mediations over just increasing the dosages of current antihypertensives, since the latter tends to increase the number of side-effects, and if that class wasn't working particularly well to begin with, a different class is likely to have a better effect on the BP level than an increased dose of the one that isn't working well. For this reason we felt assessing for a new antihypertensive medication a year later was valid, and without including this group we would not be addressing a large number of the patients seen in the ED with a primary diagnosis of hypertension (the majority). The similar findings in both groups was reassuring.** 3. The authors' previous work "auditing" blood pressures for patients diagnosed with hypertension following ED visits is supportive of the analytics but is far short of having true outcomes over time for the two cohorts. **This reviewer is unaware of any HTN guidelines that propose establishing a diagnosis of hypertension at one visit without evidence of end-organ dysfunction – i.e. malignant hypertension. Actually according to the last few iterations of the CHEP (Canadian Hypertension Education Program) guidelines, a number of 180 mm Hg systolic, or 110 mm Hg diastolic (either) makes the diagnosis of hypertension (Leung AA, Can J Cardiol, 2016;32:569-88):** **Canadian guidelines also use a lower number than the the JNC guidelines (I note the reviewer is from Colorado), which I believe were still at 150/90 for patients without specific comorbidities (until a few weeks ago when the new guideline was announced at the AHA meeting, as 130/80, with ≥10% atherosclerotic CVD [ASCVD] risk). Malignant hypertension requires immediate hospitalization and thus was not present in any of the patients in either cohort. Thus, the "HTN diagnosis" from the ED visits for the inception cohort perhaps should be more correctly coded as "elevated blood pressure without diagnosis." A sensitivity analysis for similar outcomes around the discharge diagnosis of "elevated blood pressure without a diagnosis" examining the likelihood of a new diagnosis of HTN following at least two additional primary care visits could help delineate the positive predictive value of the ED diagnosis. Again, according to the CHEP guidelines, a single measurement of 180 systolic, or 110 diastolic, makes the diagnosis of hypertension, so this wouldn't be necessary for those patients with either reading. This is based on evidence that when the BP level gets this high more than one agent is often required to get it to target (usually 140/90 by Canadian guidelines), and very rarely does it come back to normal levels (140/90) on it's own (without antihypertensives). Next, in our paper (in the Limitations section) we discussed 2 relevant studies that look at the BP in outpatient visits after ED discharge (which is essentially the sensitivity analysis the reviewer is suggesting). Both that looked at ED patients who were seen for a problem OTHER than hypertension (i.e. hypertension was found secondarily, and many of these patients were in pain), but had BPs over 140/90 (Backer HD, Ann Emerg Med, 2003; PMID: 12658251 and Shiber-Ofer S, J Clin Hypertens (Greenwich), 2015; PMID: 25706051). Over half of the patients in the former study only had a reading of 140-159 systolic, or 90-99 diastolic (stage I at that time), compared to our cohort's median BP of 181/99, but still they found that over 70% of those patients had persistently elevated readings in post-ED follow-up. Of the patients with levels up to 179/109, 80% had persistently elevated readings in follow-up. In the second paper the mean BP level in the ED was 175/103 (the median would be lower). It found that over a year later 73% had were diagnosed with hypertension. Thus both of these studies suggest that the large majority of our cohort (all of whom had a primary diagnosis of hypertension, and would not be in signficant pain) have ED BPs high enough to lead to a formal diagnosis of hypertension in follow-up. Adding in medication filling a year later after a primary care verified diagnosis might also help understand the general medication filling behavior of the cohorts.** 4. Claims data is notoriously poor for understanding HTN treatment appropriateness. When this concern is added to the potential for low positive predictive value of the diagnosis from a single ED visit the reported correlations are mildly interesting, but far from conclusive and not ready to drive any policy decisions. **As we mentioned, the diagnosis of hypertension is made (according to Canadian guidelines) in the majority of the patients, because they had a single read over**

	either 180 systolic or 110 diastolic. Next, other studies have shown that over 70% patients who are in the ED for an entirely different reason, but are found to have a BP over 140/90, have repeatedly high readings in the outpatient care setting (Backer HD, Ann Emerg Med, 2003, and Shiber-Ofer S, J Clin Hypertens (Greenwich), 2015) Thus the positive predictive value of the diagnosis is not low. The linkage of EHR data, at least from the primary care office, would seem to be of upmost importance both to establish the diagnosis as well as to understand the intent of the treating physician. We agree this would be interesting to study, and would make a great future/follow-up study, if population-based EHR data becomes available. **Thus, the filling (versus the prescribing) of a second Evidence Based Medication (EBM) may be more a function of these individual's outlook on treatment in general than on the actual intent of their primary care physicians. This is true, and we try to emphasize in the paper that the patient is an active member of their care team, and that they control prescription fills, after the doctor writes the prescription. So we are measuring the patient's outlook and influences in addition to provider prescribing. We have clarified this in the manuscript. The length of time an individual takes to follow up with his or her primary care physician could be correlated with medication filling decisions (the longer one takes to make a follow up appointment and the total lack of a follow up appointment are correlated with non-filling of provided prescriptions) and thus not independently related to time from ED visit to primary care visit at all. We discuss this option in the Interpretation, third paragraph under "Comparison with other studies": "Lastly, illness acuity could affect both follow-up and long-term EBM use. Sicker patients may be less able to attend appointments where EBM is prescribed…". The vast majority of these patients did obtain follow-up at some point (< 3% did not - see Limitations). Although we also note that access to care in Ontario (and in Canada) is poor and ranked 10th place among 11 first world countries (Commonwealth study), so for most patients it may be less a 'choice' to be seen later than it is difficult to get in to see their doctor. This is discussed in the Interpretation under Comparison with other studies, paragraph 2.** **5. As the manuscript notes, blood pressure medication adherence is well known as a poster child for poor compliance related to chronic disease. Patients are asked to take medications, that may have side effects to treat a disease with no symptoms to prevent a theoretical risk that is likely decades in the future. These issues are of particular concern for the second cohort given that is well known that poor medication compliance with treatment is a major reason for poorly controlled HTN. Thus, the filling of an additional medication at one year after a single ED visit could be as much a measure of changes in compliance with previously prescribed medications. The decision to fill a previously recommended medication could be impacted by the number of primary visits or the physician patient relationship, both of which may also point to a higher likelihood of earlier follow up. Thus, medication filling may not be a good measure of appropriate care for this group as opposed to medication ordering or actual blood pressure control. The reviewer makes an interesting point. However if we were to measure the ordering of medication (or prescription writing), this measure would miss the very important factor of patient behavior. We want to know if early follow-up affects patient behavior, as per the hypothesis now delineated in the Introduction, 3rd paragraph. It is possible that longer time to follow-up may result in less prescriptions written, if other health issues arise and take priority over prescribing an antihypertensive, but our hypothesis is that much of the effect of early care (after a scary/long visit in an ER) is on the patient and their behavior, and we can't measure that if we only assess prescription writing. Given the multitude of potential unmeasured biases between the patients, primary care visiting behavior and medication fulfillment this reviewer wonders if a propensity matching approach would be more appropriate than trying to control for these issues through population level regression analysis. Please see our response to question #6 from the EIC.** 6. While the manuscript points out some limitations of the presented analyses, the actual confounding of incorrect diagnosis from the ED. **The ED diagnosis was validated on patients charts, as "hypertension" listed as the first ED diagnosis, PPV 93%, and combined with over half having an immediate diagnosis of hypertension (>180/110) by CHEP guidelines, plus two ED studies (with lower average BPs) which show the majority are subsequently diagnosed with hypertension, this suggests that the diagnosis is correct for the large majority of the cohort coupled with viewing medication filling as a measure of treatment intent. It also measures (perhaps more importantly) patient motivation and the correlation with primary care physician avoidance with medication filling non-adherence all make the reported outcomes, short of actual patient level outcomes, difficult to interpret.**