Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

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Summary

Background Uncertainty remains about the optimal monotherapy for hypertension, with current guidelines recommending any primary agent among the first-line drug classes thiazide or thiazide-like diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and non-dihydropyridine calcium channel blockers, in the absence of comorbid indications. Randomised trials have not further refined this choice.

Methods We developed a comprehensive framework for real-world evidence that enables comparative effectiveness and safety evaluation across many drugs and outcomes from observational data encompassing millions of patients, while minimising inherent bias. Using this framework, we did a systematic, large-scale study under a new-user cohort design to estimate the relative risks of three primary (acute myocardial infarction, hospitalisation for heart failure, and stroke) and six secondary effectiveness and 46 safety outcomes comparing all first-line classes across a global network of six administrative claims and three electronic health record databases. The framework addressed residual confounding, publication bias, and p-hacking using large-scale propensity adjustment, a large set of control outcomes, and full disclosure of hypotheses tested.

Findings Using 4·9 million patients, we generated 22 000 calibrated, propensity-score-adjusted hazard ratios (HRs) comparing all classes and outcomes across databases. Most estimates revealed no effectiveness differences between classes; however, thiazide or thiazide-like diuretics showed better primary effectiveness than angiotensin-converting enzyme inhibitors: acute myocardial infarction (HR 0·84, 95% CI 0·75–0·95), hospitalisation for heart failure (0·83, 0·74–0·95), and stroke (0·83, 0·74–0·95) risk while on initial treatment. Safety profiles also favoured thiazide or thiazide-like diuretics over angiotensin-converting enzyme inhibitors. The non-dihydropyridine calcium channel blockers were significantly inferior to the other four classes.

Interpretation This comprehensive framework introduces a new way of doing observational health-care science at scale. The approach supports equivalence between drug classes for initiating monotherapy for hypertension—in keeping with current guidelines, with the exception of thiazide or thiazide-like diuretics superiority to angiotensin-converting enzyme inhibitors and the inferiority of non-dihydropyridine calcium channel blockers.

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Introduction

Patients and physicians have a wide range of pharmacological options to treat hypertension but little guidance on which specific first-line agent to initiate. The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Blood Pressure Treatment Guidelines[1] endorse any thiazide or thiazide-like diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers unless contraindicated. Similar non-specificity emerges from the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines, with the further inclusion of β blockers.[2]

These recommendations derive largely from earlier randomised clinical trials (RCTs) that provided direct comparisons between a few agents, not drug classes, and often did not restrict to therapy initiation. For example, the largest head-to-head RCT of antihypertensives, the ALLHAT trial,[3] enrolled patients from February, 1994, to January, 1998, more than two decades ago, evaluated three representative agents and a majority of participants had been previously treated. Moreover, most studies considered in the 2017 ACC/AHA Guidelines systematic review[4] were done before 2000.

The 2017 Cochrane Review[5] of first-line therapy for hypertension, an update from 2009, found no new RCTs to include. Their review concludes that "first-line low-dose