

## Editorial



# Big Challenge in Big Data Research: Continual Dispute on Big Data Analysis

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► See the article “Comparison of First-Line Dual Combination Treatments in Hypertension: Real-World Evidence from Multinational Heterogeneous Cohorts” in volume 50 on page 52.

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More than 2/3 of patients with hypertension need drugs from more than 2 drug classes with different mechanisms to achieve control of hypertension.<sup>1-4)</sup> Combination therapy is particularly helpful for patients receiving prolonged blood pressure treatment, and high-risk patients.<sup>5)</sup> Because recent hypertension guidelines recommends more intensive blood pressure control,<sup>6)</sup> most hypertensive patients require drug combination.<sup>7,8)</sup> Combination therapy is more effective than single-drug therapy at a higher dose. Therefore 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guideline even recommends dual combination treatment as initial therapy in most hypertensive patients rather than monotherapy.<sup>9)</sup>

However, it has not been fully evaluated which combination is best. Combination therapy chosen from the renin-angiotensin system inhibitors, calcium antagonists, and diuretics is recommended first because it has shown relatively good results, but beta-blockers can also be combined with drugs of other classes. In this edition of the journal, You et al.<sup>10)</sup> reported that commonly recommended combination regimens showed no significant difference in mortality in patients without previous cardiovascular disease. However, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blocker (ARB)+calcium channel blocker (CCB) combination was associated with a slightly higher risk of heart failure and stroke than ACEIs/ARB+ diuretic combination. The authors analyzed five data sources encoded in the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM) version 5 from participating research partners across the Observational Health Data Sciences and Informatics (OHDSI) community.

Recently, vigorous effort to analyze real world data documented in heterogeneous electronic medical record system by in common data model has been pursued. CDM based big data analysis will be especially powerful research material if the targeted disease has accurate disease code with low false negative as well as false positive coding error. Importantly, for the best results of big data analysis, key clinical markers of targeted disease should be included with clinically acceptable amount of missing values. Still, medical big data analyses are complicated by many technical issues, such as missing values, curse of dimensionality, and bias control.<sup>11)</sup> In this aspect, hypertension big data research has many challenges despite big promise. Especially, most important clinical parameters of hypertension care,

blood pressure, is only partially filled up in the current big data database, due to 'text-based' documentation in outpatient clinic medical record. Most hypertension drug comparison study have performed on the basis of equal blood pressure control if the study aims to evaluate the effect beyond blood pressure control. This challenge of hypertension big data research might be clearly contrasted with other diseases, for example diabetes and kidney disease, of which important clinical markers, glycated hemoglobin and serum creatinine are readily available in CDM.

Another problem is continual egg-or-chicken dispute in real world data analysis. It is the inherent limitations of observation study, namely the inability to test causality resulting from residual confounding and reverse.<sup>11)</sup> In this study, it is not surprising that ACEIs/ARB+CCB combination was associated with a slightly higher risk of heart failure, because CCB has volume retention effect.<sup>12)</sup> However, higher stroke admission in ACEIs/ARB+CCB combination than ACEIs/ARB+diuretic combination is surprising, because CCB is preferred agent for high risk of stroke. The results might come from the residual confounding effect of the clinician's preference of CCB despite propensity matching.

Big data research is an irresistible trend of medical research. However, it must be emphasized that real world evidence research should not be interpreted as randomized controlled trial with clearly discerning advantages and disadvantages of big data, especially when key parameters were missing in analysis.<sup>13)14)</sup> For cardiovascular big data research, continuous effort to transfer key clinical parameters such as blood pressure and chest pain scale, which are documented in most medical record with text-form, into analyzable parameters is warranted for quantum leap into next step.

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