

Commentary



Common data model-based real-world data for practical clinical practice guidelines: clinical pharmacology perspectives

Yoomin Jeon ^{1,2,†}, Yoona Choi ^{1,2,†}, Esther Hehsun Kim ^{1,2,†},
SeonYeong Oh ^{1,2,†}, and Howard Lee ^{1,2,3,4,*}

¹Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Seoul 08826, Korea

²Center for Convergence Approaches in Drug Development, Graduate School of Convergence Science and Technology, Seoul National University, Seoul 08826, Korea

³Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital and College of Medicine, Seoul 03080, Korea

⁴Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul 08826, Korea

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*Correspondence to

Howard Lee

Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital and College of Medicine, Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Center for Convergence Approaches in Drug Development (CCADD), Seoul 08826, Korea.

E-mail: howardlee@snu.ac.kr
leehwd@gmail.com

[†]These authors contributed equally to the present work.

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ORCID iDs

Yoomin Jeon
<https://orcid.org/0000-0002-5134-065X>

Yoona Choi
<https://orcid.org/0000-0001-8948-1880>

Esther Hehsun Kim
<https://orcid.org/0000-0002-9576-4411>

INTRODUCTION

Clinical practice guidelines (CPGs) are a set of statements systematically developed to assist healthcare professionals and decision makers to practice evidence-based medicine by promoting cost-effective interventions while discouraging ineffective, wasteful, or potentially harmful treatments [1]. CPGs can improve the consistency and quality of care by providing the gold standard, which also helps reduce variation in clinical practice [1]. To ensure the validity of CPGs, clinically important recommendations in CPGs need to be updated periodically as scientific evidence constantly expands and evolves [1].

Although CPGs have a potential to improve patient outcomes, clinicians often do not adhere to them. For example, a significant amount of variations was identified between hospitals and clinicians, which cannot be solely explained by differences in conditions or patient preferences [2]. Common barriers to adherence include any of the following: no CPG specific to a certain practice setting, poor understanding of CPGs, weak motivation to change clinical practices, and lack of time [3].

Traditionally, CPGs are developed based on scientific evidence, mostly obtained from well-controlled randomized controlled trials (RCTs), coupled with a consensus of the expert committee. However, patients enrolled in RCTs may underrepresent the populations encountered in clinical practice such that they systematically exclude the elderly and patients with comorbidities or on concomitant medications. Therefore, the findings of an RCT may not often be generalized to real-world clinical practice. This is why clinical practice by CPGs based on RCT results may result in outcomes different from, often not as good as, what was seen in RCTs.

The rapid advancement of digital health technologies and regulatory expansions paved the way to relatively easily capture data related to patient health collected as part of routine healthcare delivery under real-world conditions, collectively known as real-world data (RWD)

SeonYeong Oh 
<https://orcid.org/0000-0002-9199-8966>
 Howard Lee 
<https://orcid.org/0000-0001-6713-5418>

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[4]. RWD may come from a number of sources: electronic health records (EHRs), insurance claims and billing, product and disease registries, patient-generated data, and mobile health devices [4]. If appropriately analyzed, RWD can generate clinical evidence or real-world evidence (RWE), which can be used to assess the safety and effectiveness of medical products in the real-world [4].

The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), adopted and distributed by the Observational Health Data Sciences and Informatics (OHDSI) research network, is a unified database model to integrate various RWD sources including EHRs according to the same standard [5]. OMOP CDM, now in its version 6.0, has billions of standardized clinical observations from > 20 countries including Korea [5]. Adequately analyzed CDM-based RWD has a huge potential for creating RWE, which is relevant, appropriate, and most importantly practical enough to be incorporated into revised CPGs or updating them. This is possible because CDM-based RWD has a wide variety of information relating to patient's demographics, conditions including diagnosis, measurements such as laboratory test results, procedures, drugs, and observations including vital signs. Not only that, CDM-based RWD are standardized and structured, which can reduce, if not eliminate, lengthy, cumbersome, and laborious data pre-processing and preparation. Therefore, CDM-based RWD can contribute to narrowing the gaps between the CPGs and actual clinical practices.

The objectives of this commentary were threefold. First, we briefly overviewed the major shortcomings of the current CPGs in three common chronic diseases such as type 2 diabetes mellitus (T2DM), dyslipidemia, and chronic obstructive pulmonary disease (COPD). Second, we discussed if and how those shortcomings could be addressed using CDM-based RWD. Last, we emphasized the leadership role of clinical pharmacology in promoting the adequate and innovative use of RWD to complement the existing CPGs.

TYPE 2 DIABETES MELLITUS

T2DM is a chronic disease that increases the risk of microvascular and macrovascular complications. T2DM treatment requires multifactorial risk-reduction strategies to improve glycemic control and to prevent long-term complications [6]. The American Diabetes Association published and has annually updated the CPG in T2DM (the Standards of Medical Care in Diabetes), which recommends complicated decision-making steps to individually optimize patient care [6]. Several shortcomings are found in the current CPG for T2DM. First, although most T2DM patients have to use several drugs during their lifetime, separately or concomitantly, the current CPG is mainly focused on the initial treatment choice while being silent in guiding an optimal sequence of drug selections based on the previous treatment(s). Therefore, clinicians may be confused when and what to switch or combine with another anti-diabetic drug. Second, microvascular complications, which ~50% T2DM patients will experience during their lifetime [7], has been given little attention in the CPG for T2DM, particularly for the choice of the best medications. Last, drug compliance, especially long-term persistence, is not taken into account for when comparing drug treatment options. The drug adherence rate in T2DM patients is still suboptimal (20–50%), which is associated with poor outcomes [8].

CDM-based RWD are useful to uncover various common treatment pathways or sequences, some of which do not follow the CPG recommendations or are not even recommended by

the CPG. By comparing the clinical outcomes of competing treatment pathways, we could determine if CPG-compliant treatment actually results in better clinical outcomes in the real world. For example, using OMOP CDM-based RWD, marked heterogeneity was discovered in the prescription of the second- and third-line agents in T2DM [9]. These results showed that CDM-based RWD has the potential for separately investigating the clinical outcomes of each treatment pathway. Likewise, CDM-based RWD can be used to compare outcomes other than glucose-lowering or major cardiovascular events such as microvascular complications. This utility of the CDM-based RWD assists clinicians in optimizing treatment options for a multitude of situations that are not necessarily individualized or clearly indicated well in the CPGs. If the CPG is updated by incorporating RWE obtained from CDM-based RWD, patient adherence is also likely to increase because the updated or revised CPGs then reflect what is happening in the patient's real life.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a common preventable and treatable respiratory disease characterized by airflow limitation. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) provides recommendations for the management of COPD, which have been more widely adopted in clinical practice than more formal evidence-based guidelines published by The National Institute for Health and Clinical Excellence [10]. Since 2017, the GOLD guideline has included treatment recommendations for COPD that are stratified by symptom severity (commonly using mMRC score) and exacerbation risk [11] not just by the degree of forced expiratory volume in the first second of expiration (FEV₁).

Despite the benefits of the GOLD guideline in improving the quality of patient care, adherence to the current GOLD recommendations in clinical practice remains suboptimal in several countries [12]. A recent retrospective study on COPD management among primary care physicians in the US showed that only 21% of patients received pulmonary diagnostic testing, 31% were misdiagnosed as COPD, and only 42% were treated with recommended pharmacotherapies [12]. Poor adherence to the guideline may contribute to over- and under-treatment relative to the recommendations. Moreover, COPD patients recruited in RCTs may underrepresent typical patients seen in a real-world clinical setting [11,13]. One study found that 60% of patients received inhaled corticosteroids therapy inappropriately, which could have exerted a negative impact on long-term patient outcomes [13]. In addition, not much research has been conducted to compare the GOLD guideline-based treatment vs. non-guideline treatment regarding the relative effectiveness and safety.

The advent of CDM-based RWD enables us to understand the types of treatment prescribed for a particular group of patients, coupled with its effectiveness in a real-world clinical setting. For example, a UK-based cohort study was conducted using the Optimum Patient Care Research Database, an EHR database that includes clinical and prescribing information from 5.8 million geographically and socioeconomically diverse populations [11]. The study demonstrated that over-treated patients seen in primary care appeared to have higher exacerbation rates [11], where the exacerbation rate is a key determinant for COPD management. These results suggest RWD may be utilized to identify additional critical clinical features that are linked with exacerbations [11]. Likewise, the lack of information on new treatment initiation and its subsequent progression can be remedied by utilizing RWE derived from CDM-based RWD. Acquiring a better understanding of the comparative

effectiveness and safety associated with the guideline vs. real-world RWE is necessary to optimize real-life treatment patterns and clinical outcomes for patients with COPD.

DYSLIPIDEMIA

Dyslipidemia is a major risk factor for atherosclerotic cardiovascular diseases (ASCVDs). Currently, there are five leading dyslipidemia CPGs, each published by the American College of Cardiology/American Heart Association, the European Society of Cardiology/European Atherosclerosis Society, the Canadian Cardiovascular Society, the U.S. Preventive Services Task Force, and the U.S. Veterans Affairs/Department of Defense [14]. All of these guidelines have a common ground that reduction in the level of low-density lipoprotein cholesterol with statins is the main treatment target for the primary and secondary preventions of ASCVD [14].

Although all of the current guidelines share more similarities than differences, they differ particularly in the estimators to predict 10-year risk for ASCVD events, statin intensity, treatment of patients with particular comorbidities, and safety concerns. These multiple conflicting CPGs from different professional societies can contribute to the clinician's confusion on patient treatment [14]. One of the main dissimilarities is the variability in the risk estimators. Because most of the risk estimators are based on cohort studies performed two decades ago with patients at a much higher CVD risk but less in ethnic diversity, they typically tend to overestimate patient risks [15]. In addition, statin treatment recommendations are inconsistent between the CPGs for certain subgroups such as the elderly, patients with end-stage renal disease, solid organ transplants, human immunodeficiency virus, inflammatory and rheumatologic diseases, due to the lack of evidence that verifies the effectiveness or safety of statins in those populations [14]. Furthermore, recommendations regarding non-statin treatments are mostly outdated, requiring urgent revisions or updates [14].

RWE obtained from CDM-based RWD can be used to guide harmonious clinical practices by simplifying clinical decision-making. Therefore, CDM-based RWD are beneficial to improve consistency in various discordant CPGs by recommending a single but global risk estimator for a prediction model of ASCVDs. For example, a large prospective cohort study in New Zealand was conducted to develop the guidelines for national CVD risk factors using PREDICT decision support system, a web-based EHR-integrated system for CVD risk assessment and management [15]. National CVD risk factors or predictors were newly refined such that they included socioeconomic deprivation and multiple ethnicities, and the study also identified high-risk patient subgroups who might otherwise be undertreated [15]. Likewise, CDM-based RWD can provide evidence to support the effectiveness of various anti-dyslipidemia treatments in subgroups outside of an RCT setting, particularly in the elderly and women. Lastly, CDM-based RWD could provide strong clinical evidence in the efficacy and safety of non-statins in the treatment of patients with dyslipidemia.

CONCLUSION

As we discussed in the previous sections, CPGs solely based on RCTs may fail to adequately address individual patient's need and situation when determining treatment, management, and follow-up strategies, particularly for those underrepresented in RCTs. CDM-based

RWD, if analyzed appropriately, could fill the gap and complement the existing CPGs by providing RWE, proper and practical enough to address each patient's unique and specific requirements. Among various forms and types of RWD, CDM-based RWD has several advantages not only because they are standardized, structured, but because they are mirroring patient's clinical information, often not available in other types of RWD such as claims data or registries.

Optimal, personalized, and precise drug treatment is one of the most important objectives in clinical pharmacology. However, clinical pharmacologists have long stayed away from actual patient care due to various logistical issues. Limited data access due to ownership challenge, i.e., who owns the data, has contributed to this isolation or less involvement of clinical pharmacology in clinical practice.

But, time has changed. Exploding clinical data and relatively easy access to them has provided clinical pharmacologists with new analytic tools and methods, which could revolutionize the way clinicians treat their patients. CDM-based RWD can be one of these tools, and clinical pharmacologists are best positioned to combine this tool with their individual patient-oriented approaches and skills. Updating or making CPGs more practical and effective in the real world using CDM-based RWD is an area where clinical pharmacologists can lead experts and professionals in other clinical domains by providing a balanced perspective between the macro (i.e., big data) and micro (i.e., individual patient) approaches. Clinical pharmacology has to play a more leadership role in promoting the adequate and innovative use of RWD to complement the existing CPGs for better, practical, and effective patient care.

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