Adherence and Concomitant Medication Use among Patients on Warfarin Therapy: Insight from a Large Pharmacy Dispensing Database in Japan

Masato Takeuchi, a Sayuri Nakano, a Sachiko Tanaka-Mizuno, a,b Chika Nishiyama, a,c Yuko Doi, d Masaru Arai, e Yosuke Fujii, d Toshiyuki Matsunaga, e and Koji Kawakami* a

a Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University; Yoshida Konoe-cho, Sakyo-ku, Kyoto 606–8501, Japan; b Department of Medical Statistics, Shiga University of Medical Science; Ohtsu, Shiga 520–2192, Japan; c Department of Critical Care Nursing, Graduate School of Human Health Science, Kyoto University; Kyoto 606–8501, Japan; d Ain Holdings Inc.; Sapporo 003–0005, Japan; and e Kraft Inc.; Tokyo 100–8225, Japan.

Received July 30, 2018; accepted December 2, 2018

INTRODUCTION

Warfarin, a vitamin K antagonist, is used for the treatment of venous thromboembolism and stroke prevention in patients at risk for conditions like atrial fibrillation (AF). Although its role has been replaced by direct oral anticoagulants (DOACs),1,2 warfarin is still prescribed for thromboprophylaxis for reasons such as its lower cost relative to DOACs.1,2 Despite over 50 years of clinical implementation, warfarin remains a very challenging drug in practice.4,5 First, close adherence is needed because even 1 or 2 missed days in a week may result in a two-fold increased risk of underanticoagulation.5 In addition, patients taking warfarin typically have several comorbidities and thus use concomitant medications. For example, it is common that patients with AF receive about four to six different drug treatments.6 An increased number of concomitant drugs—often referred to as polypharmacy—is particularly problematic in the case of warfarin because this drug has multiple drug–drug interactions. Because the number of people taking warfarin will increase given that life expectancy is increasing, expanding the knowledge gained from a real-world context could provide additional insight into safe and effective warfarin use.

In this study, we sought to determine adherence and use of concomitant medications among people taking warfarin, using a large-scale pharmacy dispensing database in Japan.

MATERIALS AND METHODS

Data Source We used data obtained from three nationwide pharmacy chains in Japan (Ain Pharmacie Inc., Kraft Inc., and Nihon Chouzai Co., Ltd.)7,8, the data comprised dispensing records from more than seven million outpatients in 2012, covering approximately 4% of all outpatient dispensations in Japan that year. The patient demographic data are well matched with the entire population of Japan, but pharmacies are typically located in urban areas. The compiled database was analyzed as standalone, without linking to another data source. Data included patient age, sex, and reimbursement information, but the database did not include clinical information such as the diagnosis of each person or indication for warfarin. We were able to track patient records within the same pharmacy chain via unique identifiers. Dispensed medications were recorded using a Japan-specific code issued by the Japan Ministry of Health, Labour and Welfare,9 as well as the generic and brand names.

Patients and Concomitant Drugs We included all adults patients (≥ 20 years old) with at least one dispensing record of warfarin, the only vitamin K antagonist available in Japan during the study period. Warfarin is given in tablet units or
granule formulation in Japan, not package units or bottle units. We excluded pediatric patients because the uses of warfarin in children have substantially different characteristics from those in adults (e.g., postoperatively in patients with congenital heart disease). We considered that all adult patients were eligible for inclusion in the study if they were taking warfarin; this was to maintain consistency with most previous trials of anticoagulants because those studies included both elderly and non-elderly adults with an indication for anticoagulants. The study period was from January 2012 to December 2012. The observation period started on the date of the first dispensation at each pharmacy chain in 2012, and the last observation was defined as the date of last dispensation.

We examined the number of drugs dispensed together with warfarin; only medications with oral formulations were included for this calculation. Polypharmacy was defined as the use of more than five different concomitant drugs. Further, we investigated concomitant drug use that was associated with increased bleeding risk, with reference to the American College of Chest Physicians 2012 guideline. The drugs requiring special attention mainly include selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents, and certain antibiotics. In Japan, all these drugs are listed in a warning included in the package insert. We additionally examined the proportion of warfarin dispensation together with amiodarone, fluconazole, rifampin, and phenytoin—drugs that are associated with a high risk of major bleeding when used concurrently with DOACs—to explore the extent of eligible patients who are likely to benefit by switching from warfarin to DOACs.

**Statistical Analysis** Descriptive statistics were used to summarize data, such as patient characteristics or number of concomitant drugs and were expressed as mean with standard deviation or median with interquartile range (IQR). To compare two means of continuous values, we used the Student t-test.

Adherence was primary measured using the medication possession ratio (MPR), calculated as follows:

$$MPR = \frac{\text{Total days' supply in the observed period}}{\text{Last fill date} - \text{first fill date} + \text{last fill day's supply}}$$

To calculate the MPR, two or more pharmacy visits are required; therefore, patients with only one pharmacy use were excluded from adherence calculation. By definition, overlaps between multiple dispensations are counted twice in this formula. In Japan, there is no refill service, and only one prescription is given per each physician visit. Some previous studies of warfarin adherence used proportion of days covered (PDC) as a metric of adherence. In this study, we used MPR because, for warfarin, overadherence may be related to overanticoagulation status, and MPR can be used to measure the extent of overadherence. To determine the extent of underadherence using an alternative measure, we also calculated the PDC, which is a more conservative measure of adherence than the MPR.

Underadherence and overadherence are often defined a priori as MPR <0.8 and MPR >1.2, respectively. However, 10% of less or excess use of warfarin may be related to unfavorable anticoagulation control; thus, in this study, MPR <0.9 and MPR >1.1 were primarily used as thresholds for underadherence and overadherence, respectively.

All statistical analyses were conducted with R version 3.33 (https://cran.r-project.org/). A p-value <0.05 was used as the threshold for statistical significance.

**Ethical Statement** This study was conducted under the approval of the Ethical Committee of the Graduate School of Medicine, Kyoto University. Patient data were anonymously provided from pharmacy chains and were analyzed at Kyoto University. Informed consent from each participant was waived based on the Protection of Personal Information act and the Ethical Guidelines for Epidemiological Research of Japan.

**RESULTS**

We found a total of 443007 pharmacy encounters with warfarin dispensation among 71340 individuals (61.9% males); median age was 73 years (range: 20–105 years), with interquartile range (IQR) 64–80 years. Each person had a median of six encounters (IQR: 3–8) within the year observed. There were 10026 individuals (13.3%) with only one dispensation record; these individuals were excluded from the calculation of adherence. Among individuals with more than two encounters, the median observation window from the first to the last visits in 2012 was 308 (IQR: 250–334) days.

**Adherence** The median MPR was 1.0 (IQR: 0.96–1.0); MPR stratified by age group is presented in Fig. 1. Underadherence was found in 10702 individuals (16.3%), and overadherence was observed in 1276 (1.9%). We explored whether demographic data (age and sex) were related to MPR but found no clear trends (data not shown). When we used the conventional cut-off values for underadherence and overadherence (i.e., MPR <0.80 and MPR >1.2, respectively), the proportion of underadherence and overadherence was 9.3 and 0.6%, respectively.

The median PDC was 0.91, with IQR 0.82–0.96. Using this adherence measure, underadherence was found in 23.6% of individuals.

**Concurrent Drug Dispensation** We examined concurrent drug use with warfarin. The median number of co-dispensed drugs was eight (IQR: 5–10) at each encounter. The most common concomitant drugs were antihypertensives (n = 394937), antipeptic drugs (n = 289046), and diuretics (n = 256674). The median number of concomitant drugs did not differ among age groups (Fig. 2). Polypharmacy was found in 75.3% of pharmacy encounters among 76.9% of individuals in this study.

Drugs associated with an increased bleeding risk were dispensed in 40.0% of encounters, accounting for 16.4% of all co-dispensed drugs. The most common drug class was antplatelet agents (including low-dose aspirin), followed by NSAIDs and antibiotics (most commonly cotrimoxazole). A greater number of medications were dispensed to people taking drugs that increased bleeding risk than to those not taking such drugs (9.9 vs. 7.5 drugs, respectively; p < 0.001). We found that 0.38% of encounters involved co-dispensation with amiodarone, fluconazole, rifampin and phenytoin, all drugs with high-risk profiles associated with major bleeding when used concurrently with DOACs.
DISCUSSION

Adherence and proper concomitant drug use are keys to successful anticoagulation management among warfarin users because of its narrow therapeutic index and the array of drug–drug interactions associated with warfarin. In this study, we identified key factors involved in adherence and concomitant drug use among Japanese community-dwelling individuals.
under warfarin therapy. We demonstrated that MPR-based adherence was high and that polypharmacy and concomitant drug use related to bleeding risk were common in our study population.

In this study, we used rigid criteria for adherence—MPR <0.9 for underadherence and >1.1 for overadherence, and found 16.3% underadherence and 1.9% overadherence among warfarin users. Although MPR is an indirect estimate of “true” adherence, our results suggest that overall adherence for warfarin is optimal in the Japanese population, showing a higher rate of adherence than reports from other countries. The reason for high adherence in the Japanese population is uncertain, but our results are comparable with those of another recent report from Japan. Suzuki et al. analyzed self-reported questionnaires among 378 Japanese patients with non-valvular AF (77% warfarin users) and found that 86% of patients were adherent to anticoagulation therapy. They hypothesized that the high adherence rate was owing to patient characteristics of long-standing history of AF and comorbid heart failure; however, it is unclear whether this may hold true for the cohort in our study.

With respect to concomitant drug use with warfarin, two important issues emerged from our study. First, polypharmacy, possibly related to comorbidity, was highly prevalent in all age groups of patients on warfarin therapy. Numerous studies have shown that polypharmacy in elderly adults is related to adverse drug events and multiple coexisting impairments. We found that polypharmacy was not solely a problem among elderly adults; polypharmacy was also common among younger adults taking warfarin. Warfarin is used for individuals with high-risk conditions such as AF or venous thromboembolism. The prevalence of AF among people aged <55 years is low (ca. 0.1%); thus, younger people on warfarin therapy may have indications for warfarin that differ from those of older people. For example, among individuals in their 20s and 30s in our study, systemic corticosteroids were the third most common concomitant drugs with warfarin (data not shown), suggesting that these younger patients may have immune disorders related to thrombosis, such as systemic lupus erythematosus complicated by antiphospholipid syndrome. For several drug classes, such as anticoagulants, studies on polypharmacy involving younger adults are worth considering in the future. The second issue regarding concomitant drug use with warfarin was a concern on safety use; co-dispensation of drugs that elevate bleeding risk was relatively common among warfarin users, consistent with previous studies. These drugs are associated with a two- to four-fold increased risk of a bleeding event, according the findings of large-scale studies. In our study, antiplatelet agents were the most common concomitant drugs with a high bleeding risk. This class of drug was previously used as anticoagulant therapy in AF but its use is currently discouraged, except in patients with specific indications such as those with mechanical valve replacement, acute coronary syndrome, or recent coronary procedure. It is of clinical importance whether warfarin users taking antiplatelet agents would benefit from this combination therapy against bleeding risk, but this was not possible to examine in our database. Further efforts may be warranted, to encourage the optimal use of warfarin as well as co-dispensed medication use.

Our study has five limitations to be discussed here, three of which derived from the standalone nature of our database. First, information on several clinical factors was lacking, namely, indication for warfarin and outcome. As discussed above, because of a lack of data on indication, it is unclear why polypharmacy was common in younger adults taking warfarin or whether co-dispensation of anticoagulants existed solely among individuals with specific indications (e.g., those with mechanical valves). Moreover, we found polypharmacy in approximately three-quarters of warfarin users. Polypharmacy is associated with an increased risk of bleeding or all-cause death in patients with AF under anticoagulant therapy. Given the existence of polypharmacy in combination with the use of drugs that elevate bleeding risk and the high adherence rate for warfarin, our study population could theoretically be at increased risk of bleeding. However, this possibility could not be assessed due to a lack of clinical information. The incorporation of these clinical data would yield insights that remain unanswered in our analyses. Second, patient tracking may be incomplete because this is only possible within the same pharmacy chains. However, among people with two or more encounters, the observation window was a median of 308 d over 1 year, sufficiently high for our research purposes. Third, we could not address the issues of primary non-adherence, that is, medications that are prescribed but not dispensed. Similarly, we excluded individuals with only one dispensing record (13.3%) from the adherence calculation. These issues may result in “inflated” estimation of adherence. Fourth, stores of the pharmacy chains included herein were primarily located in urban areas; thus, our results do not represent the dispensation pattern throughout Japan. Finally, the study period was only the year 2012, when warfarin was the only oral anticoagulant available in Japan. Because of this, our results cannot be extrapolated to the current situation in which both warfarin and DOACs are available options for anticoagulant therapy. However, our findings are less susceptible to selection bias of patients, with respect to the choice of anticoagulant management in each patient.

In summary, overall adherence for warfarin was optimal among our study population. However, polypharmacy was common even among younger people, and medications with a high bleeding risk profile were often co-dispensed with warfarin. How these dispensation patterns would affect the clinical course of patients remains uncertain, owing to a lack of clinical information in the pharmacy dispensing database. With the advent of novel drugs (DOACs) that have fewer drug–drug interactions, studies on anticoagulant therapy is an evolving research area. Future studies incorporating patient clinical information and/or DOACs would be relevant to better evaluate the efficacy and safety of anticoagulant therapy.

Acknowledgments We thank Nihon Chouzai Co., Ltd. (Tokyo, Japan) for providing dispensation data analyzed in this study. We also thank Mr. Sousuke Kinugasa (a medical student at Kyoto University) for statistical assistance.

Conflict of Interest KK has received research funds from Eisai and Takeda Pharmaceutical Company Limited; both companies sell warfarin products in Japan. All other authors have no potential conflicts of interest relevant to this report.
REFERENCES

1) Fosbøl EL, Vinding NE, Lamberts M, Staerk L, Gundlund A, Gadboyl K, Kober L, Glislon GH, Olesen JB. Shifting to a non-vitamin K antagonist oral anticoagulation agent from vitamin K antagonist in atrial fibrillation. *European Heart J.*, 20(6), 378–386 (2018).

2) Husman MV, Rothman KJ, Pasquette M, Teutsch C, Dieder HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Ellisasser A, Bartels DB, Lip GY. GLORIA-AF Investigators. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF registry phase 2. *J. Am. Coll. Cardiol.*, 69, 777–785 (2017).

3) Zirlik A, Bode C. Vitamin K antagonists: relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. *J. Thromb. Thrombolysis*, 43, 365–379 (2017).

4) Kimmel SE. Warfarin therapy: in need of improvement after all these years. *Expert Opin. Pharmacother.*, 9, 677–686 (2008).

5) Kimmel SE, Chen Z, Price M, Parker CS, Metlay JP, Christie JD, Brensingar CM, Newcomb CW, Samaha FF, Gross R. The influence of patient adherence on anticoagulation control with warfarin: results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study. *Arch. Intern. Med.*, 167, 229–235 (2007).

6) Jaspers Focks J, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, Washam JB, Lanas F, Xavier D, Husted S, Wallentin L, Alexander JH, Granger CB, Verheugt FW. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *BMJ Clin. Res. Ed.*, 353, 1368 (2016).

7) Tanaka S, Sato K, Kawakami K. Pharmacoepidemiology in Japan: medical databases and research achievements. *J. Pharm. Health Care Sci.*, 1, 16 (2015).

8) Kadohara K, Sato I, Doi Y, Arai M, Fujii Y, Matsunaga T, Kawakami K. Prescription patterns of medications for Alzheimer’s disease in Japan from 2010 to 2015: a descriptive pharmacy claims database study. *Neur. Ther.*, 6, 25–37 (2017).

9) Akazawa M, Nomura K, Kusama M, Igarashi A. Drug utilization reviews by community pharmacists in Japan: identification of potential safety concerns through the brown bag program. *Value in Health Regional Issues*, 1, 98–104 (2012).

10) Nobili A, Licata G, Salerno F, Pasina L, Tettamanti M, Franchi C, De Vittorio L, Marengoni A, Corrao S, Iorio A, Marcucci M, Manucci PM. SIMI Investigators. Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. *Eur. J. Clin. Pharmacol.*, 67, 507–519 (2011).

11) Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, McLachlan AJ, Cumming RG, Handelsman DJ, Le Couteur DG. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J. Clin. Epidemiol.*, 65, 989–995 (2012).

12) Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, Svensson PJ, Veenstra DL, Crowther M, Guyatt GH. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, 141(2 Suppl.), e152S–e184S (2012).

13) Chang SH, Chou JJ, Yeh YH, Chiu MJ, Wen MS, Kuo CT, Sec LC, Kuo CF. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA*, 318, 1250–1259 (2017).

14) Rabeel MA, Schmittidell J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med. Care*, 51(Suppl. 3), S11–S21 (2013).

15) Casciano JP, Dotiwala ZJ, Martin BC, Kwong WJ. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: a commercial insurer perspective. *J. Manag. Care Pharm.*, 19, 302–316 (2013).

16) McHorney CA, Ashton V, Laliberté F, Germain G, Wynnant W, Cri- vera C, Schein JR, Lefebvre P, Peterson ED. Adherence to rivaroxa- ban compared with other oral anticoagulant agents among patients with nonvalvular atrial fibrillation. *J. Manag. Care Spec. Pharm.*, 23, 980–987 (2017).

17) Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*, 10, 3–12 (2007).

18) Veenboer PW, Bosch JL. Long-term adherence to antimuscarinic therapy in everyday practice: a systematic review. *J. Urol.*, 191, 1003–1008 (2014).

19) Obamiro KO, Chalmers L, Bereznicki LR. Summary of the litera- ture evaluating adherence and persistence with oral anticoagulants in atrial fibrillation. *Am. J. Cardiovasc. Drugs*, 16, 349–363 (2016).

20) Chen SY, Wu N, Gulseth M, LaMori J, Bookhart BK, Boulanger L, Fields L, Schein J. One-year adherence to warfarin treatment for venous thromboembolism in high-risk patients and its association with long-term risk of recurrent events. *J. Manag. Care Pharm.*, 19, 291–301 (2013).

21) Suzuki T, Shiga T, Omori H, Tatsumi F, Nishimura K, Hagiwara, MJ, Svensson PJ, Veenstra DL, Crowther M, Guyatt GH. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, 133, 352–360 (2016).