Title

Trends in use of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015.

Authors

Lars J Kjerpeseth, MD[1], Hanne Ellekjær, MD, PhD[2,3], Randi Selmer, PhD[4], Inger Ariansen, MD, PhD[4], Kari Furu, MPH, PhD[4], Eva Skovlund, PhD[1,4]

[1] Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway

[2] Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway

[3] Stroke Unit, Department of Internal Medicine, St. Olav's Hospital, Trondheim, Norway

[4] Norwegian Institute of Public Health, Oslo, Norway

Corresponding author

Lars J Kjerpeseth, NTNU, Fakultet for medisin og helsevitenskap, Institutt for samfunnsmedisin og sykepleie, Postboks 8905, N-7491 Trondheim, Norway. E-mail: lars.j.kjerpeseth@ntnu.no. Telephone: +47 46 96 86 26.

ORCID ID

LJK: 0000-0002-2033-736X	HE: 0000-0002-2887-3722	RS: Not available
IA: 0000-0001-8529-4826	KF: 0000-0003-2245-0179	ES: 0000-0002-2997-6141

Keywords

Atrial fibrillation, drug utilization, warfarin, dabigatran, rivaroxaban, apixaban

Abstract

Purpose: Since 2011, several direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban) have been introduced as alternatives to warfarin for stroke prophylaxis in atrial fibrillation. We wanted to investigate changes in utilization of oral anticoagulants for atrial fibrillation in Norway following the introduction of DOACs.

Methods: Using nationwide registries, we identified all adults with pharmacy dispensings for warfarin or DOACs between January 2010 and December 2015 in Norway, and used ambulatory reimbursement codes to identify atrial fibrillation as indication. We defined incident use by a one-year washout period. We describe trends in prevalent and incident use of warfarin and DOACs between 2010 and 2015, as well as patterns of treatment switching for incident users.

Results: 129 285 patients filled at least one prescription for an oral anticoagulant for atrial fibrillation; the yearly number of incident users increased from 262 to 421 per 100 000 person-years; and the yearly share of incident users who initiated a DOAC increased to 82 %. Half the prevalent users were on a DOAC by 2015. Within a year of drug initiation, 6, 12, 16 and 20 % of incident users of apixaban, rivaroxaban, warfarin and dabigatran respectively, switched oral anticoagulant.

Conclusions: Use of DOACs for anticoagulation in atrial fibrillation became more prevalent between 2010 and 2015 in Norway, at the expense of warfarin.

Introduction

Atrial fibrillation is the most common cardiac arrhythmia [1]; one in four middle-aged European adults is expected to develop the disease in their lifetime [2]. The prevalence of atrial fibrillation increases with age; 0.12-0.16 % in subjects younger than 50 years, 3.7-4.2 % in those 60-70 years old and 10-17 % in those 80 years or older [3]. Similar numbers have been reported for Norwegian cohorts [4, 5]. Although men are more prone to develop atrial fibrillation, women represent about half of affected adults due to their longer survival [6, 7]. An increasing incidence of atrial fibrillation has been reported globally in the last decades [8], and the number of patients with atrial fibrillation is expected to rise dramatically in the years to come, accompanying the ageing of the population as well as an increase in predisposing conditions and lifestyle factors [3, 7, 8].

The associated five-fold risk of stroke is one of the most feared complications of atrial fibrillation [9]. Prevention of atrial fibrillation-related strokes has for decades been best achieved with vitamin K antagonists such as warfarin, reducing the risk of stroke by as much as two thirds [10]. However, the narrow therapeutic range and corresponding need for frequent monitoring and dose adjustments, as well as the perceived risk of severe bleeding, has limited its systematic and safe use [11].

On August 1st 2011, December 9th 2011, and November 19th 2012; dabigatran (Pradaxa®), rivaroxaban (Xarelto®), and apixaban (Eliquis®) respectively received marketing authorization in Norway; for non-valvular atrial fibrillation in adults with one or more risk factors for stroke. These direct oral anticoagulants (DOACs) have shown at least non-inferior efficacy and safety compared to warfarin in large phase III randomized controlled trials [12-14]. Although costly, the DOACs come with an ease of use compared to warfarin due to fewer interactions, fixed dosing, and no need for routine or frequent laboratory monitoring.

Some questions have been raised about the generalisability of findings from the DOAC trials to the general atrial fibrillation population. For example, the rates of stroke and major bleeding in the warfarin comparator arms do not necessarily hold true for countries with good quality warfarin treatment, such as Norway [4, 15-17], or for the elderly [18, 19]. Nevertheless, recent updates of pivotal European and American guidelines put the DOACs on par with warfarin, and even slightly preferred, in non-valvular atrial fibrillation, as well as endorsing anticoagulation in previously untreated atrial fibrillation patients at the lower end of stroke risk [20-22]. The Norwegian national guidelines on antithrombotics supported these recommendations in November 2013 [23]. Hence, the proportion of patients with eligibility and tolerance for oral anticoagulation has likely increased significantly [24].

Komen et al. [25] have shown that in Stockholm, Sweden, the publication of the European Guidelines was associated with a statistically significant increase in DOAC initiations after 5 months. There was also a significantly increased use of apixaban and rivaroxaban, and a non-significant increase in dabigatran use following implementation of reimbursement. Regional guidelines favouring apixaban and warfarin as first-line treatment, and dabigatran second, increased apixaban initiations at expense of the two other DOACs, while national guidelines had little impact on the prescription pattern.

Knowledge is needed to ensure optimal use of oral anticoagulants in routine clinical care of atrial fibrillation patients following the introduction of DOACs. Thus, the aim of our study was to describe the utilization pattern of warfarin, dabigatran, rivaroxaban and apixaban for atrial fibrillation between 2010 and 2015 in Norway.

Methods

Data source

In this drug utilization study, we retrieved nationwide data from the Norwegian Prescription Database and the National Registry. The former register covers all prescribed drugs dispensed at Norwegian pharmacies to non-institutionalized patients since 2004 [26, 27]. A record of each dispensation is made with information on the patient, prescriber, and drug. Variables include dispense date, Anatomical Therapeutic Chemical classification, brand name, strength, package size and number, and reimbursement code.

The National Registry contains information on all residents of Norway. It provides variables on gender and year of birth in this study, as well as the date of death, emigration, and other changes in resident status. The National Registry also holds the national identification number unique to all residents of Norway, received upon birth or immigration. The identification numbers were replaced with anonymized person-identifiers before we received the datasets.

Study drugs

We retrieved information on all users of warfarin, dabigatran, rivaroxaban and apixaban in the study period; 2010-2015. A fourth DOAC, edoxaban, was authorized for stroke prophylaxis in June 2015, but we did not include it since it was not marketed in Norway in the study period. In Norway, the authorized dosages for stroke prophylaxis in atrial fibrillation are 110 mg and 150 mg twice daily for dabigatran, 15 mg and 20 mg once daily for rivaroxaban, and 2.5 mg and 5 mg twice daily for apixaban. Rivaroxaban is also available in strengths of 2.5 mg and 10 mg and dabigatran in 75 mg. All dosages of the drugs were included in the analyses, and prescriptions of ≤110 mg for dabigatran, ≤15 mg for rivaroxaban, and ≤2.5 mg for apixaban were defined as 'reduced dose' treatment.

Reimbursement policy

Long-term drug treatment of chronic conditions such as atrial fibrillation is partially reimbursed in Norway using a reimbursement code approved by the Norwegian Medicines Agency. Prescribed drugs are fully reimbursed if the patient's combined expenditures on medicines and health care services reaches a set threshold during a year. From 2010 to 2015, this threshold increased from €198 to €235 (2016 average exchange rate). The physician can also apply for reimbursement if the drug is not on the reimbursement list (i.e. if a drug has marketing authorization, but is not (yet) approved for reimbursement). In March 2008, the 10th revision of International Classification of Diseases (ICD-10) and the 2nd edition of International Classification of Primary Care (ICPC-2) codes were implemented as reimbursement codes in Norway. Atrial fibrillation was introduced as a reimbursement code for warfarin at this point; replacing a non-specific code for general cardiovascular disease in use since the 1960s. Preapproved reimbursement for use in non-valvular atrial fibrillation was granted for Pradaxa® and Xarelto® on January 1st 2013, and for Eliquis® on July 15th 2013.

Study population and study period

The patients had to fulfil the following criteria to be included in the study: At least one dispensing on tablets/capsules of warfarin, dabigatran, rivaroxaban and/or apixaban between January 1st 2010 and December 31st 2015; reimbursement code for atrial fibrillation/-flutter, I48 (ICD-10) or K78 (ICPC-2) on one or more of these prescriptions; and at least 18 years of age the year the drug was dispensed [28, 29]. A period of no available DOACs on the market, from January 2010 to July 2011, was included to get a better understanding of the impact of DOACs on the prescription trends. We excluded individuals who did not match on the person-identifier in the datasets from the Norwegian Prescription Database and the National Registry, as well as citizens with permanent residency abroad. Patients were followed from the date of the first prescription that was reimbursed for atrial fibrillation. In the case of DOACs, the prescription also had to be made on or after the date of marketing authorization for atrial fibrillation.

Measures

Prevalence

We defined prevalent users as individuals who were dispensed an oral anticoagulant for atrial fibrillation at least once during a calendar year. Indication for atrial fibrillation was assumed if the prescription had a reimbursement code for atrial fibrillation. This assumption was also made when a prescription, or a number of following prescriptions, were lacking reimbursement code for atrial fibrillation, but the first following prescription with a reimbursement code for atrial fibrillation occurred within 365 days. The denominator was gender- and age-specific numbers for the midyear population of Norway, which were retrieved from Statistics Norway.

Incidence

We defined incident users as patients who were dispensed an oral anticoagulant at least once during a calendar year, who did not receive any oral anticoagulant during the 365 days beforehand, and who had an indication for atrial fibrillation as defined in the prevalence section. The use of a one-year washout period was supported by the estimated waiting time distribution, which levels off after 12 months (online resource 1) [30]. The denominator was gender- and age-specific figures for the midyear Norwegian population minus the number of prevalent users in the year beforehand. It was possible to be an incident user more than once.

Switches

A switch of drugs in a user was defined as a dispensing of one drug followed by a dispensing of one of the three other study drugs (e.g. a dispensing of apixaban followed by a dispensing of either warfarin, dabigatran or rivaroxaban) within 365 days. To accommodate a fair comparison of the drugs, we limited our switch analyses to patients who became incident users January 1st 2013 or later, after apixaban's marketing authorization for atrial fibrillation in late 2012. A Kaplan-Meier plot of the time to first switch in incident users of each drug was made

using the time from the first prescription to the first switch. We censored at day 366 past the last prescription; at the date of emigration, death, or expired national identification number; or at study end – whichever occurred first.

Statistical analyses

We analysed the data at an individual level using Stata/MP version 13. Aside from the Kaplan-Meier plot for first switches, we used descriptive statistics to analyse the use of each drug separately and combined, as well as DOACs combined. We also compared the temporal trends in drug prescribing practice by gender, age, physician specialty, and first and second switches. Yearly and monthly trends are presented as population incidence rates, prevalences, or percentages of cases.

Results

In all, 195 047 individuals filled at least one prescription for warfarin, dabigatran, rivaroxaban or apixaban in the study period, and 129 285 of these individuals (66.3 %) were reimbursed for atrial fibrillation on at least one of the prescriptions. Their median age was 76 years (41.2 % women) at the start of follow-up, and they filled a total of 1 687 591 prescriptions during follow-up (table 1). The dabigatran users were younger, and among users older than 64 years a larger proportion received a reduced dose on their first prescription of dabigatran compared with rivaroxaban and apixaban. After washout, we identified 81 441 incident users, of which 77 068 were unique individuals. The incident user subgroup median age was 75 years, but they otherwise had similar baseline characteristics as the prevalent users (online resource 2).

Between 2010 and 2015, the number of incident users of oral anticoagulation for atrial fibrillation increased by 60 %, from 262 to 421 per 100 000 person-years, while the number of prevalent users rose by 50 %, from 1366 to 2044 per 100 000 citizens. The use of DOACs increased each year throughout the study period (Fig. 1), and slightly more than half the prevalent users were on a DOAC by 2015 (online resource 3). Among prevalent users, dabigatran was the most common DOAC until 2014, but was replaced by apixaban and rivaroxaban in 2015.

Yearly incidence rates of anticoagulant users stratified by age, sex and drug can be seen in table 2. The yearly rate of incident users increased in all strata of age and gender from 2010 to 2015. The incidence rates for women increased by 62 % among 18-64 year-olds, 76 % among the 65-74 year-olds, 47 % among the 75-84 year-olds and 108 % among the ≥85 year-olds from 2010 to 2015. The corresponding figures for men were 39 %, 49 %, 52 % and 90 %, respectively. The prevalence rates showed similar, but slightly weaker increase by age and gender strata (online resource 4). The yearly incidence rate was higher for men than women in all age groups, but the relative difference showed a decreasing trend with age and time. Between 2010 and 2015, the male to female ratio in incidence rate decreased from 3.5 to 3.0 for those 18-65 years, from 2.3 to 1.9 for those 65-74 years and from 1.5 to 1.4 in those ≥85 years, while the ratio remained stable at 1.6 for the 75-84 year age group. The male to female ratio in total incidence rates decreased from 1.5 in 2010 to 1.4 in 2015. Similar gender differences were observed for yearly prevalence rates in 2010 and 2015, both specific to age groups and in total.

The percentage of incident dabigatran users per month gradually increased following its market authorization for non-valvular atrial fibrillation; from 1.1 % in August 2011 to 14.6 % in December 2012 (Fig. 2). Likewise, after rivaroxaban's market authorization in December 2011 the percentage of incident rivaroxaban users rose slowly to 4.0 % in December 2012. Both dabigatran and rivaroxaban saw a prominent adoption in January 2013; being dispensed to 37.9 % and 11.8 % of initiators respectively. However, while the proportion of incident rivaroxaban prescriptions stabilized at 20-30 % throughout the rest of the study period, the percentage of incident dabigatran users dwindled, reaching 5.9 % in the last month of follow-up.

Despite its market authorization in December 2012, apixaban saw its first use in incident users in June 2013. Its monthly share then increased incrementally from 0.1 % at this point to 30.2 % in September 2014, when it became the most prescribed oral anticoagulant in initiators, to 54.5 % in December 2015. The share of warfarin initiators gradually decreased with the launch of the DOACs. However, warfarin was still the third most initiated drug in the last year of follow-up; being prescribed to 18.1 % of incident users. The corresponding figures for dabigatran, rivaroxaban and apixaban were 8.8 %, 24.4 % and 48.6 % respectively.

A few differences in prescribing pattern became apparent when stratifying the incident users in age groups of 18-64, 65-74, 75-84 and ≥85 years (online resource 5). The adaption of DOACs was a bit slower in those 75 years and older, and in December 2015 warfarin was still the second most initiated drug in the eldest group. The

adaption of apixaban increased with age; about 60 % of those 85 years and older initiated the drug in December 2015 compared to slightly less than half in those <65 years.

Specialists in family medicine both initiated and maintained far more treatments than any other specialist groups. Cardiologists were the second most prevalent oral anticoagulant initiators of the specialists. Compared to specialists in family medicine, they were quicker to adapt DOACs; 21.9 % of their incident user prescriptions were for a DOAC in 2012, and 79.3 % and 94.2 % in 2013 and 2015 respectively. The corresponding numbers for specialists in family medicine were 7.7 %, 52.8 % and 73.2 % respectively. For both specialist groups, the time-trends for drug choice was similar to the incident user cohort as a whole (results not shown).

We registered at least one drug switch in 15.3 % of those who became incident users between January 1st 2013 and 31st December 2015, and 3.1 % switched more than once. Initiators of dabigatran had the shortest time to first switch and apixaban initiators the longest; within a year of drug initiation, 6.1 % of apixaban users, 12.4 % of rivaroxaban users, 16.1 % of warfarin users, and 20.3 % of dabigatran users had switched (online resource 6). There was an increasing preference for apixaban at the expense of dabigatran as the new drug at first switch in warfarin users. At first switch in incident users of dabigatran or rivaroxaban, other DOACs gradually replaced warfarin as the new drug of choice. For incident apixaban users however, the percentage who received warfarin at first switch remained quite stable over time, at about 40-45 % (Fig. 3). In the minority of switchers who had a second switch (20 %), most switched back to their original drug (online resource 7).

Discussion

In this study covering the entire adult Norwegian population with pharmacy dispensings for warfarin or DOACs, we found a yearly increase in prevalent and incident users of oral anticoagulants for atrial fibrillation between 2010 and 2015.

One reason could be due to an increasing incidence and/or prevalence of atrial fibrillation in Norway during the study period. Though few studies exist on the subject in Norway, an increasing incidence and prevalence of atrial fibrillation has been reported globally [8, 22]. Apart from ageing populations, better survival from other cardiovascular diseases, and surges in risk factors such as hypertension and obesity; better detection of silent atrial fibrillation has been cited as contributors of the nearly epidemic growth of atrial fibrillation [8, 22].

On the other hand, the introduction of CHA_2DS_2-VASc score in 2010 as an alternative to the less comprehensive $CHADS_2$ score in predicting the stroke risk in patients with non-valvular atrial fibrillation may have lowered the threshold for prescribing anticoagulants [20]. While DOACs are rapidly replacing warfarin as stroke prophylaxis in atrial fibrillation in Norway, we also found that the increase in incident DOAC users was higher than the decrease in incident warfarin users, especially in 2013. This may indicate a lower threshold for anticoagulation with DOACs, especially for patients with expected intolerance for warfarin.

The timeline of drug choice in incident users per month clearly showed a sharp uptake of dabigatran and rivaroxaban following their reimbursement in January 2013, and similarly for apixaban in June 2013. There is also a small increase in initiators of dabigatran and rivaroxaban between August and December 2012, following the publication of the European guidelines. Any effect of national guidelines is hard to discern in our material. These observations are in line with a Swedish study on the effect of policy changes on DOAC dispensing [25].

An increasing use of DOACs and especially apixaban in atrial fibrillation patients, superseding the use of warfarin seen in our study, has also been reported in Sweden [25] and Denmark since 2011 [31]. The GLORIA-AF registry (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) has also seen a high uptake of DOACs at registry sites across the world during the same period as our study; the frequency of prescriptions for DOACs superseded that for vitamin K antagonists in Europe and North America 32].

Despite the higher prevalence of atrial fibrillation in men at all ages, women account for about half of all adults with atrial fibrillation in Western populations because women outnumber men at old age [6, 7]. Even though the rates of incident and prevalent users were higher among men than women in our study, the relative difference in the rates became smaller from 2010 to 2015. One possible explanation is the implementation of the CHA_2DS_2-VASc risk score [20] during the study period; unlike the $CHADS_2$ score it replaced, it emphasizes female sex as a risk factor for stroke. A meta-analysis by Pancholy et al. suggests that women who take maximum doses of DOACs have a similar protective effect and lower rates of major bleeding compared to men, while they have higher risk of stroke and systemic embolism and similar bleeding rates on warfarin [33]. This is perhaps due to

more difficulty in maintaining women than men within therapeutic range with warfarin [33]. Women could thus be poised to benefit the most on the transition from warfarin to DOACs observed for Norway.

From 2013 to 2015 in Norway, 20 %, 16 %, 12 % and 6 % of incident users of dabigatran, warfarin, rivaroxaban and apixaban respectively, switched to another oral anticoagulant within 12 months of first dispensing. A Danish nationwide study reported similar switch rates within one year; 17%, 14 % and 8 % for initiators of dabigatran, rivaroxaban and apixaban, respectively [34]. In the Dresden DOAC registry, 8 % of rivaroxaban users and 26 % of dabigatran users switched to another oral anticoagulant during a median follow-up of 18 and 24 months, respectively [35, 36].

Medical procedures such as cardioversion and ablation could have necessitated a temporary switch to warfarin in DOAC users. Considering the DOACs differing dependency on kidney function; greatest for dabigatran and lowest for apixaban [37]; a reduction in kidney function related to old age or interim disease is perhaps more likely to motivate a switch in dabigatran users and to some extent in rivaroxaban users, compared to apixaban users. In the Dresden DOAC registry, unstable international normalized ratio, bleeding complications and frequent falls were the main reasons for switching from a vitamin K antagonist to dabigatran or rivaroxaban in atrial fibrillation patients [35, 38]. Bleeding complications, nonhaemorrhagic side effects, stable sinus rhythm and worsening renal function were some of the most common reasons for discontinuation of rivaroxaban and dabigatran [35, 36]. Thromboembolic complications rarely induced a change of treatment [35, 36, 38].

The Norwegian Prescription Database does not register drugs dispensed during stays in hospital, and nursing and retirement homes. Patients with permanent residency in nursing and retirement homes, such as frail elderly and younger adults with physical or mental disabilities, could be underrepresented in our material. As of 2011, residents in long-term municipal care in Norway had a female share of 70 % and mean age 84 years at the start of the stay, and 46 % stayed in the institution more than a year [39]. Thus, we might expect particularly elderly women to be underrepresented. The percentage of elderly with residency in such institutions has been steadily declining in Norway over the last decades however [39]. As more elderly live at home and have their drugs dispensed at the pharmacy instead of an institution, this could partly explain why we observe an especially large increase in oral anticoagulant use among elderly men and women.

We used reimbursement codes to identify atrial fibrillation patients in this study. This ensured inclusion of patients treated in primary and/or more specialized care. Reimbursement codes based on ICD-10 and ICPC were implemented in the Norwegian Prescription Database between March 2008 and March 2009. The old codes, which are not specific to a diagnosis, were used on a few prescriptions as late as 2013 in our data; any underestimation of incidence or prevalence will likely be very small however. Also, the dispensed drugs could have been used later or not at all, overestimating the incidence and prevalence numbers. We lack information on individual dosing, but assumed standard dosing of DOACs, i.e. one tablet twice daily for dabigatran and apixaban and one tablet once daily for rivaroxaban, regardless of strength. The ‘reduced dose’ classification does not necessarily hold true if another regimen was used.

Conclusion

Use of oral anticoagulants for prophylactic anticoagulation in atrial fibrillation became more prevalent between 2010 and 2015 in Norway, with an increasing use of DOACs at the expense of warfarin.

Authors’ contribution

LJK and RS did the analyses. LJK wrote the manuscript. All authors helped plan and design the study, interpret findings, and revise the manuscript. All authors approved the final version of the manuscript.

Compliance with ethical standards

The Regional Committee for Medical and Health Research Ethics in Central Norway approved the study protocol before the study commenced. The Norwegian Data Protection Authority gave a license to link registry data. We have no conflicts of interest to declare.

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Table captions

Table 1 Baseline characteristics of cohort (N=129 285). Numbers and percentages of the cohort at their first prescription of warfarin, dabigatran, rivaroxaban, and apixaban for atrial fibrillation from January 1st 2010 to December 31st 2015 in Norway.

Table 2 Incident users per year from 2010 to 2015 according to oral anticoagulant, gender and age. Numbers per 100 000 person-years with total number observed in parentheses for incident users of warfarin, dabigatran, rivaroxaban and apixaban for atrial fibrillation according to oral anticoagulant, gender and age group at initiation from January 1st 2010 to December 31st 2015 in Norway.

Figure legends

Fig. 1 Yearly number of incident users of warfarin, dabigatran, rivaroxaban, and apixaban for atrial fibrillation per 100 000 person-years from January 1st 2010 to December 31st 2015 in Norway

Fig. 2 Percentages per month of incident users who initiated warfarin, dabigatran, rivaroxaban, or apixaban for atrial fibrillation from August 1st 2011 to December 31st 2015 in Norway

Fig. 3 Drug selected at first switch by percentage per year for incident users of warfarin, dabigatran, rivaroxaban, or apixaban for atrial fibrillation from January 1st 2010 to December 31st 2015 in Norway.

Captions for electronic supplementary material

Online resource 1 Waiting time distribution during 2014 and 2015 using monthly intervals

Online resource 2 Baseline characteristics of incident users (N=81 433)

Online resource 3 Yearly prevalence of oral anticoagulant users for atrial fibrillation from 2010 to 2015

Online resource 4 Prevalent users per year from 2010 to 2015 according to oral anticoagulant, gender and age

Online resource 5 Time trends for drug initiated among incident users from 2011 to 2015 according to age

Online resource 6 Time to first switch in incident users from 2013 to 2015

Online resource 7 Time trends in drug selected at second switch in incident users from 2013 to 2015