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ORIGINAL REPORT

A comparison of two methods for estimating refill adherence to statins in Sweden: the RARE project

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ABSTRACT

Purpose To analyse and compare refill adherence to statins estimated with two different methods with a focus on sensitivity to definitions.
Methods Individuals aged 18–85 years who filled a statin prescription for the first time in 1.5 years during 1 January–30 June 2007 were followed until emigration or death or until 2 years after their first statin purchase. The data were collected via linkage between the Swedish Prescribed Drug Register, the National Patient Register and the Total Population Register. Days' supply was estimated based on amount dispensed and prescribed dosage. Refill adherence was estimated with the continuous measure of medication acquisition (CMA) and the maximum gap method (cut-off 45 days). The impact of altering definitions, for example, regarding hospitalisations, length of observation period and management of overlapping supply, was analysed.
Results The study included 36661 individuals (mean age 64 years, 47% women). The median proportion of days with statins was 95%, and 76% were classified as adherent with a cut-off at ≥80% with CMA. With the maximum gap method, 65% were adherent. Disregarding hospitalisations did not alter the results. Emigration or death at least one year after statin initiation was associated with a lower adherence with both methods, and a shorter observation period and adding overlapping supply to the subsequent prescription increased the adherence estimates.
Conclusions The choice of method and definitions, particularly regarding the management of overlapping supplies and the length of observation period, has a substantial impact on estimates of refill adherence to statins. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—medication adherence; drug utilisation; Swedish Prescribed Drug Register; statins

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INTRODUCTION

Adherence to long-term treatments is on average 50%, and poor adherence is associated with adverse health outcomes and increased health care costs.[1] *Adherence* has been defined as 'the extent to which a person's behaviour–taking medication [...] corresponds with agreed recommendations from a health care provider'.[1]

Adherence can be measured directly or indirectly using different types of data.[2] Refill adherence measures the amount of dispensed drugs in relation to time between refills and is an indirect measure of adherence.[2] In countries with universal drug coverage, such as Sweden, refill adherence is considered an accurate measure of overall adherence.[2] However, the methods used to estimate refill adherence vary between studies; they can be continuous or apply a cut-off, the number of included drug purchases varies, and they may focus on drug availability or gaps.[3–9] The cut-off for classifying individuals as adherent or non-adherent at ≥80% is commonly applied in adherence research, but cut-offs should be used with caution, unless they have been validated for the particular drug or disease.[1]

Several previous studies have compared different methods of refill adherence.[4–7] However, drug utilisation patterns are sensitive to characteristics of the

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reimbursement system, and these systems differ between countries.[10–14] Thus, regulations and reimbursement systems also have an impact on estimates of refill adherence. To our knowledge, no previous study has analysed the impact of different methods and definitions on refill adherence to long-term treatment in a Swedish setting using the nationwide Swedish Prescribed Drug Register (SPDR). The SPDR was established in 2005, and data for a sufficient time period are now available to study long-term adherence in a large, population-based sample. For this methodological study, statins were considered a suitable drug group because they are prescribed for long-term treatments and are available on prescription only, thus ensuring full coverage of outpatient use of statins in the SPDR. Statins have also been included in previous studies focusing on methodological aspects of refill adherence.[6,15] The aim of this study was to analyse and compare refill adherence to statins estimated with two different methods, the continuous measure of medication acquisition (CMA) and the maximum gap method, with a focus on sensitivity to definitions. The two measures of refill adherence were chosen because they represent two different approaches to study refill adherence that are commonly used.[4–7,9]

METHODS

This study is part of the RARE (Refill Adherence in REgisters) project, which was initiated to analyse refill adherence to long-term treatments in the Swedish setting in relation to patient-related and structural factors.

Data sources

Data on dispensed drugs were collected from the SPDR[16] and included information on age, sex, drug type and amount and date of dispensing. Dosage instructions from the prescriber are included in the SPDR as a free text variable. SPDR includes all dispensed prescriptions irrespective of reimbursement status, but not drugs provided during hospital admissions. Information on time and duration of hospital admissions was collected from the National Patient Register. Date of emigration or death for censoring purposes was collected from the Total Population Register. The register linkages were performed with the unique person identification number as the identification key.

Study population

Individuals aged 18–85 years who during 1 January–30 June 2007 (the index period) purchased a statin were identified (N=579 288) in the SPDR (Table 1). The date of their first statin purchase during the index period was defined as their index date. To include incident users only, individuals who purchased a statin during 1.5 years before their index date were excluded. The length of this period, that is, 18 months, was chosen because the Swedish reimbursement system allows an individual to fill 3 months' supply at each purchase, and drug supplies for 15 months or more can be purchased during the 12-month reimbursement period. A 12-month washout period, as is often applied, was therefore not considered sufficiently long in this context, and an 18-month period was chosen instead. Individuals with multidose dispensed drugs (ApoDos) were excluded because information on the prescribed daily dose, which is important for this study, is missing for these individuals. Furthermore, individuals with ApoDos generally receive their prescribed drugs automatically from the pharmacy every 2 weeks, which creates an artificially regular drug dispensing pattern. Those who emigrated or died within 1 year from their index date were excluded from the study. Individuals were followed until date of emigration or death or until 2 years after their index date, whichever occurred first. To exclude those who did not initiate statin treatment, at least one additional statin purchase within 120 days following the index date was required. Individuals with more than five overlapping treatment episodes were excluded. The final sample included 36 661 incident statin users.

Table 1. Description of exclusion criteria applied stepwise to the 600 377 individuals who purchased a statin during 1 January–30 June 2007 to identify the study population (N=36 661)

Exclusion criteria	Excluded	Remaining
Age younger than 18 years or older than 85 years at index date	21 089	579 288
Purchased a statin within 1.5 years prior to index date	518 816	60 472
Purchase of multidose dispensed drugs during the study period	2168	58 307
Died or emigrated within 1 year from index date	855	57 452
Purchase of two or more different statin substances	6241	51 211
Only one purchase of a statin during the study period	5138	46 073
Second purchase more than 120 days from index date	9073	37 000
No interpretable dosage instructions	36	36 964
Interpretable dosage instruction missing for the first purchase	278	36 686
More than five overlapping treatment episodes	25	36 661

Estimation of days' supply

The number of days' supply of statins was estimated based on information on number of dispensed units (e.g.

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tablets) and an interpretation of the dosage instructions. An algorithm for the interpretation of dosage instructions was developed by the first author. The number of dispensed units, for example, 180 tablets, was divided by the number of prescribed units per day (e.g. 2 tablets daily) as interpreted by the algorithm, in this example yielding 90 days' supply. The algorithm was validated in two rounds: (i) authors E.L., A.C., A.M., A.K.J. and K.A.S. reviewed 2000 unique dosage instructions each (total 10 000), and inaccuracies in the algorithm were corrected, and (ii) all unique dosage instructions ($n = 16\,118$) were reviewed by the same authors, and the algorithm was further adjusted to correct for inaccuracies. Dosage instructions such as "1–2 tablets daily" or "1 tablet per day during the first two weeks and thereafter 2 tablets per day" were regarded as non-interpretable. When an interpretable dosage instruction was missing, the preceding interpretable dosage instruction for that individual was used instead.

Methods for estimating refill adherence

Continuous measure of medication acquisition (CMA) and the maximum gap method are described below.

$$\textbf{CMA}(\text{continuous measure of medication acquisition}) = \frac{\text{Number of days' supply}}{\text{Number of days in the observation period}}$$

Maximum gap method

= no more than 45 consecutive days with gaps during the observation period

CMA is similar to the Medication possession ratio and measures the proportion of days' supply obtained during a given time period, whereas the maximum gap method identifies gaps in drug supply, which exceeds a predetermined time period.[4,6,7] The cut-off for the maximum gap method (45 days) in this study was chosen based on the structure of the Swedish reimbursement system, where a maximum of 3 months' supply can be dispensed within the reimbursement at each occasion.[17]

Treatment episodes were estimated based on date of purchase and days' supply as estimated with the interpretation algorithm. Statins were assumed to be provided by the hospital during hospital admissions. When treatment episodes overlapped, the overlapping days were added to the subsequent prescription.

To facilitate comparison with previous studies, we employed a cut-off for adherence or non-adherence. For CMA, patients with ≥80% of days with statins available during the entire observation period were defined as adherent. The cut-off at 80% was chosen because a lower adherence has been associated with an increased risk for adverse outcomes.[18,19] The maximum gap method defined patients without gaps longer than 45 days at any time during the observation period as adherent.

Sensitivity analyses

To assess the stability in the estimates of refill adherence, the following sensitivity analyses were performed: (i) the study population was restricted to individuals aged 40–85 years, that is, the population constituting the majority of statin users, in an effort to exclude patients with a deviant cardiovascular risk profile; (ii) the second statin purchase had to occur within 100 days and (iii) the second statin purchase had to occur within 140 days to assess the stability of the 120-day limit in the primary analysis; (iv) the individuals were assumed to consume statins from their own supply during hospital admissions to analyse whether accounting for periods of hospitalisations had an impact on the estimates; (v) the observation period ended 1 year after index date to assess the influence of a shorter observation period; (vi) to assess the impact of accumulation of drug supplies, the overlapping supplies were disregarded, that is, not added to the subsequent prescription; and (vii) all patients were assumed to consume one tablet per day to analyse the impact of the algorithm to interpret the dosage instructions. Furthermore, the maximum allowed gap was adjusted to 30 and 60 days, respectively, to assess the stability of the selected cut-off. Because the study population was expanded ($N = 38\,916$) in the third sensitivity analysis, all new dosage instructions were validated by the first author.

Data management and analyses was performed in SAS Version 9.1.3 (SAS Institute, Cary, NC). The RARE project has been approved by the regional ethics board in Gothenburg, Sweden (No. 284-09).

RESULTS

The characteristics of the study population are presented in Table 2. The mean age was 63.6 years (62.5 years among men and 64.8 years among women), and 47% were women. The most common statin substance was simvastatin. One fourth of the study population had been hospitalised during the observation period, and 10% had been hospitalised two times or more. Among those who were hospitalised, the median (mean) number of hospital admissions was 1 (2.1), and 10% were hospitalised four times or more.

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Table 2. Characteristics of the study population of incident statin users (*N*=36 661)

	Men (*N*=19 530)	Women (*N*=17 131)	Total (*N*=36 661)
Age, *n* (%), years			
18–39	468 (2.4)	235 (1.4)	703 (1.9)
40–49	2073 (10.6)	1042 (6.1)	3118 (8.5)
50–59	4695 (24.0)	3631 (21.2)	8326 (22.7)
60–69	6937 (35.5)	6312 (36.9)	13249 (36.1)
70–79	4238 (21.7)	4629 (27.0)	8867 (24.2)
80–85	1119 (5.7)	1279 (7.5)	2398 (6.5)
Statin substance, *n* (%)			
Atorvastatin	805 (4.1)	655 (3.8)	1 460 (4.0)
Fluvastatin	31 (0.2)	23 (0.1)	54 (0.2)
Pravastatin	83 (0.4)	77 (0.5)	160 (0.4)
Rosuvastatin	260 (1.3)	193 (1.1)	453 (1.2)
Simvastatin	18351 (94.0)	16183 (94.5)	34534 (94.2)
Hospitalised during the study period, *n* (%)	5440 (27.9)	4028 (23.5)	9468 (25.8)
Death or emigration after 1 year from index date, *n* (%)	246 (1.3)	126 (0.7)	372 (1.0)

Further, the median (mean) number of total days in hospital was 5 (10.3), and 10% of those hospitalised spent 25 days or more in the hospital. One percent emigrated or died during the study period, and 79% of these had been hospitalised during the study period.

The prescribed daily dosage was 1 tablet or capsule for 98.4% of dispensed prescriptions. Two units per day was prescribed in 0.7% of the dispensed prescriptions, and 0.5 and 1.5 in 0.2% each. The proportion of non-interpretable dosage instructions was 0.6%.

As presented in Table 3, the proportion of days with statins during the study period was 95%. With a cut-off at ≥80% applied to CMA, 76% were classified as adherent. With the maximum gap method, 65% were classified as adherent. Among those classified as adherent with CMA, 85% (*n*/*N*=23661/27782) were adherent according to the maximum gap method. On the other hand, among those who were adherent according to the maximum gap, 100% (*n*/*N*=23661/23672) were classified as adherent with CMA.

The sensitivity analyses showed that disregarding overlapping supplies resulted in lower adherence estimates according to both methods (Table 4). Reducing the observation period to 1 year increased the adherence estimates. Assuming one tablet or capsule per day or assuming that patients consume statins from their own supply during hospital admissions did not alter the adherence estimates. When the cut-off for the maximum gap method was set to 30 and 60 days, respectively, the proportions classified as adherent were 57% and 69%.

Table 3. Refill adherence to statins as estimated with CMA and the maximum gap method in the study population of incident statin users (*N*=36661)

	CMA	CMA	Maximum gap
	Proportion of days with statins, median (Q1–Q3)	Proportion adherent (%)*	Proportion adherent (%)†
Total	95.2 (80.8–99.7)	75.8	64.6
Sex			
Men	95.1 (81.1–99.7)	76.6	65.3
Women	95.2 (79.8–99.7)	74.9	63.8
Age, years			
18–39	84.0 (57.9–96.2)	56.6	43.2
40–49	91.4 (70.5–98.6)	69.2	56.4
50–59	94.3 (78.8–99.5)	74.0	62.5
60–69	95.8 (81.7–99.9)	77.6	66.3
70–79	96.4 (82.9–100.0)	78.2	67.9
80–85	96.3 (81.8–100.0)	77.2	66.9
Statin substance			
Simvastatin	95.2 (81.1–99.7)	76.4	65.1
Atorvastatin	94.2 (68.0–99.9)	68.6	58.6
Other	88.7 (54.0–99.2)	60.4	50.1
Hospitalised during study period			
No	94.8 (80.0–99.6)	75.0	63.8
Yes	96.6 (82.4–100.0)	78.0	66.7
Death or emigration after 1 year from index date			
No	95.2 (80.8–99.7)	75.9	64.7
Yes	88.9 (73.9–99.1)	66.9	49.2

CMA, continuous measure of medication acquisition; Q1–Q3, first and third quartiles.
*Adherent: ≥80% of days with statins.
†Adherent: no gap longer than 45 days.

DISCUSSION

This study illustrates that the estimates of refill adherence vary considerably between the different methods. The median proportion of days with statins during the study period was 95%. With an 80% cut-off, 76% of the individuals were classified as adherent according to CMA. With the maximum gap method, 65% were classified as adherent. The two methods for estimating refill adherence in this study focus on different aspects

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Table 4. Sensitivity analyses applied to estimates of refill adherence to statins as measured with CMA and the maximum gap method in the study population of incident statin users (N=36661)

	CMA	CMA	Maximum gap
	Proportion of days with statins, median (Q1–Q3)	Proportion adherent, %*	Proportion adherent, %†
1. Age 40–85 years (N=35958)	95.3 (81.1–99.7)	76.2	65.0
2. Second purchase within 100 days (N=31733)	96.0 (81.5–100.0)	76.9	66.3
3. Second purchase within 140 days (N=38916)	94.5 (78.5–99.6)	74.1	62.7
4. Statins not provided by hospital during admissions (N=36661)	94.9 (80.6–99.6)	75.5	64.1
5. Observation period 1 year (N=36661)	98.4 (89.3–100.0)	87.3	81.8
6. Overlapping treatment episodes were disregarded (N=36661)	87.6 (74.0–93.8)	67.8	43.8
7. One tablet per day (N=36657)	95.2 (80.8–99.7)	75.9	64.8

CMA, continuous measure of medication acquisition; Q1–Q3, first and third quartiles.
*Adherent: ≥80% of days with statins.
†Adherent: no gap longer than 45 days.

of adherence, and they contribute with complementing information. The CMA considers the average supply of drugs during the entire observation period, whereas the maximum gap method identifies gaps in drug supply. For example, CMA of 85% does not give information on whether the 15% of time without drug supply was distributed on a several short gaps or on one long gap. However, the maximum gap method does not give information on the proportion of the time with drug supply during the observation period.

The applicability of these two methods is likely to be affected by the setting, for example, how the reimbursement system is constructed and if the system encourages filling prescriptions before the preceding prescription has been consumed. Previous studies comparing methods to estimate refill adherence are scarce in settings that are generalisable to the Swedish one.[4,6] The findings presented in this study thus contribute to new information about methods to estimate refill adherence in such a setting. Further, assessments of sensitivity to various definitions are often lacking in such comparative studies. In this study, several sensitivity analyses were performed to analyse the stability of the resulting estimates in relation to different definitions. A shorter observation period increased the estimates of adherence, whereas disregarding overlapping supplies decreased the estimates. Increasing or decreasing the time allowed before the second statin purchase yielded only marginal differences in adherence estimates in the expected directions. Assuming one tablet or capsule per day did not influence the results. This was expected because statins are available in a range of different strengths, which enhances the possibility of applying a once-daily dosage regimen. Further, this is in line with previous findings from Denmark.[15] Moreover, there were no marked differences in adherence between those who were hospitalised during the study period and those who were not. Emigration or death at least 1 year after statin initiation was associated with lower adherence estimates according to both methods.

A trend of increasing adherence with increasing age was observed for both adherence estimates. This trend is in agreement with previous studies on statins as well as other drug groups.[3,20–23] The proportion of individuals classified as adherent in this study was however somewhat higher compared with that in previous studies from other countries, where between 36% and 62% of patients using statins were defined as adherent.[20–24] This discrepancy may be explained by differing patient characteristics; definitions in methods, such as length of the observation period; or structural factors, such as reimbursement systems. The current study excluded patients who purchased more than one statin substance during the study period because it was not possible to determine whether this was caused by switching or combination use. It was therefore not possible to establish if the remaining supply from the initial statin should be added to the estimated treatment episode or to be disregarded. Further, at least two statin purchases were requested for inclusion in the study. These definitions may also have contributed to the relatively high adherence estimates compared with previous research.

This study linked information on dispensed drugs to registers on hospitalisations and date of emigration or death. Disregarding information on hospitalisations did not significantly alter the results. However, it is possible that accounting for hospitalisations may have a larger impact in other settings, for example, other drug groups, patient groups or indications where longer hospital stays are more common. However, information on date of emigration or death appears to be of greater importance because emigration or death at least 1 year after statin initiation was associated with a markedly lower adherence.

The adherence estimates were sensitive to the management of overlapping supplies. Disregarding overlapping supplies resulted in markedly lower adherence estimates compared with adding oversupplies to the subsequent prescription. These findings are likely to be connected to the construction of the Swedish reimbursement system, where prescriptions can be filled when two thirds of the supplies from the previous prescription are theoretically consumed.[17] For continuous treatments, a 3 months' supply is generally dispensed at each occasion. Thus, 15 months' supply can be purchased within the reimbursement during an individual's 12-month reimbursement period. This provides economical incentives to stockpile and can therefore lead to overlaps in supplies. Further, the resulting adherence estimates, especially with the maximum gap method, increased when the observation period was reduced to 1 year, which might be connected to the construction of the Swedish reimbursement system. Previous studies have reported similar results, which supports that adherence to statins declines after 1 year of use.[22,25]

Strengths and limitations

This study used the novel approach of building an algorithm for interpreting dosage instructions in free text in the SPDR. The algorithm was manually validated and subsequently corrected in two rounds. The prescribed dosage was 1 tablet or capsule per day in the vast majority of dispensed prescriptions, and as expected, the sensitivity analyses where all prescriptions were assumed to be for 1 unit per day did not affect the results. Applying an algorithm for dosage interpretation is likely to have a more substantial influence when other drug or patient groups are studied. Another strength is that only new users were included in the present study.

Individuals who purchased more than one statin substance during the study period (i.e. switching or combination use), individuals with ApoDos, and those who died or emigrated within 1 year from statin initiation were excluded. This has likely resulted in a healthier-than-average population of incident statin users. Previous cardiovascular events or risk factors are associated with higher adherence,[25] but whether the statins were prescribed for primary or secondary prevention was not known in this study. Individuals who filled only one statin prescription were excluded to only include initiators of statin treatment. Although this exclusion criterion enabled the focus of adherence during a long period, it might have yielded an underestimation of initial non-persistence and increased the estimates of refill adherence.

Conclusions

The choice of method and definitions has a substantial impact on estimates of refill adherence to statins. CMA with 80% cut-off resulted in a higher adherence estimate than did the maximum gap method. CMA and the maximum gap method focus on different aspects of refill adherence, and they contribute with complementing information. The sensitivity analyses showed that a shorter observation period increased the estimates of refill adherence, whereas disregarding overlapping supplies decreased the estimates.

KEY POINTS

- The CMA and the maximum gap method focus on different aspects of refill adherence and contribute with complementing information.
- A higher proportion of the population was classified as adherent with CMA compared with the maximum gap method.
- Disregarding hospitalisations did not alter the refill adherence estimates; however, the estimates were higher when applying a shorter observation period and accounting for overlapping supplies.

CONFLICT OF INTEREST

The data collection for this work has been supported by the National Corporation of Swedish Pharmacies (Apoteket AB). The authors have no conflicts of interest to report. The sponsor had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. The authors' work was independent from the sponsor.

DISCLAIMER

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Medical Product Agency.

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