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ORIGINAL ARTICLE

Self-reported medication use among coronary heart disease patients showed high validity compared with dispensing data

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Abstract

Objective: To validate self-reported use of medications for secondary prevention of coronary heart disease (CHD) in a population-based health study by comparing self-report with pharmacy dispensing data, and explore different methods for defining medication use in prescription databases.

Study design and setting: Self-reported medication use among participants with CHD ($n = 1483$) from the seventh wave of the Tromsø Study was linked with the Norwegian Prescription Database (NorPD). Cohen's kappa, sensitivity, specificity, and positive and negative predictive values were calculated, using NorPD as the reference standard. Medication use in NorPD was defined in three ways; fixed-time window of 180 days, and legend-time method assuming a daily dose of one dosage unit or one defined daily dose (DDD).

Results: Kappa-values for antihypertensive drugs, lipid-lowering drugs and acetylsalicylic acid all showed substantial agreement (kappa $\geq$0.61). Validity varied depending on the method used for defining medication use in NorPD. Applying a fixed-time window gave higher agreement, positive predictive values and specificity compared with the legend-time methods.

Conclusion: Self-reported use of medication for secondary prevention of CHD shows high validity when compared with pharmacy dispensing data. For CHD medications, fixed-time window appears to be the most appropriate method for defining medication use in prescription databases.

Keywords: Medication use; validation; agreement; population-based study; prescription database

What is new?

Key findings

- Self-reported use of lipid-lowering drugs, antihypertensive drugs and acetylsalicylic acid among patients with coronary heart disease showed high agreement when compared with pharmacy dispensing data. Using a fixed-time window to define current medication use gave higher agreement, positive predictive values and specificity compared with the legend-time methods.

What this adds to what is known?

- Self-reported medication use for coronary heart disease collected with a questionnaire combining pre-specified and open-ended questions gives a valid measure of medication use.
- For coronary heart disease medication, a fixed-time window is better than legend-time methods in defining current use from prescription data. If legend-time is used and the prescribed dose is unavailable, assuming a daily dose of one dosage unit is a better choice than one defined daily dose for these medications.

Abbreviations: ASA, acetylsalicylic acid; CHD, coronary heart disease; DDD, defined daily dose; LLD, lipid-lowering drug; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value.

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What is the implication, what should change now?

- Though a combination of self-report and prescription data classifies medication exposure most accurately, self-reported information on medication for secondary prevention of coronary heart disease has adequate validity to be used for epidemiological research if prescription data is unavailable.
- When investigating current use of medications for coronary heart disease using prescription databases, fixed-time window appears to be a more appropriate method than the legend-time method.

1. Introduction

Medication use is an important factor in many epidemiological studies, either as exposure or outcome. Poor measurement of medication use can lead to over- or underestimation of true associations and risks [1].

There are several ways to measure medication use, where self-reported use, e.g. questionnaires or interviews, and pharmacy dispensing data are common methods. Unfortunately, no method provides information about the true medication exposure. Self-reported use may be biased by poor recall and underreporting of socially stigmatized medication classes [2,3]. Despite being collected objectively and nondifferentially, dispensing data cannot account for secondary nonadherence, i.e., dispensed medication is not necessarily used. It may also be prone to selection bias as some data sources include only reimbursed medications, and others are based on claims from selected insurance companies or pharmacies [4–10]. A few countries, like the Scandinavian countries, have complete prescription registries that include all prescription-based medications dispensed from pharmacies [11].

Several studies have compared medication use measurements from different data sources [4–10,12–17]. Most studies find good agreement and validity between self-reported and dispensing data when investigating medications used for long-term conditions. Results are less consistent for medications used as needed [9,10,12,13]. Cardiovascular medications, such as antihypertensive drugs, lipid-lowering drugs (LLDs) and antiplatelet drugs, are normally used on a daily basis, and agreement and validity between different data sources are usually found to be high [4–7,9,10,12–17]. However, few studies have investigated this in a population with established coronary heart disease (CHD) or compared data from complete prescription registries with self-reported data from a large population study.

A methodological concern with prescription registry data entails defining "current medication use". The two most commonly applied methods are fixed-time window and legend-time duration. Fixed-time window is most frequently applied and defines participants as medication-users if they have been dispensed the medication within a set time window before an index date [8,17]. The legend-time method uses information from the last prescription dispensed before the index date to calculate whether the dispensed medication will last to the index date [8,17]. Some studies have compared the two methods, but no consensus have been reached concerning which is the most appropriate for defining current medication use [8,12,18].

This study aimed to validate self-reported use of medications for secondary prevention of CHD in a population-based health study by comparing self-report with pharmacy dispensing data using the Norwegian Prescription Database (NorPD) as the reference standard, and exploring different methods for defining medication use in NorPD.

2. Methods

2.1. The Tromsø study

The Tromsø Study is a population-based health study that has been conducted seven times from 1974 to 2016 [19]. The study includes inhabitants in the municipality of Tromsø, Norway, a town with approximately 73,000 inhabitants in 2016. The present study used data collected during 2015-16 from the seventh wave of the Tromsø Study (Tromsø 7), where all inhabitants $\geq$ 40 years (n = 32,591) were invited to participate. The response rate was 65% (n = 21,083).

Participation in Tromsø 7 included answering two questionnaires, donating blood samples and going through clinical examinations. Most questions about diseases and medication use were posed in questionnaire 1, which could be answered either on paper or electronically anytime between invitation and attending the health examination. Links to the questionnaires can be found at the Tromsø Study's webpage [19].

2.2. The Norwegian Prescription Database (NorPD)

NorPD contains complete information about all prescribed medications dispensed from Norwegian pharmacies to individuals since January 2004. Medications used in hospitals/nursing homes and over-the-counter medications are not included. We included the following variables from NorPD: date of dispensing and information on medications dispensed (including Anatomical Therapeutic Chemical (ATC) code, and number of dosage units and defined daily doses (DDDs) dispensed [20]). DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" [20].

2.3. Study population

From Tromsø 7, we included participants reporting established CHD (n = 1483). CHD was defined as reporting either previous myocardial infarction, present or previous

angina pectoris, previous percutaneous coronary intervention or coronary artery bypass graft surgery.

2.4. Medications included

We included medications for secondary prevention of CHD (Fig. 1), which according to the prevailing European guidelines in 2015/2016 was acetylsalicylic acid (ASA), LLDs (mainly statins) and antihypertensive drugs (angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium-channel blockers (CCBs), thiazides and other antihypertensives) [21].

2.5. Defining medication use

In Tromsø 7, medication use was self-reported through i) questions about specific medication use and ii) participants listing the brand names for all medications used regularly the previous four weeks. We defined users of LLDs and antihypertensive drugs as participants answering "currently" to the two specific questions "*Do you use, or have you used cholesterol-lowering drugs?*" and *"Do you use, or have you used blood pressure lowering drugs?",* (response alternatives were "currently", "previously, not now" and "never used") and/or listing the brand name of an LLD or antihypertensive drug, respectively. We defined users of ASA as participants answering "yes" when asked *"If you have used analgesics and anti-inflammatory medication regularly in the past year - did you use "Baby" or low dose acetylsalicylic acid (ASA), i.e. Acetylsalisylsyre®, Albyl-E®, Asasantin Retard® (75/160 mg per tablet)?"* (response alternatives were "yes" and "no"), or denoting a brand name for ASA.

From NorPD, current use was defined by three approaches; one using a fixed-time window and two using the legend-time method (Fig. 2). For all approaches, index date was the day the participants completed the Tromsø 7 questionnaire. Using a fixed-time window definition, medication-users were participants who had been dispensed at least one prescription within 180 days before index date. A sensitivity analysis was performed using time windows of 90 and 365 days. The legend-time method requires knowledge about the duration of use. As prescribed daily dose is not available in NorPD, we calculated the duration supplied assuming the daily dose was equal to: i) one dosage unit (e.g. tablet, capsule etc.), and ii) one DDD. In both legend-time approaches, we added 10% to the duration to account for imperfect adherence before assessing whether the duration of the last dispensation covered the index date. Sensitivity analyses were performed by not adding any additional units/DDDs, and by adding 20% additional units/DDDs.

2.6. Statistical analysis

Data from Tromsø 7 was linked with NorPD data using the unique national identity number assigned to all citizens in Norway. NorPD performed the record linkage according to standard procedures. Agreement between Tromsø 7 and NorPD was measured by percent observed agreement and Cohen's kappa. Kappa-values were interpreted as proposed by Landis and Koch: poor (<0.00), slight (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.00) [22].

To determine the validity of self-reported medication use, we calculated sensitivity and specificity using NorPD as the reference standard. Positive (PPV) and negative (NPV) predictive values were also calculated.

Analyses were conducted applying IBM SPSS 25 for Windows. Confidence intervals were calculated using VassarStats [23,24]. Results are expressed as proportions and kappa-values with 95% confidence intervals.

2.7. Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics of North Norway (2015/1775) and had an approved Data Protection Impact Assessment from UiT The Arctic University of Norway. All participants in the Tromsø Study have given written informed consent for their data to be used in research.

3. Results

In the study population (n = 1483), 70% were male and mean age was 68.7 (standard deviation 10.8) years. Medication use is shown in Table 1.

Agreement was substantial for antihypertensive drugs, LLDs and ASA, with kappa-values ≥0.61 (Table 2). An exception was for ASA when using either of the legend-time methods, in which case the kappa-value was 0.60. The fixed-time window method gave higher agreement than either of the legend-time methods, both in terms of percent agreement and kappa. For antihypertensive drugs, the kappa-value showed an almost perfect agreement when using a fixed-time window.

Among participants where the two data sources did not agree, more participants were identified as ASA-users in NorPD than in Tromsø 7, while the result was opposite for LLD-users (Table 2). For antihypertensive drugs, more participants were identified as users in NorPD than in Tromsø 7 when using a fixed-time window, but opposite when using the legend-time methods.

PPV was high for all three main medication classes, which shows that when participants report using these medications, the likelihood that they had it dispensed is high. Highest values were found using fixed-time window, while legend-time with DDD gave the lowest values. NPV was high for antihypertensive drugs and LLDs but lower

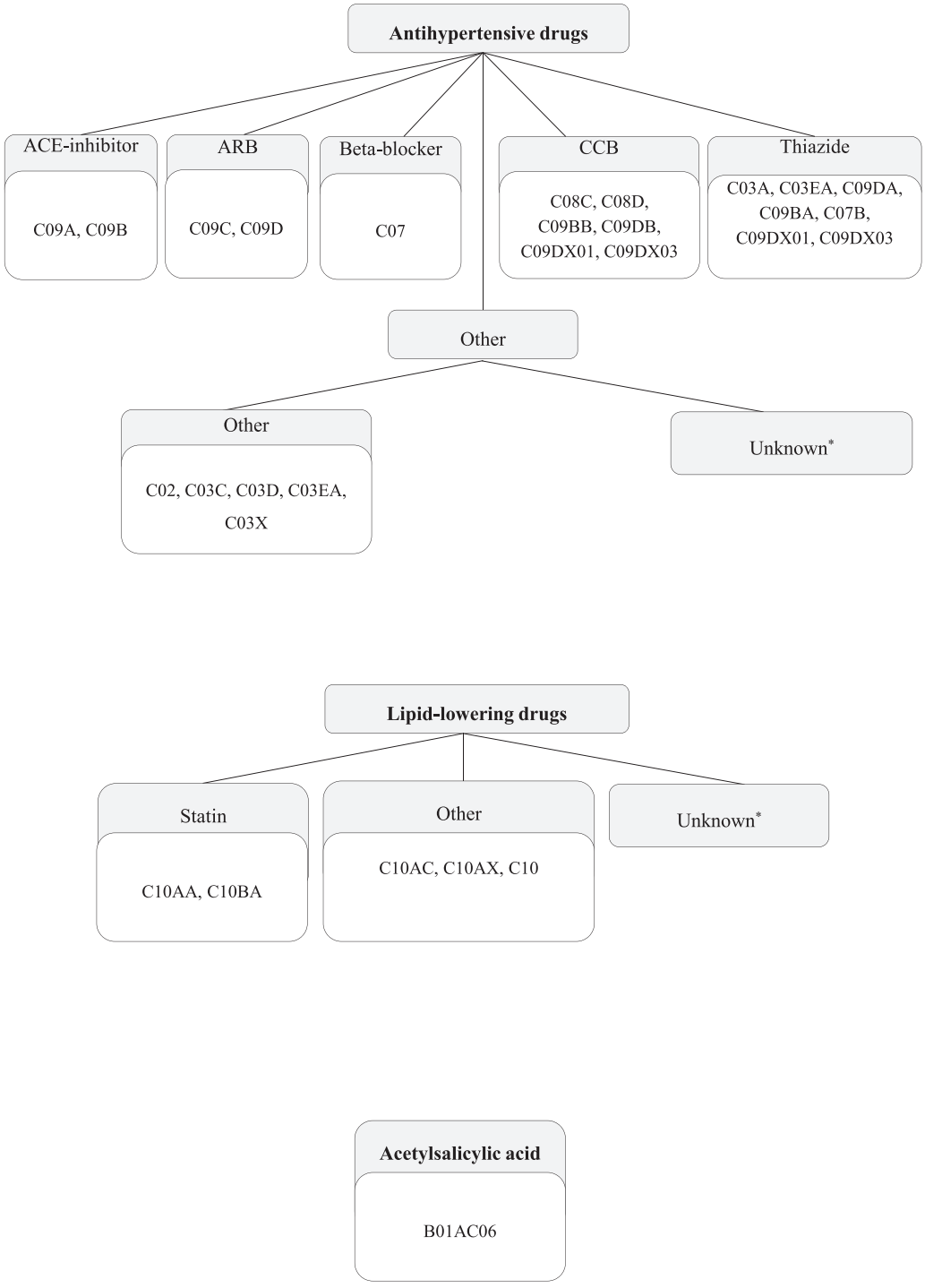

Fig. 1. Overview of included ATC-codes and aggregation into medication groups.
*When, instead of brand name, the participants in free text reported using medication interpretable as "blood pressure lowering" or "cholesterol lowering", it was registered under the respective medication category.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ATC, anatomical therapeutic chemical classification system; CCB, calcium-channel blocker.

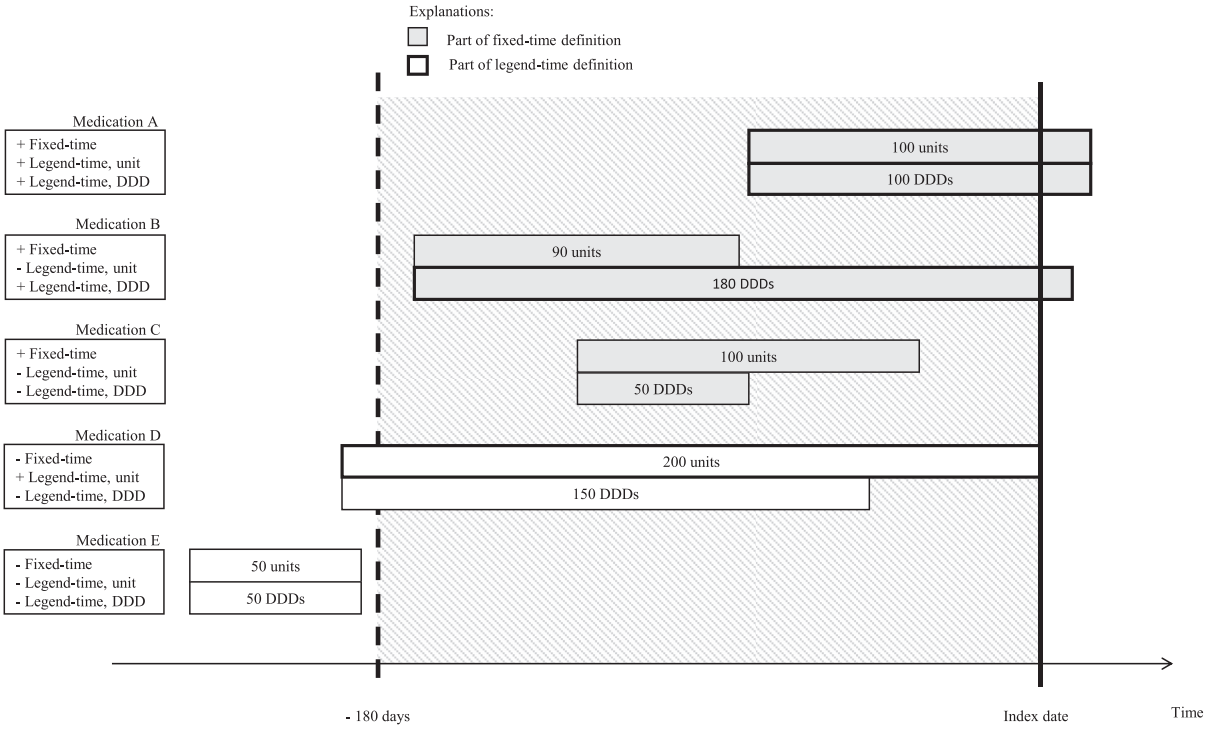

Fig. 2. The three different methods used to define medication users in NorPD. Index date is the day of questionnaire completion. Using fixed-time window, participants were defined as medication-users if they had a medication dispensed ≤180 days before index date. The legend-time methods defined a participant as user if the supply of medication most recently dispensed would last past the index date, assuming a daily dosage of either one unit (e.g., tablet) or one DDD. Medications A, B and C are in use according to fixed-time window; A and D are in use when applying legend-time with one unit a day; A and B are in use applying legend-time with one DDD a day. Medication E is not defined as in use by any of the methods. Abbreviations: DDD, defined daily dose; NorPD, Norwegian Prescription Database

Table 1. Prevalence of use (*n* (%)) of medications for secondary prevention of coronary heart disease in Tromsø 7 and the three approaches for defining medication use in NorPD ($n = 1483$)

	Tromsø 7		NorPD, Fixed-time		NorPD, Legend-time, Unit		NorPD, Legend-time, DDD	
Antihypertensive drugs	1069	(72.1)	1087	(73.3)	1032	(69.6)	865	(58.3)
Lipid-lowering drugs	1133	(76.4)	1074	(72.4)	960	(64.7)	928	(62.6)
Acetylsalicylic acid	980	(66.1)	1098	(74.0)	991	(66.8)	991	(66.8)

Abbreviations: DDD, defined daily dose; NorPD, Norwegian Prescription Database

for ASA. For NPV, the legend-time methods and especially using DDDs gave the highest values, but the difference between methods was small.

Sensitivity was also high for all three main medication classes. This indicates that a high proportion of those registered as users in NorPD also self-reported use of these medications in Tromsø 7. Specificity was lower than the sensitivity for antihypertensive drugs and LLDs, but higher for ASA. The specificity was lowest when using the legend-time methods, and especially with one DDD as the daily dosage.

Among the antihypertensive drugs, an almost perfect agreement was found for angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs) and calcium-channel blockers (CCBs) when using fixed-time window, while the legend-time methods gave substantial to almost perfect agreements (Table 3). The kappa-values for thiazides showed substantial agreement. For beta-blockers, agreement was substantial when using fixed-time window and legend-time method with one unit a day, and fair with legend-time method with one DDD a day. For statins, agreement was substantial when using the fixed-time window method and fair with either legend-time method.

Sensitivity analyses showed higher agreement for a 180 days than a 90 days fixed-time window, and the main analysis (with 10% extra added to the duration) for the legend-time methods showed higher agreement than no addition. Using a 365 days fixed-time window or adding 20% to the duration in the legend-time methods gave results similar to the main analysis (supplementary tables A.1-A.3).

Table 2. Self-reported use of antihypertensive drugs, lipid-lowering drugs and acetylsalicylic acid in the Tromsø 7 questionnaire compared with the three approaches for defining medication use in NorPD ($n = 1483$)

	Antihypertensive drugs			Lipid-lowering drugs			Acetylsalicylic acid		
	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed- time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD
Observed agreement*, *n*	1371	1346	1221	1358	1276	1242	1287	1216	1216
(%)	(92.5)	(90.8)	(82.3)	(91.6)	(86.0)	(82.0)	(86.8)	(82.0)	(82.0)
Kappa	0.81	0.78	0.62	0.78	0.67	0.63	0.69	0.60	0.60
(95% CI)	(0.78–0.84)	(0.74–0.81)	(0.58–0.66)	(0.74–0.82)	(0.63–0.71)	(0.55–0.64)	(0.65–0.73)	(0.55–0.64)	(0.55–0.64)
Both sources, *n*	1022	982	836	1041	943	910	941	852	852
(%)	(68.9)	(66.2)	(56.4)	(70.2)	(63.6)	(61.4)	(63.5)	(57.5)	(57.5)
Tromsø 7 only, *n*	47	87	233	92	190	223	39	128	128
(%)	(3.2)	(5.9)	(15.7)	(6.2)	(12.8)	(15.0)	(2.6)	(8.6)	(8.6)
NorPD only, *n*	65	50	29	33	17	18	157	139	139
(%)	(4.4)	(3.4)	(2.0)	(2.2)	(1.2)	(1.2)	(10.6)	(9.4)	(9.4)
Neither, *n*	349	364	385	317	333	332	346	364	364
(%)	(23.5)	(24.6)	(26.0)	(21.4)	(22.5)	(22.4)	(23.3)	(24.6)	(24.6)
Sensitivity	0.94	0.95	0.97	0.97	0.98	0.98	0.86	0.86	0.86
(95% CI)	(0.92–0.95)	(0.94–0.96)	(0.95–0.98)	(0.96–0.98)	(0.97–0.99)	(0.97–0.99)	(0.84–0.88)	(0.84–0.88)	(0.84–0.88)
Specificity	0.88	0.81	0.62	0.78	0.64	0.60	0.90	0.74	0.74
(95% CI)	(0.84–0.91)	(0.77–0.84)	(0.58–0.66)	(0.73–0.81)	(0.59–0.68)	(0.56–0.64)	(0.86–0.93)	(0.70–0.78)	(0.70–0.78)
PPV	0.96	0.92	0.78	0.92	0.83	0.80	0.96	0.87	0.87
(95% CI)	(0.94–0.97)	(0.90–0.93)	(0.76–0.81)	(0.90–0.93)	(0.81–0.85)	(0.78–0.83)	(0.95–0.97)	(0.85–0.89)	(0.85–0.89)
NPV	0.84	0.88	0.93	0.91	0.95	0.95	0.69	0.72	0.72
(95% CI)	(0.80–0.88)	(0.84–0.91)	(0.90–0.95)	(0.87–0.93)	(0.92–0.97)	(0.92–0.97)	(0.65–0.73)	(0.68–0.76)	(0.68–0.76)

* Includes agreement of both users and nonusers.

Abbreviations: CI, confidence interval; DDD, defined daily dose; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value

Table 3. Self-reported use of statins and different classes of antihypertensive drugs in the Tromsø 7 questionnaire compared with the three approaches for defining medication use in NorPD ($n = 1483$)

	ACE-inhibitor			ARB			Beta-blocker			CCB			Thiazide			Statin		
	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD
Observed agreement*, *n*	1426	1421	1410	1391	1376	1372	1308	1277	1058	1411	1401	1412	1395	1385	1384	1218	1178	1162
(%)	(96.2)	(95.9)	(95.1)	(93.8)	(92.8)	(92.5)	(88.2)	(86.1)	(71.3)	(95.2)	(94.5)	(95.2)	(94.1)	(93.4)	(93.3)	(82.1)	(79.4)	(78.4)
Kappa	0.85	0.83	0.80	0.83	0.80	0.79	0.77	0.72	0.40	0.83	0.80	0.83	0.76	0.71	0.71	0.61	0.57	0.55
(95% CI)	(0.82–0.89)	(0.79–0.87)	(0.75–0.84)	(0.80–0.87)	(0.76–0.84)	(0.76–0.83)	(0.73–0.80)	(0.69–0.76)	(0.36–0.44)	(0.80–0.87)	(0.76–0.84)	(0.79–0.87)	(0.71–0.80)	(0.66–0.77)	(0.66–0.76)	(0.57–0.65)	(0.52–0.61)	(0.50–0.59)
Both sources, *n*	199	184	174	319	294	292	643	595	309	226	208	215	164	148	147	839	761	742
(%)	(13.4)	(12.4)	(11.7)	(21.5)	(19.8)	(19.7)	(43.4)	(40.1)	(20.8)	(15.2)	(14.0)	(14.5)	(11.1)	(10.0)	(9.9)	(56.6)	(51.3)	(50.0)
Tromsø 7 only, *n*	6	21	31	7	32	34	27	75	361	5	23	16	7	23	24	51	129	148
(%)	(0.4)	(1.4)	(2.1)	(0.5)	(2.2)	(2.3)	(1.8)	(5.1)	(24.3)	(0.3)	(1.6)	(1.2)	(0.5)	(1.6)	(1.6)	(3.4)	(8.7)	(10.0)
NorPD only, *n*	51	41	42	85	75	77	148	131	64	67	59	55	81	75	75	214	176	173
(%)	(3.4)	(2.8)	(2.8)	(5.7)	(5.1)	(5.2)	(10.0)	(8.8)	(4.3)	(4.5)	(4.0)	(3.7)	(5.5)	(5.1)	(5.1)	(14.4)	(11.9)	(11.7)
Neither, *n*	1227	1237	1236	1072	1082	1080	665	682	749	1185	1193	1197	1231	1237	1237	379	417	420
(%)	(82.7)	(83.4)	(83.4)	(72.3)	(73.0)	(72.8)	(44.8)	(46.0)	(50.5)	(79.9)	(80.5)	(80.7)	(83.0)	(83.4)	(83.4)	(25.6)	(28.1)	(28.3)
Sensitivity	0.80	0.82	0.81	0.79	0.80	0.79	0.81	0.82	0.83	0.77	0.78	0.80	0.67	0.66	0.66	0.80	0.81	0.81
(95% CI)	(0.74–0.84)	(0.76–0.87)	(0.75–0.86)	(0.75–0.83)	(0.75–0.84)	(0.75–0.83)	(0.78–0.84)	(0.79–0.85)	(0.79–0.87)	(0.72–0.82)	(0.72–0.83)	(0.74–0.84)	(0.61–0.73)	(0.60–0.73)	(0.60–0.72)	(0.77–0.82)	(0.79–0.84)	(0.78–0.84)
Specificity	1.00	0.98	0.98	0.99	0.97	0.97	0.96	0.90	0.68	1.00	0.98	0.99	0.99	0.98	0.98	0.88	0.76	0.74
(95% CI)	(0.99–1.00)	(0.97–0.99)	(0.97–0.98)	(0.99–1.00)	(0.96–0.98)	(0.96–0.98)	(0.94–0.97)	(0.88–0.92)	(0.65–0.70)	(0.99–1.00)	(0.97–0.99)	(0.98–0.99)	(0.99–1.00)	(0.97–0.99)	(0.97–0.99)	(0.85–0.91)	(0.73–0.80)	(0.70–0.78)
PPV	0.97	0.90	0.85	0.98	0.90	0.90	0.96	0.89	0.46	0.98	0.90	0.93	0.96	0.87	0.86	0.94	0.86	0.83
(95% CI)	(0.93–0.99)	(0.85–0.93)	(0.79–0.89)	(0.95–0.99)	(0.86–0.93)	(0.86–0.93)	(0.94–0.97)	(0.86–0.91)	(0.42–0.48)	(0.95–0.99)	(0.85–0.94)	(0.89–0.96)	(0.91–0.98)	(0.80–0.91)	(0.80–0.91)	(0.93–0.96)	(0.83–0.88)	(0.81–0.86)
NPV	0.96	0.97	0.97	0.93	0.94	0.93	0.82	0.84	0.92	0.95	0.95	0.96	0.94	0.94	0.94	0.64	0.70	0.71
(95% CI)	(0.95–0.97)	(0.96–0.98)	(0.96–0.98)	(0.91–0.94)	(0.92–0.95)	(0.92–0.95)	(0.79–0.84)	(0.81–0.86)	(0.90–0.94)	(0.93–0.96)	(0.94–0.96)	(0.94–0.97)	(0.92–0.95)	(0.93–0.96)	(0.93–0.96)	(0.60–0.68)	(0.66–0.74)	(0.67–0.74)

* Includes agreement of both users and nonusers.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; DDD, defined daily dose; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value

4. Discussion

This study demonstrates high agreement between self-reported use of CHD medications and pharmacy dispensing data among participants with CHD in the seventh wave of the Tromsø Study. High PPV was shown for all medications, especially when using a fixed-time window. This indicates that participants reporting use of such medications can be presumed to be actual medication-users. Sensitivity and specificity was also found to be high for the investigated medication classes. This is in accordance with previous studies [4-7,9,10,12,14–16].

Negative predictive values were also high for most medication classes, showing that almost all who do not report use of CHD medications are nonusers in NorPD as well. Lower NPVs for statins and ASA suggest that among participants not reporting use of these medications, some have been dispensed such medications. It is possible that these participants do not actually use statins or ASA, but it is more likely that they have forgotten to report them in the questionnaire, thereby being misclassified as nonusers according to self-report. Predictive values are affected by prevalence and the high prevalence of use in our study population contributes to the high PPVs.

In addition to lower NPV, ASA had a lower kappa-value, as more participants were classified as ASA-users by NorPD, and not by Tromsø 7. This was particularly clear using fixed-time window, where 10.7% of the participants were defined as medication-users in NorPD only, while 2.6% were defined as users only in Tromsø 7. Unlike for antihypertensive drugs and LLDs, we could only include those who specified an ASA brand name, and we would lose users who wrote "blood-thinning medication". As this could represent any antithrombotic drug, we could not include these as ASA-users. We did include answers to a prespecified question about use of low-dose ASA, but this question was conditional on a positive answer to a previous question ("Have you used analgesics and anti-inflammatory medication regularly in the past year?"). So, ASA-users did not have the same opportunity as LLD-/antihypertensive drug-users to report their use, leading to a likely underestimated agreement for ASA.

Like ASA, statins had lower agreement and NPV than the other medication classes. However, the values for all LLDs combined were higher than for statins alone, especially when using fixed-time window. Many LLD-users remember that they use LLDs, but might not report which type. This again underlines the importance of including the prespecified question about LLD-use in addition to the open-ended question when evaluating use of statins. Interestingly, LLDs is the only medication class with a higher proportion of users defined in Tromsø 7 than in NorPD. The number of users defined by Tromsø 7 alone is lower when using a fixed-time window of 365 days, indicating lower adherence among LLD-users.

The lowest sensitivity was found for thiazides, indicating that the Tromsø 7 questionnaire does not identify all thiazide-users. Only the open-ended question was used to define thiazide-users, and we are therefore dependent on the participants being specific when listing their medications. In Norway, thiazides are usually sold as part of a combination product with another antihypertensive drug. Self-reported use of combination products can be misclassified as single active substances. The thiazide is usually mentioned at the end of a brand name, e.g. "candesartan hydrochlorothiazide", leaving it easy to forget, and resulting in lower sensitivity for thiazides.

The structure of the questions in a questionnaire can affect how a participant reports medication use [25]. A study by Klungel et al. [2] compared questions about medications for prespecified conditions with open-ended question and concluded that prespecified indication alternatives gave higher recall sensitivity. However, the open-ended question and the question with prespecified indications did not ask about the same medication type. Combining the information from different types of questions should yield higher prevalence of medication use [25]. In our study, we combined prespecified questions and an open-ended question. Thereby we could capture participants who forgot to list some of their medicines in the open-ended question and participants who use antihypertensive drugs and LLDs without understanding exactly what the medication is for. The two questions might lead to different responses as the prespecified questions ask about current medication use, while the open-ended one asks about regular use in the last four weeks. As CHD medications are used chronically, it is reasonable to assume that both questions would capture the participants' recent use of these medications.

It is not possible to define current use in a prescription registry in the same way as in a questionnaire. NorPD states that a medication was dispensed at a certain date and amount, but not if, when or how the medication was taken. Two main methods have been used when assessing current medication use in pharmacy records: fixed-time windows (also called fixed look-back periods) and legend-time (also called legend-duration or medication-on-hand) [18]. As there is no consensus on the best method for defining current medication use in pharmacy records, it has been recommended to compare different approaches [18]. We chose to use both fixed-time window and legend-time methods to define current medication use in NorPD. A fixed-time window of 180 days was chosen because a typical dispensing in Norway covers around 90 days of use, and we added another 90 days to account for poor adherence and stockpiling. For the same reason we added 10% to the units and DDDs before calculating whether the dispensed duration would last to the index day when using the legend-time method [2,12,15,17]. The sensitivity analyses suggest that this was satisfactory.

Using one unit compared with one DDD to calculate legend duration gave similar results for most of the medication classes. The sensitivity was slightly higher when using DDDs, while using units generally gave higher agreement, specificity and PPV. The differences were largest for beta-blockers. This indicates that the DDD for beta-blockers is higher than the most commonly prescribed dose of beta-blockers in Norway. As most of the medications used for secondary prevention of CHD are used as one unit daily, this appears to be a better estimate for the prescribed daily dosage than DDD. The only exception among the medication classes was calcium-channel blockers, where the DDD gave slightly higher agreement, sensitivity and PPV than the unit. This is not unexpected, as some calcium-channel blockers are recommended to be taken more than once a day.

We used NorPD as the reference standard in calculating our validity measures. NorPD can be considered more reliable than self-report as the registry has complete coverage of dispensed medications used for secondary prevention of CHD. These medications are also not available over-the-counter in Norway. Using dispensing data as the reference standard is common in validation studies [4–6,9,10]. However, the choice of definition matters, and careful considerations are needed when choosing fixed-time or legend-time, and dosage unit or DDD as unit of use. We found that for CHD medications used chronically, a fixed-time window of 180 days gave the best results with higher values of both percent agreement and kappa as well as higher specificity and PPV for all medications. Though sensitivity and NPV was higher for most medications when using the legend-time methods, the differences from fixed-time window were small. The fixed-time window is also more easily applicable than the legend-time method. Overall, using a fixed-time window could be recommended for most studies investigating use of these medications. For other medication classes this might be different.

5. Conclusion

Self-reported information on current use of medications for secondary prevention of coronary heart disease collected with a questionnaire combining prespecified and open-ended questions shows high validity compared with pharmacy dispensing data. Though a combination with dispensing data is preferable, this questionnaire provides a sufficiently accurate classification of such medication exposure should prescription data be unavailable.

Validity and agreement measures varied depending on the definition of medication use in NorPD. For CHD medications, using a fixed-time window gave better results than the legend-time methods. However, this may vary depending on medication class, setting and data source.

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CRediT authorship contribution statement

Elisabeth Pedersen: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Kieu Nhi Lise Truong:** Conceptualization, Formal analysis, Writing - review & editing. **Beate Hennie Garcia:** Conceptualization, Writing - review & editing. **Kjell H. Halvorsen:** Writing - review & editing. **Kristian Svendsen:** Formal analysis, Writing - review & editing. **Anne Elise Eggen:** Writing - review & editing. **Marit Waaseth:** Conceptualization, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.02.015.

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