Perceptions of generic medicines and medication adherence after percutaneous coronary intervention: a prospective multicentre cohort study

Trond Roed Pettersen,1,2 Jan Schjøtt,2,3 Heather G Allore,4,5 Bjørn Bendz,6,7 Britt Borregaard,8,9 Bengt Fridlund,1,10 Alf Inge Larsen,2,11 Jan Erik Nordrehaug,2 Svein Rotevatn,1 Tore Wentzel-Larsen,12,13 Tone Merete Norekvål1,2

ABSTRACT

Objective To determine patient perceptions of generic medicines 2 and 6 months after percutaneous coronary intervention (PCI), and to determine whether these perceptions moderate medication adherence.

Design Prospective multicentre cohort study with repeated measures of perceptions of generic medicines and medication adherence.

Setting The CONCARDPCI study conducted at seven large referral PCI centres in Norway and Denmark between June 2017 and May 2020.

Participants A total of 3417 adults (78% men), using both generic and brand name medicines, with a mean age of 66 years (SD 11) who underwent PCI were followed up 2 and 6 months after discharge from hospital.

Main outcome measures Perceptions of generic medicines were the main outcome. The secondary outcome was medication adherence.

Results Perceptions of generic medicines were significantly more negative at 2 than at 6 months (1.10, 95% CI 0.41 to 1.79, p=0.002). Female sex (−4.21, 95% CI −6.75 to −1.71, p=0.001), older age (−0.12, 95% CI −0.23 to −0.02, p=0.020), lower education level (overall p<0.001), ethnicity (overall p=0.002), Norwegian nationality (10.27, 95% CI 8.19 to 12.40, p<0.001) and reduced self-reported health status (0.19, 95% CI 0.09 to 0.41, p=0.003) were significantly associated with negative perceptions of generic medicines. There was no evidence to suggest that perceptions of generic medicines moderate the association between sociodemographic and clinical variables and medication adherence (p=0.077 for all covariates). Moreover, self-reported medication adherence was high, with 99% scoring at or above the Medication Adherence Report Scale midpoint at both time points. There were no substantial correlations between negative perceptions of generic medicines and medication non-adherence at 2 months (r=0.041, 95% CI 0.002 to 0.081, p=0.037) or 6 months (r=0.038, 95% CI −0.005 to 0.081, p=0.057).

Conclusions Mistrust and uncertainty about the safety and efficacy of generic medicines remains in a sizeable proportion of patients after PCI. This applies especially to those of lower socioeconomic status, older age, female sex, immigrants and those with poorer mental health. However, this study demonstrated a shift towards more positive perceptions of generic medicines in the longer term.

INTRODUCTION

Generic medicines are bioequivalents to brand name medicines. Thus, they contain the same active substance(s) as brand name medicines, are used at the same dosage(s) to treat the same disease(s) and are used interchangeably once approved by the health authorities. Nevertheless, their inactive ingredients, name, appearance and packaging may differ from the brand name medicines.1 Most studies have demonstrated evidence of the safety and efficacy of generic medicines.2-5 However, a recent large-scale retrospective observational study found that generic losartan, valsartan and candesartan were associated with higher rates of adverse events (defined as any causes of emergency room consultations or hospitalisations) than brand name medicines.6 Furthermore, some manufacturing issues have raised concerns about the quality and production of generic medicines.7 In 2008, contaminated heparin caused
serious adverse events in countries in the European Union, the USA and Asia, making quality an international issue.8 However, as global spending on prescription medicines may exceed €1.3 trillion by 2023,9 cost-containment measures, such as generic substitution, could play a part in reducing healthcare expenditure.10 Moreover, generic substitution is among the most cost-effective interventions to implement when healthcare expenditure increases to unaffordable levels.11

Nonetheless, there is public scepticism about the safety and efficacy of generic medicines.12–15 Further, acceptance of generic medicines is significantly higher in patients with transient conditions, such as headaches and fever, than in patients with chronic and more severe conditions, such as diabetes and hypertension.16 This is concerning because negative perceptions of generic medicines can reduce medication adherence, and thereby the efficacy of the treatment.12–14 The results are inconsistent, however.26 Adherence to prescribed therapy, including dual antiplatelet therapy and other medicines used for secondary prevention of cardiovascular diseases, is of crucial importance to patients after percutaneous coronary intervention (PCI) to improve the patient risk profile and avoid adverse events.21 Nevertheless, regardless of whether generic or brand name medicines are prescribed, adherence rates to prescribed therapy are often suboptimal in patients with cardiovascular diseases.22–25

Mistrust in the efficacy, safety and quality of generic medicines remains a barrier that is essential to overcome if their utilisation is to be increased.26 27 Previous studies have used either a cross-sectional survey design, focus groups or qualitative interview studies to investigate perceptions of generic medicines.12 13 17 However, few longitudinal studies have been conducted to assess whether patients’ perceptions change over time or to determine associations between perceptions and clinical characteristics. To address this gap in the literature, we determined perceptions of generic medicines in patients 2 and 6 months after PCI. Furthermore, we determined whether these perceptions moderate medication adherence.

METHODS
Study design and setting
CONCARDPCI is a prospective multicentre cohort study based on real-world data, including patients after PCI. Patient-reported outcomes were collected between June 2017 and May 2020 at seven large referral PCI centres in Norway and Denmark. On average, the centres perform 1700 (range 900 to >2000) PCI procedures annually, have 629 to 1400 beds (mean 943) and are referral centres for coronary angiography and PCI for 37 local hospitals.28

STUDY POPULATION
The study population comprised all patients included in CONCARDPCI.29 To identify eligible patients, daily admission records and operating programmes were reviewed. In total, 5608 patients were screened for eligibility during index hospitalisation by trained CONCARDPCI study nurses based on the following inclusion criteria: patients undergoing PCI according to diagnostic criteria set out in the European Society of Cardiology revascularisation guidelines,21 ≥ 18 years of age, and community-dwelling. Of these, 1399 patients were excluded based on the following exclusion criteria: (1) inability to speak Norwegian/Danish, (2) unable to fill in the questionnaires due to impaired capacity or needed a proxy to complete the questionnaires, (3) institutionalised, (4) life expectancy less than 1 year, (5) undergoing PCI without stent implantation, (6) PCI related to transcatheter aortic valve implantation or a MitraClip examination and (7) previously enrolled in CONCARDPCI (readmissions) (figure 1). If cognitive impairment was suspected in patients with no previous medical record of the problem, the Confusion Assessment Scale29 and the 4AT30 were used to determine whether patients should be excluded. Patients who were delirious or too clinically unstable to give informed
consent after PCI, and who would otherwise be eligible for inclusion, were reassessed before discharge. Non-participants were compared with participants on a limited number of variables from the Norwegian Registry on Invasive Cardiology to account for potential selection bias.

**SOCIODEMOGRAPHIC CHARACTERISTICS**
Sociodemographic characteristics were obtained by self-reporting during index hospitalisation after PCI: sex, age, marital status (married or never married, and widow or widower), cohabitation status (living alone or with someone), ethnicity (categorised as native born, born to immigrant parents or immigrant), educational level (primary school, vocational school, upper secondary school, college or university <4 years, college or university ≥4 years), work status (full/part-time work, retired, sick leave full time/part time, disability pension, job seeker, student/initial compulsory military service, homemaker, unpaid leave) and total household gross income (denominated in EUR).

**CLINICAL CHARACTERISTICS**
Disease-related outcomes were collected from patients’ medical records and national quality registries. They included the number and class of discharge medications, clinical status on admission (blood pressure, heart rate and rhythm, body weight, height, waist and upper arm circumference), medical history including comorbidity (cardiovascular and medical) and previous hospital admissions for cardiovascular diseases, procedural and angiographic findings, complications during hospital stay, procedures additional to PCI and length of hospital stay. In addition, standard laboratory tests provided data on disease severity and comorbidities (full blood count, electrolytes, creatine, C reactive protein, glucose, cardiac troponin T/troponin I, total density lipoprotein, low-density lipoprotein and high-density lipoprotein cholesterol). All laboratory tests were analysed using standard hospital assays. Information about the use of healthcare services after discharge (consultation with a general practitioner, cardiologist, physiotherapist, psychologist or psychiatrist, admission to a hospital or private hospital, follow-up by community care nursing services, short-term stay at a nursing home, participation in cardiac rehabilitation programmes, or outpatient consultation) was obtained at the 2-month (T1) and 6-month follow-up (T2).

**Assessment of perceptions of generic medicines**
We adapted four questions about perceptions of generic medicines from Kesselheim et al[31] to strengthen the comparability of results. Patients were asked whether they perceived generic medicines being as effective, as safe, as producing the same side effects, and consisting of the same active ingredients as brand name medicines. All items were answered on a 5-point Likert response scale (definitely yes=1, probably yes=2, unsure=3, probably not=4, definitely not=5). To avoid misunderstandings of the term generic medicines, patients were provided with a written explanation of the term in the questionnaire. For our study, the internal consistency of the scale was satisfactory at both T1 (α=0.88) and T2 (α=0.89).

**Assessment of medication adherence**
The Medication Adherence Report Scale (MARS-5) is a five-item scale assessing intentional and unintentional, self-reported non-adherence to medicines in a non-threatening and non-judgemental way. Each item is scored on a Likert scale ranging from 1 (always) to 5 (never). The total score is scaled to range from 1 to 5, with higher scores indicating higher self-reported adherence. This implies that patients are categorised in terms of their position on the dynamic adherence continuum, rather than categorised as being ‘adherent/non-adherent’. The instrument has shown good psychometric properties.[32] For our study, the internal consistency of the scale was satisfactory at both T1 (α=0.85) and T2 (α=0.87).

**Assessment of self-reported health status**
The RAND-12 is a 12-item scale used to assess self-reported health status, to estimate the disease burden and evaluate disease-specific benchmarks compared with other populations. Furthermore, the scale corresponds to eight physical and mental health domains, which are summarised in a physical and mental component score. The instrument has shown good psychometric properties.[33] For this study, we used the two component scores as measures of self-reported health status.

**DATA COLLECTION**
Data were collected from medical records, national quality registries and patient-reported outcome measures at baseline registration during index hospitalisation after PCI (T0). To ensure that extracted data were standardised, a comprehensive data dictionary and case report form (CRF) were used. For the Danish centres, electronic CRFs were used.

Vital status was identified before conducting the large-scale survey to avoid sending questionnaires to deceased patients or their families. Non-responders received one reminder. Postal or electronic questionnaires were distributed at T1 and T2. The time intervals were chosen to ensure that a sufficient amount of time had elapsed for prescription refills to be necessary.

For the Norwegian centres, responses from the patient-reported outcome measures were entered manually in the statistical software platform by trained study nurses. For the Danish centres, patient-reported outcomes were collected either electronically via a questionnaire-based survey tool (SurveyXact V.12.9) or by postal questionnaires, as requested by the patient. Collected data were entered in the SurveyXact database by trained study nurses.

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nurses before being transferred to the statistical software platform.

**STATISTICAL ANALYSIS**

Descriptive statistics were used to depict patients’ socio-demographic and clinical characteristics, perceptions of generic medicines and self-reported medication adherence. Means, SDs and ranges were calculated for continuous variables, and absolute numbers and percentages were used for categorical variables. Mean scores were computed for perceptions of generic medicines and medication adherence. In the event of missing data, the ‘half rule’ was applied, whereby scale scores were computed based on the means of valid items if at least half the items were valid. Thus, patients were excluded from the scale scores if more than two items were missing from the questions on generic medicine, and if more than three items were missing from the questions on medication adherence.

Consistent with the coding scheme used by Kesselheim et al., we initially categorised patients who answered ‘unsure’, ‘probably not’ or ‘definitely not’ to any of the four questions about generic medicines as having negative perceptions of generic medicines compared with their brand name counterparts. However, for the linear regression analysis, the scale was converted to a 0–100 scale, with higher scores indicating more positive perceptions of generic medicines. Mixed effect models were used to compare the difference in perceptions of generic medicines at T1 and T2. Pearson’s correlation was used to assess whether negative perceptions of generic medicines were correlated with low self-reported medication adherence. Bootstrap CIs were calculated using 10 000 replications. Linear regression analysis was performed at both time points to determine associations between socio-demographic and clinical characteristics as independent variables and perceptions of generic medicines as the dependent variable. Due to a strong ceiling effect and the skewness of the data on both scales, bootstrapping (5000 samples) was performed. To determine the potential moderation effect of perceptions of generic medicines on the association between sociodemographic and clinical variables (independent variables) and medication adherence (dependent variable), a moderator analysis was performed (figure 2). All the models included known and potential factors associated with negative perceptions of generic medicines as covariates (sex, age, education, ethnicity, nationality, self-reported health status measured by the physical and mental components of RAND-12, consultation with a general practitioner, comorbidities and polypharmacy (≥5 medications)), together with perceptions of generic medicines and their interaction with these variables. In the moderation analysis, centring within the main range of the data of the values for the continuous variables was applied.

The following subgroup analyses were performed: \( \chi^2 \) test was applied to determine if perceptions of generic medicines differed between participating countries. Logistic regression analysis was performed to investigate relationships of sex, age and indication for PCI with participation. Statistical significance was set at a p<0.05. Analyses were conducted using SPSS V.26 (Released 2016. IBM SPSS Statistics for Windows, V.26), the nlme package (V.3.1–152; Pinheiro et al) and the R boot package (V.1.3–27; Canty and Ripley).

**Patient and public involvement**

Two patient representatives with a history of coronary artery disease (CAD), who had been trained as patient representatives in healthcare and research settings, were involved in setting the research question and outcome measures, as well as in the reporting of the results from the study. They were also asked to advise on the interpretation of results.

**RESULTS**

**Population characteristics**

At baseline, 4209 patients were eligible for inclusion. Of these, 3430 gave informed consent and were included in the study (inclusion rate 82%). Thirteen patients withdrew their consent after discharge from hospital. Thus, 3417 patients were available for analysis at baseline (figure 1). The majority were men (78%), with a mean age of 66 years (SD 11, range 20–96 years), native born (92%), married or living with a partner (75%) and retired (42%). Seventeen per cent were current smokers, 21% had previously suffered a myocardial infarction, 52% had hypertension and 47% had high cholesterol levels. Twenty-six per cent had previously undergone PCI and 9% had undergone coronary artery bypass grafting. Most admissions for PCI were due to acute coronary syndrome (62%), while 61% were currently using five or more medicines. Table 1 shows the baseline characteristics of patients.

**Perceptions of generic medicines at T1 and T2**

At T1, generic medicines were perceived to be as effective (70%), as safe (68%), as producing the same side effects (64%), and containing the same active ingredients as brand name medicines (64%) (table 2). The percentage of patients who answered ‘unsure’, ‘probably not’ or ‘definitely not’ to any of the four questions and were categorised as having negative perceptions of generic medicines,
was 52% at T1 (figure 3). The percentage of patients who were categorised as having negative perceptions of generic medicines decreased to 28% at T2 (figure 3). At T2, 73% perceived generic medicines to be as effective, as safe (71%), as producing the same side effects (65%) and containing the same active ingredients as brand name medicines (66%) (table 2).

Mixed effect models showed a statistically significant shift towards more positive perceptions of generic medicines at T2 compared to T1. The percentage of patients who perceived generic medicines to be as effective as brand name medicines increased by 21% from T1 to T2 (28% to 52%). Similarly, there was a 25% increase in the percentage of patients who perceived generic medicines to be as safe as brand name medicines (71% to 96%).

Table 1 Baseline characteristics of patients undergoing percutaneous coronary intervention (N=3417)

| Characteristics N (%) |
|------------------------|
| Sex                    |
| Men    2673 (78)        |
| Age, mean (SD)         |
| 66 (11)                |
| Cohabitation status    |
| Married/cohabitating  2389 (75) |
| Separated/divorced 272 (9) |
| Widow/widower 263 (8)  |
| Never married 262 (8)  |
| Living alone 750 (24)  |
| Ethnicity              |
| Native born 2829 (92)  |
| Born of immigrant parents 114 (4) |
| Immigrant 135 (4)      |
| Education              |
| Primary school 640 (20) |
| Vocational school 1375 (43) |
| Upper secondary school 298 (9) |
| University college or university, <4 years 488 (15) |
| University college or university, ≥4 years 380 (12) |
| Employment             |
| Full-time work 957 (28) |
| Part-time work 134 (4)  |
| Retired 1422 (42)      |
| Sick-leave (100% or partial) 41 (1) |
| Disability benefits 181 (5) |
| Total household gross income (in Euro) |
| No information 370 (11) |
| ≤15 000 68 (2)         |
| 15 000+–22 000 255 (8) |
| 22 000+–33 000 449 (15) |
| 33 000+–44 000 425 (14) |
| 44 000+–60 000 507 (17) |
| 66 000+–77 000 448 (15) |
| 77 000+–93 000 307 (10) |
| >93 000 590 (19)       |
| Smoking status         |
| Never smoker 943 (30)  |
| Former smoker 1712 (54) |
| Current smoker 529 (17) |
| Indication for PCI     |
| Stable coronary artery disease 1020 (30) |
| Unstable angina pectoris 437 (13) |
| Non-ST-segment elevation myocardial infarction 912 (27) |

Table 1 Continued

| Characteristics N (%) |
|------------------------|
| ST-segment elevation myocardial infarction 739 (22) |
| Other 295 (9)         |
| Previous PCI 873 (26) |
| Previous CABG 312 (9) |
| Previous cardiovascular comorbidities |
| Atrial fibrillation/flutter 406 (12) |
| Coronary artery disease 1156 (34) |
| Chronic heart failure 264 (8) |
| Hypercholesterolaemia 1569 (47) |
| Hypertension 1773 (52) |
| Myocardial infarction 699 (21) |
| Peripheral artery disease 205 (6) |
| Previous medical comorbidities |
| Anxiety and depression 333 (10) |
| Cancer 395 (12)        |
| Cerebrovascular disease 215 (6) |
| Chronic obstructive pulmonary disease 247 (7) |
| Chronic renal failure 156 (5) |
| Diabetes (type I or II) 701 (21) |
| Medications at discharge |
| ACE-inhibitors 925 (27) |
| Anticoagulants 715 (21) |
| ARB-inhibitors 805 (24) |
| Acetylsalicylic acid 3285 (96) |
| Beta-blockers 1790 (53) |
| Calcium channel blockers 700 (21) |
| Clopidogrel 1596 (47) |
| Diuretics 613 (18)     |
| Prasugrel 89 (3)       |
| Statins 3151 (92)      |
| Ticagrelor 1613 (47)   |
| ≥5 medications 2084 (61) |

ACE-inhibitors, angiotensin-converting-enzyme inhibitors; ARB-inhibitors, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention; PCI, Previous CABG.
Table 2  Perceptions of generic medicines at 2-month and 6-month follow-up

| All centres | T1—2 months after discharge from hospital | T2—6 months after discharge from hospital | Low trust in generic medicines* n (%) |
|-------------|------------------------------------------|------------------------------------------|-------------------------------------|
|             | Definitely yes n (%) | Probably yes n (%) | Unsure n (%) | Probably not n (%) | Definitely not n (%) | Definitely yes n (%) | Probably yes n (%) | Unsure n (%) | Probably not n (%) | Definitely not n (%) | Low trust in generic medicines* n (%) |
| Do you believe generic medicines to be as effective as brand name medicines? | 752 (29) | 1054 (41) | 523 (20) | 116 (5) | 138 (5) | 777 (30) | 778 (31) | 1049 (42) | 467 (19) | 89 (4) | 132 (5) | 688 (27) |
| Do you believe generic medicines to be as safe as brand name medicines? | 707 (27) | 1048 (41) | 571 (22) | 121 (5) | 129 (5) | 82 (32) | 740 (30) | 1042 (42) | 501 (20) | 99 (4) | 126 (5) | 726 (29) |
| Do you believe generic medicines to have the same side effects as brand name medicines? | 589 (23) | 1053 (41) | 772 (30) | 90 (4) | 66 (3) | 928 (36) | 619 (25) | 1013 (40) | 710 (28) | 94 (4) | 71 (3) | 878 (35) |
| Do you believe generic medicines to be made of the same active ingredients as brand name medicines? | 571 (22) | 1073 (42) | 713 (28) | 129 (5) | 91 (4) | 933 (36) | 620 (25) | 1022 (41) | 654 (26) | 114 (5) | 96 (4) | 867 (34) |

*Combined percentage of patients who answered 'Unsure', 'Probably not' or 'Definitely not'.
medicines from T1 to T2 (p=0.002); however, the fixed effect estimate was low (1.10, 95% CI 0.41 to 1.79).

At T1, female sex (−3.94, 95% CI −6.39 to −1.41, p=0.002), lower education level (overall p<0.001), ethnicity (overall p=0.009), Norwegian nationality (10.42, 95% CI 8.34 to 12.50, p<0.001) and lower mental component score on the RAND-1233 (0.25, 95% CI 0.09 to 0.41, p=0.003) were significantly associated with negative perceptions of generic medicines (table 3 and figure 4).

Statistically significant differences in perceptions of generic medicines were found between the two countries at both time points, with Danish patients having more positive perceptions of generic medicines than Norwegian patients (online supplemental table 1).

At T2, female sex (−4.21, 95% CI −6.75 to −1.71, p=0.001), age (−0.12, 95% CI −0.23 to −0.02, p=0.020), lower education level (overall p<0.001), ethnicity (overall p=0.002), Norwegian nationality (10.27, 95% CI 8.19 to 12.40, p<0.001) and a lower mental component score on the RAND-1233 (0.19, 95% CI 0.01 to 0.37, p=0.033) were significantly associated with negative perceptions of generic medicines (table 4 and figure 4).

**Table 3** Association between sociodemographic and clinical characteristics and perceptions of generic medicines 2 months after discharge from hospital

| Characteristic                              | Coefficient | Lower    | Upper   | P value |
|---------------------------------------------|-------------|----------|---------|---------|
| Female sex                                  | −3.94       | −6.39    | −1.41   | 0.002   |
| Age                                         | 0.08        | −0.02    | 0.18    | 0.131   |
| Living alone                                 | −2.26       | −4.67    | 0.05    | 0.063   |
| Education                                   | <0.001†     |          |         |         |
| Primary school                               | −9.8        | −13.24   | −6.32   | <0.001  |
| Vocational school                           | −8.39       | −11.13   | −5.59   | 0.001   |
| Upper secondary school                      | −3.9        | −7.5     | −0.3    | 0.036   |
| College/university <4 years                 | −4.57       | −7.73    | −1.53   | 0.004   |
| versus college/university >4 years          |             |          |         |         |
| Ethnicity                                   | 0.009†      |          |         |         |
| Immigrant                                   | −4.89       | −10.87   | 0.94    | 0.1     |
| Born of immigrant parents                   | −6.56       | −12.44   | −0.94   | 0.019   |
| versus native-born                          |             |          |         |         |
| Norwegian nationality                       | 10.42       | 8.34     | 12.5    | <0.001  |
| Comorbidities                               | 0.61†       |          |         |         |
| No comorbidities                            | 0.61        | −2.24    | 3.42    | 0.676   |
| One comorbidity                             | 1.62        | −1.08    | 4.39    | 0.243   |
| Two comorbidities                           | −0.47       | −2.99    | 2.03    | 0.719   |
| versus Three or more comorbidities          |             |          |         |         |
| Polypharmacy‡                               | 1.45        | −0.45    | 3.35    | 0.158   |
| Consultation with general practitioner       | 0.18†       |          |         |         |
| Before 4 weeks                              | −0.47       | −2.8     | 1.75    | 0.681   |
| Within 4–8 weeks                            | −2.35       | −4.91    | 0.19    | 0.08    |
| versus no consultation                      |             |          |         |         |
| Self-reported health status                  |             |          |         |         |
| Physical component score RAND-12            | −0.04       | −0.219   | 0.14    | 0.67    |
| Mental component score RAND-12              | 0.25        | 0.09     | 0.41    | 0.003   |

*Bootstrap results are based on 5000 bootstrap samples.
†Overall p values for education, ethnicity, comorbidities and consultation with general practitioner.
‡Currently using five or more medications.
In the moderation analysis, polypharmacy was a potential moderator of the association between sociodemographic and clinical variables and medication adherence. However, the interaction was not statistically significant (p=0.077). No significant interactions were found for age, sex, living alone, level of education, ethnicity, nationality, comorbidities, consultation with general practitioner or self-reported health status (p≥0.11).

Medication adherence at T1 and T2

The mean MARS-5 total score was 4.83 (SD 0.41) at T1. In addition, more than 99% scored at or above the MARS-5 midpoint, indicating high levels of self-reported medication adherence. No significant difference was found in self-reported medication adherence between the measuring time points, as the mean total score for MARS-5 was 4.78 (SD 0.50) and 99% scored at or above the MARS-5 midpoint at T2 (table 5).

There were no substantial correlations between negative perceptions of generic medicines and low self-reported medication adherence at T1 (r=0.041, 95% CI 0.002 to 0.081, p=0.037) or T2 (r=0.038, 95% CI –0.005 to 0.081, p=0.057).

DISCUSSION

In this prospective multicentre cohort study of patients after PCI, a sizeable proportion of the patients had negative perceptions of generic medicines or were uncertain about the safety and efficacy of generic medicines. Significant improvement in perceptions of generic medicines were found between T1 and T2; however, the estimated improvement was low. Female sex, older age, lower education level, ethnicity, Norwegian nationality, and poorer mental health were significantly associated with negative perceptions of generic medicines. There was no evidence to suggest that perceptions of generic medicines moderate the association between sociodemographic and clinical characteristics and medication adherence. The overall self-reported medication adherence was high at both time points. However, the negative perceptions of generic medicines were not significantly correlated with low self-reported medication adherence.

A sizeable proportion of the patients in our study had negative perceptions of generic medicines. Global spending on prescription medicines is steadily increasing, largely driven by the high cost of brand name medicines, market exclusivity and monopoly rights, and it has become a major concern for patients, prescribers and policy-makers. Thus, this lingering mistrust in generic medicines is concerning and important for policy-makers to consider as healthcare expenditure increases to unaffordable levels. A possible explanation for the persisting negative perceptions of generic medicines might be the set-up of the healthcare systems in the participating countries. All the Nordic countries have a tax-supported healthcare system founded on the principle of universal access to both hospital-based and primary healthcare services, which secures access to medicines regardless of the patients’ financial situation. For medicines that are available for reimbursement (by the hospital or national insurance scheme), the pharmacies are obliged at all times to have at least one of the cheapest generic medicines available in both Norway and Denmark. Furthermore, they are obliged to offer the cheapest generic competitor to the patients, if the physician has not opposed to such substitution for any (medical) reason, and to inform them about the safety and efficacy of generic medicines. The premise for generic substitution is that the medicines have been considered interchangeable in terms of bioequivalence and therapeutic equivalence by the countries’ medicines agencies. Which medicines that should be considered interchangeable are regularly evaluated, and the list of interchangeable medicines are updated monthly. The rationale behind the introduction of generic substitution was primarily cost containment, since a sizeable proportion of the patients’ pharmaceutical expenditure is covered by the government in the Nordic countries. This is unlike the USA, where private healthcare insurance is the predominant source of healthcare coverage, and, as a result, 9 out of 10 prescriptions filled are for generic medicines.

Universal healthcare, combined with a high standard of living, means that switching to a generic medicine leads to no or small personal savings. Thus, patients may need stronger financial incentives to increase their acceptance and use of generic medicines. Furthermore, a recent systematic literature review found that a lack of communication between patients and healthcare professionals contributed negatively to perceptions and the utilisation of generic medicines. Although we did not investigate the extent to which patients were informed about the possibility of generic substitution, these results are consistent with findings from our recent qualitative interview...
study. As patients' knowledge is a prerequisite for acceptance and use of generic medicines, physicians should be encouraged to inform patients about the possibility of generic substitution before discharge from hospital in order to avoid confusion, misunderstandings and subsequent negative perceptions of generic medicines when they are offered generic substitutes by pharmacies.

Our finding that perceptions of generic medicines are associated with sociodemographic characteristics such as sex, age, socioeconomic status and ethnicity is in line with previous studies in other patient populations. Our finding that perceptions of generic medicines are associated with sociodemographic characteristics such as sex, age, socioeconomic status and ethnicity is in line with previous studies in other patient populations.12 16 27 Surprisingly, significant differences in perceptions were found between the two countries despite comparable healthcare systems. This could be explained by a historic difference as regards generic substitution, which is reflected in a lower prescription rate for generic medicines in Norway (54%) than in Denmark (67%).40 41 Generic substitution was first allowed in Denmark in the early 1990s. However, in 1997, the legislation was amended and pharmacists were expected to offer generic substitution unless the prescribing physician was explicitly opposed to this. In Norway, generic substitution was not introduced until 2001.

In our study, a lower mental component score, reflecting poorer mental health, was significantly associated with negative perceptions of generic medicines. Moreover, poorer mental health has not been reported to be significantly associated with negative perceptions of generic medicines in previous systematic reviews.12 13 16 27

Table 4 Association between sociodemographic and clinical characteristics and perceptions of generic medicines 6 months after discharge from hospital

| Characteristic                        | Coefficient | 95% CI*          | P value |
|---------------------------------------|-------------|------------------|---------|
| Female sex                            | −4.21       | −6.75 to −1.71   | 0.001   |
| Age                                   | −0.12       | −0.23 to −0.02   | 0.02    |
| Living alone                          | −1.7        | −4.15 to 0.77    | 0.186   |
| Education                             |             |                  |         |
| Primary school                        | −9.13       | −12.64 to −5.63  | <0.001  |
| Vocational school                     | −7.23       | −9.96 to −4.45   | <0.001  |
| Upper secondary school                | −5.15       | −8.85 to −1.56   | 0.008   |
| College/university <4 years           | −1.83       | −4.72 to 1.03    | 0.239   |
| versus college/university >4 years    |             |                  |         |
| Ethnicity                             |             |                  |         |
| Immigrant                             | −7.33       | −13.1 to −1.8    | <0.001  |
| Born of immigrant parents             | −6.54       | −12.98 to −0.59  | 0.028   |
| versus native-born                     |             |                  |         |
| Norwegian nationality                 | 10.27       | 8.19 to 12.4     | <0.001  |
| Comorbidities                         |             |                  |         |
| No comorbidities                      | 1.77        | −1.15 to 4.45    | 0.236   |
| One comorbidity                       | 2.98        | 0.28 to 5.67     | 0.033   |
| Two comorbidities                     | 1.21        | −1.38 to 3.76    | 0.372   |
| Three or more comorbidities           |             |                  |         |
| Polypharmacy‡                         | 1.85        | −0.15 to 3.91    | 0.071   |
| Consultation with general practitioner |             |                  |         |
| Before 4 weeks                        | −2.02       | −4.44 to 0.5     | 0.09    |
| Within 4–8 weeks                      | −3.73       | −6.43 to −1.07   | 0.008   |
| Versus no consultation                 |             |                  |         |
| Self-reported health status            |             |                  |         |
| Physical component score RAND-12     | −0.01       | −0.18 to 0.18    | 0.937   |
| Mental component score RAND-12 44     | 0.19        | 0.01 to 0.37     | 0.033   |

*Bootstrap results are based on 5000 bootstrap samples. †Overall p values for education, ethnicity, comorbidities and consultation with general practitioner. ‡Currently using five or more medications.
Thus, this important finding seems to be underinvestigated and is an area for future research.

Contrary to our hypothesis, clinical characteristics were not significantly associated with perceptions of generic medicines. A recent study investigating physician-related factors associated with opposing generic substitution for 18 distinct therapeutic classes (including antiplatelet agents, lipid-lowering agents, ACE inhibitors, angiotensin II receptor blockers and beta blockers) found that patients’ clinical characteristics, such as comorbidity and polypharmacy, negatively influenced prescription rates for generic medicines. Thus, comorbidity may be an influencing factor in the physician’s decision not to allow generic substitution. However, results are inconclusive, warranting further research.

Unlike previous studies where adherence to secondary preventive medicines have been found to be poor in patients after PCI, the overall self-reported medication adherence decreased with an increase in generic substitution. Furthermore, perceptions of generic medicines were not significantly correlated with self-reported adherence in this study. In contrast, a cross-sectional study analysing healthcare claims data for ambulatory care showed that generic substitution on persistence and medication adherence was associated with improved medication adherence. In addition, a large-sample retrospective study analysing healthcare claims data for ambulatory care showed that generic substitution on persistence and medication adherence was associated with improved medication adherence.

The perfect method to measure medication adherence does not exist as all methods have their advantages and disadvantages. In our study, medication adherence was assessed by self-report. Although self-reported measures may overestimate medication adherence compared with objective measures, patient-reported outcomes are found to be powerful tools valued by patients, clinicians, and policy-makers. Thus, results from our cohort study add important results to the existing literature on medication adherence and generic substitution.

Table 5: Responses to the medication adherence report scale at 2-month and 6-month follow-up

| Item                                      | T1—2 months after discharge from hospital | T2—6 months after discharge from hospital |
|-------------------------------------------|----------------------------------------|-------------------------------------------|
|                                           | Always n (%) | Often n (%) | Sometimes n (%) | Rarely n (%)   | Never n (%) | Always n (%) | Often n (%) | Sometimes n (%) | Rarely n (%) | Never n (%) |
| Forget to take medications                | 22 (1)       | 5 (0.2)     | 94 (4)          | 895 (39)       | 1571 (61)   | 37 (2)       | 14 (1)       | 109 (4)          | 980 (39)   | 1375 (55)   |
| Modify doses                              | 21 (1)       | 6 (0.2)     | 47 (2)          | 126 (5)        | 2365 (92)   | 34 (1)       | 6 (0.2)      | 60 (2)          | 131 (5)    | 2266 (91)   |
| Stop taking medicines during a certain period | 18 (1)       | 4 (0.2)     | 25 (1)          | 71 (3)         | 2445 (95)   | 35 (1)       | 4 (0.2)      | 37 (2)          | 75 (3)     | 2338 (94)   |
| Decide to miss a dose                     | 17 (1)       | 4 (0.2)     | 25 (1)          | 96 (4)         | 2420 (95)   | 31 (1)       | 4 (0.2)      | 53 (2)          | 96 (4)     | 2310 (93)   |
| Take less than what is prescribed         | 29 (1)       | 11 (0.4)    | 26 (1)          | 87 (3)         | 2416 (94)   | 40 (2)       | 7 (0.3)      | 34 (1)          | 86 (3)     | 2326 (93)   |

Mean total score MARS-5 (SD): 4.83 (0.41) 4.78 (0.50)

MARS-5, Medication Adherence Report Scale.
and T2, respectively. Age and sex distribution in our study are comparable with data provided by the Norwegian Registry of Invasive Cardiology and the Danish Heart Registry for this patient population, strengthening the generalisability of results. Finally, patient representatives were involved in setting the research question and outcome measures. Furthermore, they provided invaluable input to the development of the CRF, including the choice of self-report questionnaires, thereby ensuring the relevance of the questionnaire.

Despite these strengths, our study is not without limitations. First, as language barriers were an exclusion criterion, our results may not be extrapolated to all segments of the target population. Most Western countries advocate the use of generic medicines and impose strict control on their pharmaceutical markets regarding the quality of generic medicines. However, many low-income and middle-income countries struggle with an insufficient regulatory system for their pharmaceutical markets and lack bioequivalence testing facilities. Furthermore, studies have shown that physicians in low- and middle-income countries tend to have mixed perceptions of generic medicines. Thus, immigrants from low-income and middle-income countries may also have different perceptions of generic medicines compared with the population at large. Second, we assessed perceptions of generic medicines in general, and did not distinguish between different classes of medicines or therapeutic use (eg, transient vs severe conditions). As patients tend to be more susceptible to using generic medicines for what they perceive to be mild conditions compared with severe conditions, our results may not reflect all aspects of patients’ perceptions of generic medicines. Thirdly, Norwegian patients who declined to participate in the study were older and more often had other indications for PCI compared with participants (online supplemental table 2). However, the propensity to complete the questionnaire at T1 and T2 increased with age for those remaining in the study (online supplemental tables 3 and 4). Fourth, we categorised those answering ‘unsure’ as having negative perceptions of generic medicines. Fifth, despite being validated for patients with chronic conditions, we found that 99% scored at or above the MARS-5 midpoint. This indicates that the use of both generic and disease-specific instruments are needed to obtain a correct picture of patients’ medication adherence after PCI. In addition, the skewed distribution of the instrument may have affected the results of the moderation analysis as a higher number of non-adherent patients would be needed to adequately test the hypothesis. However, given the large study sample, this limitation is reduced. Finally, due to legislation in the Nordic countries in question, patients can freely choose to use generic or brand name medicines regardless of what is prescribed. Thus, the only way to collect data on whether patients filled their prescription for generic or brand name medicines is through prescription registries. However, due to restructuring of the Norwegian Prescription Database, these data are currently not available. Thus, we were unable to compare clinical outcomes or investigate correlations between perceptions of generic medicines and clinical outcomes between those using generic medicines and those using brand name medicines.

CONCLUSION

Mistrust and uncertainty about the safety and efficacy of generic medicines remains in a sizeable proportion of patients after PCI. This applies especially to those of lower socioeconomic status, older age, female sex, immigrants and those with poorer mental health. However, this study demonstrates a shift towards more positive perceptions of generic medicines in the longer term.

Author affiliations
1 Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
2 Department of Clinical Science, University of Bergen Faculty of Medicine and Dentistry, Bergen, Norway
3 Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway
4 Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA
5 Department of Biostatistics, Yale University School of Public Health, New Haven, Connecticut, USA
6 Department of Cardiology, Oslo University Hospital, Oslo, Norway
7 Institute of Clinical Medicine, University of Oslo Faculty of Medicine, Oslo, Oslo, Norway
8 Department of Cardiothoracic and Vascular Surgery, Odense Universitetshospital, Odense, Denmark
9 Department of Clinical Research, University of Southern Denmark, Odense, Denmark
10 Centre of Interprofessional Collaboration within Emergency Care (CICE), Linnaeus University, Kalmar, Sweden
11 Department of Cardiology, Stavanger University Hospital, Stavanger, Norway
12 Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway
13 Centre for Child and Adolescent Mental Health Eastern and Southern Norway, Oslo, Norway

Twitter Trond Reed Pettersen @EdTrond, Britt Borregaard @BorregaardBritt and Tone Merete Norekvål @TNorekvål

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ORCID ids Trond Reede Pettersen http://orcid.org/0000-0002-3757-4847
Brett Borregaard http://orcid.org/0000-0003-2702-0231
Tone Merete Norekvål http://orcid.org/0000-0003-3640-2119

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