ORIGINAL RESEARCH

Education of Migrant and Nonmigrant Patients Is Associated With Initiation and Discontinuation of Preventive Medications for Acute Coronary Syndrome

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Background—The benefits of preventive medications after acute coronary syndrome are impeded by low medication persistence, in particular among marginalized patient groups. Patient education might increase medication persistence, but the effect is still uncertain, especially among migrant groups. We, therefore, assessed whether use of patient education was associated with medication persistence after acute coronary syndrome and whether migrant background modified the potential associations.

Methods and Results—A cohort of patients discharged with a diagnosis of acute coronary syndrome (N=33 199) was identified in national registers. We then assessed number of contacts for patient education during a period of 6 months after discharge and the initiation and discontinuation of preventive medications during a period of up to 5 years. Results were adjusted for comorbidity and sociodemographic factors. Three or more contacts for patient education was associated with a higher likelihood of initiating preventive medications, corresponding to adjusted relative risks ranging from 1.12 (95% CI, 1.06–1.18) for statins to 1.39 (95% CI, 1.28–1.51) for ADP inhibitors. Lower risks of subsequent discontinuation were also observed, with adjusted hazard ratios ranging from 0.86 (95% CI, 0.79–0.92) for statins to 0.92 (95% CI, 0.88–0.97) for β blockers. Stratification and test for effect modification by migrant status showed insignificant effect modification, except for initiation of ADP inhibitors and statins.

Conclusions—Patient education is associated with higher chance of initiating preventive medications after acute coronary syndrome and a lower long-term risk of subsequent discontinuation independently of migrant status. **(*J Am Heart Assoc*. 2019;8: e009528. DOI: 10.1161/JAHA.118.009528.)**

Key Words: acute coronary syndrome • ethnicity • medication discontinuance • patient education

Patient education is a core part of modern secondary prevention of acute coronary syndrome (ACS).[1–3] It is a complex intervention, which aims to increase patients' competencies to act rationally about their disease, symptoms, risk factors, and medical treatment. The intervention is not consistently defined in the literature, but assumptions of transfer of knowledge into behavioral changes are fundamental. The effects of patient education may differ across population groups because of factors like educational level, language proficiency, social support, and other socioeconomic factors; and compared with local majority groups, migrant and ethnic minority groups are disproportionally affected by these factors.[4,5] Nevertheless, migrants are underrepresented in research on secondary prevention of ACS.[1,6]

Both nonpharmacological and pharmacological interventions are effective in secondary prevention of ACS.[2,3] Current clinical guidelines consequently recommend physical exercise, patient education, dietary advice, and psychological counseling in combination with use of aspirin, statins, ADP receptor inhibitors, and β blockers, as well as angiotensin-converting enzyme (ACE) inhibitors in selected patients.[2,3] Among migrants with ACS, studies have found worrisome low use of preventive medications,[7,8] and a recent study found that patients with ACS with a migrant background, compared with local-born patients, were at higher risks of low use of both preventive medications and patient education.[7]

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Clinical Perspective

What Is New?

- The study is a real-world assessment of the associations of patient education and medication persistence among patients with acute coronary syndrome.
- Knowledge gaps related to outcomes after acute coronary syndrome among vulnerable populations are addressed through a population-based nationwide study with stratification into migrant status.

What Are the Clinical Implications?

- Patient education is positively associated with medication persistence.
- Thus, this supports current clinical guidelines that clinicians should encourage patients' participation in patient education.
- Stratification into migrant status shows similar associations, indicating that efforts to engage migrant groups in patient education are needed.

A recent review finds that patient education may improve quality of life and reduce heart-related complications in patients with recent cardiovascular disease (CVD),[1] but the effect on medication adherence is not included in the review. In patients with chronic disease, a review on any type of interventions to improve medication adherence finds a lack of convincing evidence on the effects of the interventions,[9] but a few studies have found effect on adherence of a patient education intervention in patients with CVD.[10,11] Among migrants, studies on interventions to increase medication adherence are too few and inconsistent to be conclusive.[5] We follow the taxonomy in pharmacotherapeutic research as proposed by a systematic review,[12] which defines medication adherence as the process by which patients take their medications as prescribed, composed of initiation, implementation, and discontinuation. The assessment of implementation requires data on patient behavior. We had access to data on time between initiation and discontinuation of medications, which is termed persistence. Therefore, the objective of this study was to assess whether participation in patient education is associated with higher medication persistence among patients with ACS in general as well as among subgroups of patients with a migrant background.

Methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines,[13] and was approved by the Danish Data Protection Agency (identification: 2014-41-2922). Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Danish National eHealth Authority. According to national legislation on use of register data for research purposes, there was no requirement of informed consent from included subjects.

Setting

The study was conducted in Denmark, which has a population of ≈5.7 million. The healthcare system is primarily financed through taxation. Individuals with Danish citizenship or a long-term residency permit have free access to healthcare services and partial reimbursement of the costs of prescribed medicines.

Study Design and Patient Population

We conducted a nationwide, population-based follow-up study (N=33 199) using data from the Danish National Patient Register (NPR)[14] (Figure 1). The NPR contains information on discharge diagnoses, hospital, department, and day of discharge for inpatients and outpatients, and the

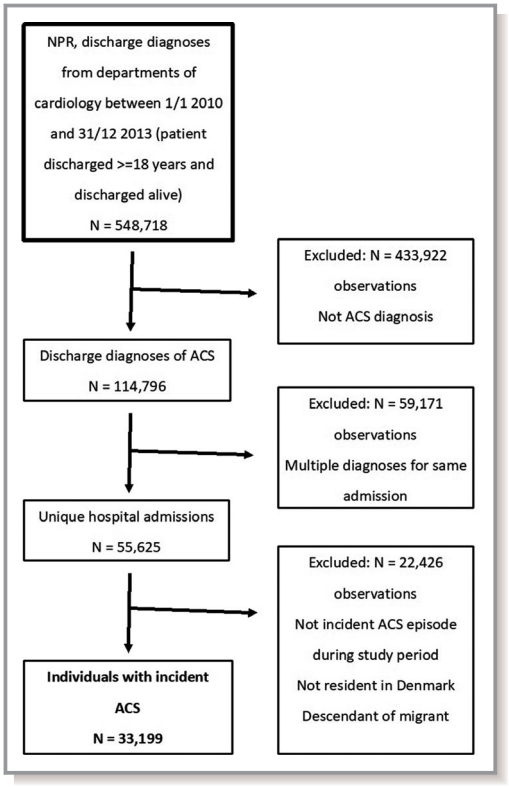

Figure 1. Flowchart of inclusion in the population on the basis of data from the Danish National Patient Register, the Central Person Register, and Statistics Denmark. ACS indicates acute coronary syndrome; NPR, Danish National Patient Register.

International Classification of Diseases, Tenth Revision (*ICD-10*), has been used for classification of diagnoses from 1994 and onwards. The register also contains information on hospital-based activities, including patient education. The Personal Identification Number Register contains basic data on all Danish citizens and people with a long-term residency permit and provided data on death and age. Relevant patients included subjects hospitalized on a short-term basis, according to the following criteria: (1) being ≥18 years of age, with a Danish civil registration number; (2) being discharged alive January 1, 2010, to December 31, 2013, from a department of cardiology; and (3) experiencing ACS, including myocardial infarction and unstable angina pectoris (*ICD-10* codes DI21, DI248, DI249, DI240, and DI200). Patients were excluded if they had been admitted for ischemic heart disease within the previous 12 months.

Patient Education

Danish clinical guidelines recommend patient education after ACS to include education about the disease, symptoms, risk factors, prevention, medications, screening of mental health status, and psychosocial counseling. The educator should be a health professional trained within health education. In the Danish setting, patient education is usually conducted within 2 to 6 months after discharge, organized in groups or 1:1, and led by a nurse.[15] The number of individual contacts related to patient education in NPR data was determined and divided into 3 groups (cutoffs at 0, 1–2, and ≥3 contacts). Cutoffs were determined by national guidelines, which recommend patient education to be structured into one introductory session, the actual patient education program, and a final individual session.[15] Therefore, patients who had ≥3 contacts were likely to have completed at least parts of the educational program. The data did not allow for further determination of the local design of the intervention; and it is an example of a nationally implemented real-world intervention, which is not necessarily following the guidelines point by point.

Secondary Prevention Medications

Outcome was medication persistence, defined as the time between initiation and discontinuation of relevant types of medication. These included statins (anatomical therapeutic chemical classification code C10A), ADP inhibitors (B01AC04, B01AC22, and B01AC24), β blockers (C07), and ACE inhibitors (C09). Aspirin can be bought over the counter and was, therefore, not included. Initiation was defined as filling at least one prescription within 6 months from the date of discharge. Discontinuation was defined as failing to fill a new prescription within 90 days after estimated date of expiry of a reimbursed prescription during the years 2010 to 2014. Data on reimbursed prescriptions were retrieved from the Register of Medicinal Products Statistics.[16]

Migrant Status

The study population was linked to registers at Statistics Denmark containing information on country of origin and sociodemographic variables. The population was classified as Danish-born (n=30 686), Western (n=882), or non-Western (n=1631) migrants. A migrant was defined as a person born outside of Denmark by parents who are both non-Danish citizens. This definition is in accordance with the definition by The International Organisation for Migration (IOM) that a migrant is a person who has moved across an international border or within a state away from his/her habitual place of residence.[17] The division into Western/non-Western migrants follows the practice of Statistics Denmark, in which Western migrants include migrants born in Western Europe, North America, or Australia. The non-Western countries category includes all other countries.[18] We excluded descendants of migrants.

Covariates

Statistics Denmark provided data on family income, education, employment, and cohabiting status, Personal Identification Number Register on age and sex, and NPR on comorbidity and whether patient education was delivered by university-affiliated or regional hospitals. We used the Charlson Comorbidity Index to assess comorbidity.[19] However, as congestive heart failure and types 1 and 2 diabetes mellitus were a priori expected to influence the outcomes independently, they were included as separate variables and, therefore, excluded from the Charlson Comorbidity Index.

Statistical Analysis

We performed binomial regression analyses to compute relative risk (RR) for initiating medications within 180 days after discharge. During the 180 days, 14 of the 33 199 subjects emigrated and 3058 died. Sensitivity analyses only including subjects who had not died or emigrated during the 180 days resulted in RRs that were virtually unchanged, and we, therefore, chose to present results for the entire population. Including only subjects who had initiated time to discontinuation was analyzed using Cox proportional hazards regression analyses and presented as hazard ratios (HRs). Subjects were followed up from the time of the first reimbursement until estimated time of discontinuation, death, emigration, or end of follow-up (December 31, 2014), whichever came first. The assumptions of proportional

Table 1. Population Characteristics According to Number of Contacts for Patient Education

	Patient Education							
	0 Contacts		1–2 Contacts		≥3 Contacts		Total	
Characteristics	No.	%	No.	%	No.	%	No.	%
All	9647	29.1	8291	25.0	15 261	46.0	33 199	100
Danish	8879	92.0	7628	92.0	14 179	92.9	30 686	92.4
Western	274	2.8	242	2.9	366	2.4	882	2.7
Non-Western	494	5.1	421	5.1	716	4.7	1631	4.9
Women	3909	40.5	2938	35.4	4915	32.2	11 762	35.4
Age, y*								
18–64	3356	34.8	3229	38.9	6591	43.2	13 176	39.7
65–74	2088	21.6	2135	25.8	4478	29.3	8701	26.2
≥75	4203	43.6	2927	35.3	4192	27.5	11 322	34.1
Cohabiting	5293	54.9	4922	59.4	10 026	65.7	20 241	61.0
Tertiary education†								
None	4379	45.4	3746	45.2	6342	41.6	14 467	43.6
Low	3258	33.8	3126	37.7	6423	42.1	12 807	38.6
Medium	783	8.1	695	8.4	1454	9.5	2932	8.8
Long	348	3.6	270	3.3	516	3.4	1134	3.4
Missing	879	9.1	454	5.5	526	3.4	1859	5.6
Family income‡								
Low	3731	38.7	3019	36.4	4344	28.5	11 094	33.4
Medium	2988	31.0	2607	31.4	5026	32.9	10 621	32.0
High	2539	26.3	2373	28.6	5362	35.1	10 274	30.9
Employed	2382	24.7	2213	26.7	4926	32.3	9521	28.7
Retired	6811	70.6	5670	68.4	9599	62.9	22 080	66.5
Sick leave or unemployed	319	3.3	308	3.7	544	3.6	1171	3.5
Others	135	1.4	100	1.2	192	1.3	427	1.3
Discharged from university hospital	4198	43.5	3995	48.2	8390	55.0	16 583	50.0
Percutaneous cardiac intervention*	3698	38.3	4414	53.2	8956	58.7	17 068	51.4
Coronary artery bypass grafting§	148	1.5	418	5.0	2443	16.0	3009	9.1
Atrial fibrillation	1547	16.0	1085	13.1	1908	12.5	4540	13.7
Congestive heart failure	1138	11.8	990	11.9	1437	9.4	3565	10.7
Diabetes mellitus, types 1 and 2	1056	10.9	1045	12.6	2025	13.3	4126	12.4
CCI								
Low	4928	51.1	4306	51.9	8301	54.4	17 535	52.8
Moderate	3462	35.9	2873	34.7	5053	33.1	11 388	34.3
High	1257	13.0	1112	13.4	1907	12.5	4276	12.9

CCI indicates Charlson Comorbidity Index, excluding congestive heart failure and types 1 and 2 diabetes mellitus.
*Cutoffs according to the Danish right to retirement at the age of 65 years.
†Cutoffs according to the International Standard Classification of Education.
‡Cutoffs according to tertiles.
§During index admission.

hazards in the data set were assessed visually and found to be met. We then stratified according to migrant status, and including the entire study population, we used Wald's tests to determine whether the effectiveness of patient education differed significantly according to migrant status. The test for effect modification was performed on a multiplicative scale in

the adjusted multivariable model. RRs and HRs were presented as unadjusted and adjusted by multivariable analyses, with the inclusion of all covariates as potential confounders. In addition, a Fine and Gray model was used to construct cumulative incidence curves of medication discontinuation. Death or emigration was considered as a competing risk when computing the cumulative incidence. Gray's test was used to compare curves. Finally, test for trend was computed by including the actual number of visits as continuous variable and using a χ^2 test. Statistical analyses were performed using SAS 9.4 statistical software (SAS Institute Inc, Cary, NC).

Results

Population Characteristics

Three or more contacts for patient education was more frequent (n=15 261 [46%]) than 0 (n=9647 [29.1%]) or 1 to 2 (n=8291 [25.0%]) contacts (Table 1). Most sociodemographic and health-related factors were evenly distributed, according to participation in patient education. Exceptions were subjects aged >75 years, with low family income, not discharged from a university hospital, or with missing information on education, where ≥3 contacts were less frequent. Percutaneous cardiac intervention or coronary artery bypass grafting seemed to be linked with having at least one encounter. As expected, death or emigration was more frequent in the group of nonattendees to patient education (n=1448 [15.0%]) compared with the groups with 1 to 2 (n=696 [8.4%]) and ≥3 (n=928 [6.1%]) contacts.

Initiation of Preventive Medications

Compared with those without patient education contacts, subjects with contacts had a higher chance for initiation of medication (Table 2). Subjects with 1 to 2 contacts had adjusted RRs ranging from 1.15 (95% CI, 1.14–1.17) for statins to 1.23 (95% CI, 1.21–1.25) for ADP inhibitors. Subjects with ≥3 contacts had adjusted RRs ranging from

Table 2. Associations Between Participation in Patient Education and Initiation of Preventive Medications in the Entire Cohort and in Subgroups

	Patient Education						
	0 Contacts (RR=1)	1–2 Contacts			≥3 Contacts		
Therapy	No. (%)	No. (%)	Crude RR	Adjusted RR	No. (%)	Crude RR	Adjusted RR
All							
Statin	6812 (70.6)	6956 (83.9)	1.19 (1.17–1.21)	1.15 (1.14–1.17)	13 639 (89.4)	1.27 (1.25–1.28)	1.19 (1.17–1.20)
ADP inhibitor	5938 (61.6)	6336 (76.4)	1.24 (1.22–1.27)	1.23 (1.21–1.25)	12 416 (81.4)	1.32 (1.30–1.35)	1.29 (1.27–1.31)
β Blocker	6411 (66.5)	6492 (78.3)	1.18 (1.16–1.20)	1.17 (1.15–1.19)	12 907 (84.6)	1.27 (1.25–1.29)	1.25 (1.23–1.27)
ACE inhibitor	4343 (45.0)	4467 (53.9)	1.20 (1.16–1.23)	1.18 (1.14–1.21)	9231 (60.5)	1.34 (1.31–1.38)	1.30 (1.27–1.33)
Danish-born individuals							
Statin	6243 (70.3)	6372 (83.5)	1.19 (1.17–1.21)	1.15 (1.13–1.17)	12 640 (89.1)	1.27 (1.25–1.29)	1.18 (1.17–1.20)
ADP inhibitor	5497 (61.9)	5814 (76.2)	1.23 (1.21–1.26)	1.22 (1.19–1.24)	11 513 (81.2)	1.31 (1.29–1.34)	1.28 (1.25–1.30)
β Blocker	5907 (66.5)	5958 (78.1)	1.17 (1.15–1.20)	1.16 (1.14–1.18)	11 967 (84.4)	1.27 (1.25–1.29)	1.24 (1.22–1.26)
ACE inhibitor	4020 (45.3)	4104 (53.8)	1.19 (1.15–1.23)	1.17 (1.14–1.21)	8628 (60.9)	1.34 (1.31–1.38)	1.30 (1.26–1.33)
Western migrants							
Statin	185 (67.5)	215 (88.8)	1.32 (1.20–1.44)	1.12 (1.04–1.21)	331 (90.4)	1.34 (1.23–1.46)	1.13 (1.05–1.21)
ADP inhibitor	163 (59.5)	199 (82.2)	1.38 (1.23–1.55)	1.32 (1.19–1.48)	317 (86.6)	1.46 (1.31–1.62)	1.37 (1.24–1.52)
β Blocker	180 (65.7)	189 (78.1)	1.19 (1.07–1.33)	1.08 (1.00–1.17)	320 (87.4)	1.33 (1.21–1.46)	1.15 (1.07–1.24)
ACE inhibitor	114 (41.6)	142 (58.7)	1.41 (1.18–1.68)	1.21 (1.07–1.37)	213 (58.2)	1.40 (1.19–1.65)	1.21 (1.08–1.36)
Non-Western migrants							
Statin	384 (77.7)	369 (87.6)	1.13 (1.06–1.20)	1.07 (1.02–1.13)	668 (93.3)	1.20 (1.14–1.26)	1.12 (1.06–1.18)
ADP inhibitor	278 (56.3)	323 (76.7)	1.36 (1.24–1.50)	1.32 (1.21–1.44)	586 (81.8)	1.45 (1.34–1.58)	1.39 (1.28–1.51)
β Blockers	324 (65.6)	345 (81.9)	1.25 (1.16–1.35)	1.24 (1.15–1.34)	620 (86.6)	1.32 (1.23–1.42)	1.31 (1.22–1.41)
ACE inhibitors	209 (42.3)	221 (52.5)	1.24 (1.08–1.42)	1.06 (0.98–1.15)	390 (54.5)	1.29 (1.14–1.46)	1.12 (1.04–1.20)

ACE indicates angiotensin-converting enzyme; RR, relative risk.

1.19 (95% CI, 1.17–1.20) for statins to 1.30 (95% CI, 1.27–1.33) for ACE inhibitors. When stratifying according to migrant status, we also found statistically significant associations among non-Western migrants, with adjusted RRs ranging from 1.07 (95% CI, 1.02–1.13) for initiation of statins to 1.39 (95% CI, 1.28–1.51) for initiation of ADP inhibitors. Statistically significant associations were found for all but for initiation of ACE inhibitors among non-Western migrants with 1 to 2 contacts (adjusted RR, 1.06; 95% CI, 0.98–1.15) and for initiation of β blockers among Western migrants with 1 to 2 contacts (adjusted RR, 1.08; 95% CI, 1.00–1.17). Overlapping CIs in general indicated no significant differences between Danish-born, Western, and non-Western migrants. However, Wald's test for effect modification, according to migrant status, showed a statistically significantly stronger association between patient education and initiation of ADP inhibitor therapy in Western and non-Western migrants with 1 to 2 and ≥3 contacts compared with Danish-born individuals (P=0.004 and P<0.001, respectively). In contrast, the association between patient education and initiation of statins was marginally weaker among migrants with 1 to 2 contacts (P=0.04). Higher RRs for initiation of medications among those with ≥3 contacts, compared with 1 to 2 contacts, indicated a dose-response relationship for all types of medication both overall and according to migrant status (test for trend P<0.001 in all analyses).

Discontinuation of Secondary Prevention Medications

The associations between patient education contacts and the risk of discontinuation of medication are presented in Table 3. Discontinuation risks are also illustrated in cumulative incidence curves in Figure 2. Compared with no contacts, 1 to 2 contacts was associated with a lower risk of discontinuing statins (adjusted HR, 0.90; 95% CI, 0.83–0.99) and >3 contacts was associated with adjusted HRs of discontinuing statins (0.86; 95% CI, 0.79–0.92), β blockers (0.92; 95% CI, 0.88–0.97), and ACE inhibitors (0.89; 95% CI, 0.80–0.98). Tests for trend indicated a dose-response association in the overall population for statins, β blockers, and ACE inhibitors (P<0.05) but not ADP inhibitors (P=0.05). Similar patterns were found when stratifying according to migrant status, with the lowest adjusted HRs of discontinuation among non-Western migrants with >3 contacts (statins: 0.66 [95% CI, 0.51–0.86]; β blockers: 0.77 [95% CI, 0.64–0.93]; and ACE inhibitors: 0.62 [95% CI, 0.43–0.88]). Western migrants' risks of discontinuation were not significantly associated with patient education contacts. No significant effect modification by migrant status (Wald's test) was observed for discontinuation (ie, P values ranged from 0.21–0.98).

Discussion

In this nationwide cohort study, we assessed the associations between participation in patient education after ACS and subsequent initiation and discontinuation of preventive medications, and we assessed whether migrant status modified the associations. Participation in patient education was associated with initiation and discontinuation of all the included medication groups, except discontinuation of ADP inhibitors. Adjustment for a broad range of potential confounding factors, including comorbidity, sociodemographic factors, and discharge from a university-affiliated hospital, did not change the associations substantially. Stratification according to migrant status showed that, compared with Danish-born individuals, associations were stronger in migrants' initiation of ADP inhibitors but weaker in migrants' initiation of statins. No other significant effect modifications according to migrant status were found for discontinuation. Finally, we found indications on a dose-response relationship, with higher persistence among subjects with ≥3 contacts.

Our findings support current guidelines, which recommend patient education to promote lifestyle changes and medication persistence among patients with CVD.[2,3] Previous studies include a longitudinal cohort study, which found that patients following a patient education program for up to 3.5 years, had high medication persistence.[11] A randomized study found higher persistence among patients who participated in a patient education intervention, compared with

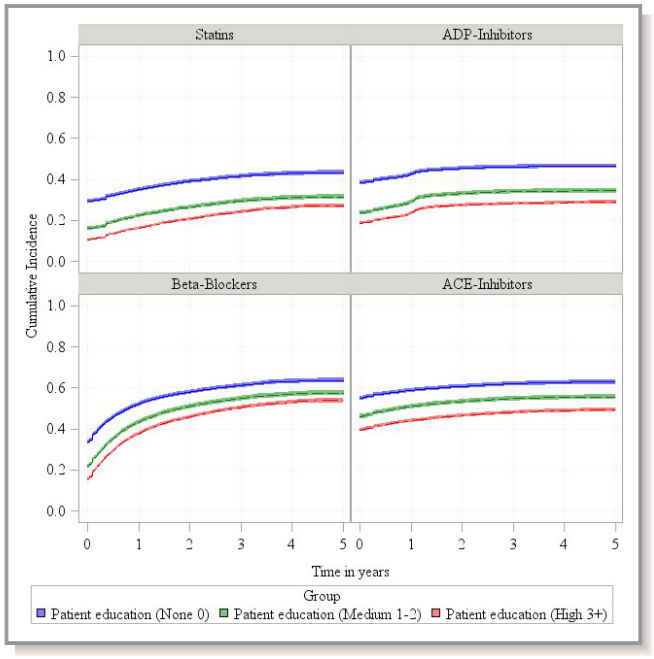

Figure 2. Medication discontinuation among subjects with 0, 1 to 2, and ≥3 contacts for patient education. Time 0 is the date of the first reimbursement of a prescription. Colored spectrums indicate CIs. ACE indicates angiotensin-converting enzyme.

usual care.[10] However, none of the studies focused on migrants or other groups at high risk of low medication persistence, and thus, were at risk of selection bias. A Cochrane review on interventions to improve medication persistence in general suggests that keeping patients in care may be the one most important factor.[9] Related to the design of patient education, cognitive-educational interventions, behavioral counseling, and feedback to the patients of their recent dosing history might be effective, but cost-effectiveness of the interventions is low.[9] It is stated that mobile technology with personalized applications shows promising results, may be more cost-effective, and offers possibilities for linguistic and cultural adaptations.[9] Studies on long-term persistence after CVD found that the main problem is that patients who do not initiate medication shortly after the event are unlikely to initiate at all, whereas those who initiate are likely to remain persistent.[20,21] These findings, therefore, support the inclusion of all patients in patient education shortly on discharge. Our data allowed us to follow up patients for up to 5 years. Few studies on medication persistence after CVD have followed up patients beyond 5 years, but 2 studies find that persistence rates continue a light decline for up to 12 years after discharge.[22,23] To our knowledge, no studies have assessed associations between patient education and medication persistence beyond 5 years. It is, therefore, unknown whether the observed associations linger beyond the observation period of the present study.

We stratified into migrant groups because language barriers might reduce the learning outcomes, and because patient education is embedded in the culture of the local healthcare system and, therefore, may not encompass the understandings of healthcare systems or pharmacological secondary prevention of the migrant.[5] We did not find indications for any systematic differences in the association between patient education and medication initiation and discontinuation, according to migrant status. This is in particular important because of the low medication persistence found among non-Western migrants.[7,8,24] A review from the United States assessed the effects of culturally adapted

Table 3. Associations Between Patient Education and Risk of Discontinuation of Preventive Medications in the Entire Cohort and in Subgroups

	Patient Education						
	0 Contacts (HR=1)	1–2 Contacts			≥3 Contacts		
Therapy	No. (%)	No. (%)	Crude HR	Adjusted HR	No. (%)	Crude HR	Adjusted HR
All							
Statins	1094 (11.3)	1023 (12.3)	0.91 (0.84–1.00)	0.90 (0.83–0.99)	1850 (12.1)	0.86 (0.80–0.93)	0.86 (0.79–0.92)
ADP inhibitors	710 (7.4)	825 (10.0)	1.10 (0.99–1.21)	1.08 (0.97–1.19)	1377 (9.0)	0.94 (0.86–1.03)	0.93 (0.85–1.03)
β Blockers	2590 (26.8)	2639 (31.8)	1.00 (0.95–1.06)	0.98 (0.93–1.03)	5009 (32.8)	0.97 (0.92–1.01)	0.92 (0.88–0.97)
ACE inhibitors	641 (6.6)	673 (8.1)	1.02 (0.92–1.14)	1.01 (0.91–1.13)	1196 (7.8)	0.89 (0.81–0.98)	0.89 (0.80–0.98)
Danish-born individuals							
Statins	951 (10.7)	912 (12.0)	0.94 (0.86–1.03)	0.93 (0.85–1.02)	1668 (11.8)	0.89 (0.82–0.96)	0.88 (0.81–0.96)
ADP inhibitors	618 (7.0)	729 (9.6)	1.13 (1.01–1.25)	1.11 (1.00–1.24)	1229 (8.7)	0.96 (0.87–1.06)	0.96 (0.87–1.06)
β Blockers	2334 (26.3)	2340 (30.7)	0.99 (0.94–1.05)	0.97 (0.91–1.02)	4571 (32.2)	0.98 (0.93–1.03)	0.93 (0.89–0.98)
ACE inhibitors	563 (6.3)	588 (7.7)	1.03 (0.91–1.15)	1.02 (0.91–1.15)	1087 (7.7)	0.91 (0.82–1.01)	0.92 (0.83–1.02)
Western migrants							
Statins	33 (12.0)	29 (12.0)	0.74 (0.45–1.22)	0.70 (0.41–1.20)	52 (14.2)	0.88 (0.57–1.36)	0.83 (0.52–1.31)
ADP inhibitors	18 (6.6)	22 (9.1)	1.01 (0.54–1.89)	0.91 (0.48–1.72)	32 (8.7)	0.91 (0.51–1.62)	0.87 (0.48–1.58)
β Blockers	70 (25.5)	91 (37.6)	1.27 (0.93–1.74)	1.20 (0.87–1.66)	128 (35.0)	1.00 (0.74–1.34)	0.91 (0.67–1.24)
ACE inhibitors	19 (6.9)	29 (12.0)	1.23 (0.69–2.20)	1.31 (0.70–2.44)	36 (9.8)	0.99 (0.56–1.72)	1.06 (0.58–1.93)
Non-Western migrants							
Statins	110 (22.3)	82 (19.5)	0.75 (0.56–1.00)	0.75 (0.56–1.01)	130 (18.2)	0.66 (0.51–0.85)	0.66 (0.51–0.86)
ADP inhibitors	74 (15.0)	74 (17.6)	0.82 (0.60–1.14)	0.83 (0.59–1.16)	116 (16.2)	0.73 (0.54–0.97)	0.74 (0.55–1.00)
β Blockers	186 (37.7)	208 (49.4)	1.01 (0.83–1.23)	1.02 (0.83–1.25)	310 (43.3)	0.79 (0.66–0.95)	0.77 (0.64–0.93)
ACE inhibitors	59 (11.9)	56 (13.3)	0.88 (0.61–1.26)	0.84 (0.58–1.22)	73 (10.2)	0.66 (0.47–0.92)	0.62 (0.43–0.88)

ACE indicates angiotensin-converting enzyme; HR, hazard ratio.

interventions to improve medication persistence among ethnic minorities, and found that studies were too few and too inconsistent in their reporting to show any statistically significant effect.[5] Among South Asian groups in English-speaking countries, it has been found that factors affecting use of secondary prevention interventions are previous negative experience of healthcare services, communication difficulties, referral, timing, and location.[25] Hence, future efforts to enhance medication persistence could focus on minimizing these barriers.

Methodological Strengths and Limitations

Our use of administrative registers offered both advantages and limitations. It was an advantage that we could include all eligible subjects, even elderly individuals and those with low native-language proficiency. We thereby eliminated selection bias, which is a common weakness of studies on secondary prevention.[1,11,26] Limitations of the administrative registers were that the primary objective of data collection is management. Therefore, data may not be as detailed as we could have preferred, and the registers can be incomplete or biased. We used data from NPR to establish our population, and this use of NPR has been validated.[14,27] NPR also provided data on patient education contacts. The established quality indicators of patient education of the Danish Cardiac Rehabilitation Database[28] were in accordance with our findings and serve to validate this use of the register. Although there are clear national guidelines on the availability and design of patient education, the recommendations are not standard everywhere.[28] Therefore, the lack of homogeneity may impede the generalizability of our findings. This is a common weakness of studies on patient education and probably reflects the myriad of determining factors in management of chronic disease and medication persistence.[1] We assessed medication persistence by electronically compiled drug dosing histories, which minimizes the risk of report bias.[16]

There was limited confounding by comorbidity, sociodemographic factors, and discharge by university-affiliated hospitals. In healthcare systems with more user payment, economic strains might hinder both access to patient education and medication persistence, and sociodemographic factors might, therefore, act as confounders in other settings.[29] Three types of confounders may have played a role in our findings: (1) confounding by health-seeking behavior,[30] suggesting that patients who are persistent with their medications are more likely to engage in preventive health services, such as patient education; (2) confounding by health status, in which physical or cognitive functioning affects both medication persistence and use of preventive health services; and (3) confounding by provider, suggesting that some physicians may be more likely to prescribe medicine to patients who are engaging in preventive health services.[30] The observational design and available data did not allow us to exclude these possible confounders. A randomized experimental design could remove this risk, but might instead introduce selection bias. Therefore, the present study adds important knowledge related to the large and unselected population and the assessment of the role of patient education in migrant populations, but we must abstain from definite conclusions on causal inferences.

Conclusion

In patients discharged after ACS, use of patient education was associated with a higher likelihood of initiating and a lower risk of discontinuing preventive medications. There were indications of a dose-response relationship, with favorable associations among those who had had ≥3 contacts for patient education. Adjustment for comorbidity and sociodemographic factors did not eliminate the associations, and patients with a migrant background showed associations that were almost similar to those among the Danish-born individuals, indicating that engaging all population groups in patient education is important.

Disclosures

S.P.J. has received fees from Bristol-Myers Squibb, grants and personal fees from Pfizer, personal fees from Bayer, personal fees from Boehringer-Ingelheim, outside the submitted work.

References

1. Anderson L, Brown JP, Clark AM, Dalal H, Rossau HK, Bridges C, Taylor RS. Patient education in the management of coronary heart disease. *Cochrane Database Syst Rev*. 2017;6:CD00889.
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
3. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.
4. Scheppers E, van Dongen E, Dekker J, Geertzen J, Dekker J. Potential barriers to the use of health services among ethnic minorities: a review. *Fam Pract*. 2006;23:325–348.
5. Conn VS, Enriquez M, Ruppar TM, Chan KC. Cultural relevance in medication adherence interventions with underrepresented adults: systematic review and meta-analysis of outcomes. *Prev Med*. 2014;69:239–247.
6. Anderson L, Thompson DR, Oldridge N, Zwisler A-D, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2016;1:CD001800.
7. Frederiksen HW, Zwisler A-D, Johnsen SP, Öztürk B, Lindhardt T, Norredam M. Differences in initiation and discontinuation of preventive medications and use

of non-pharmacological interventions after acute coronary syndrome among migrants and Danish-born. *Eur Heart J*. 2018;39:2356–2364.

8. Hempler NF, Diderichsen F, Larsen FB, Ladelund S, Jorgensen T. Do immigrants from Turkey, Pakistan and Yugoslavia receive adequate medical treatment with beta-blockers and statins after acute myocardial infarction compared with Danish-born residents? *Eur J Clin Pharmacol*. 2010;66:735–742.
9. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2014;11:CD000011.
10. Ho PM, Lambert-Kerzner A, Carey EP, Fahdi IE, Bryson CL, Melnyk SD, Bosworth HB, Radcliff T, Davis R, Mun H, Weaver J, Barnett C, Barón A, Del Giacco EJ. Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. *JAMA Intern Med*. 2014;174:186–193.
11. Fitzpatrick P, Fitz-Simon N, Lonergan M, Collins C, Daly L. Heartwatch: the effect of a primary care-delivered secondary prevention programme for cardiovascular disease on medication use and risk factor profiles. *Eur J Cardiovasc Prev Rehabil*. 2011;18:129–135.
12. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, Dobbels F, Fargher E, Morrison V, Lewek P, Matyjaszczyk M, Mshelia C, Clyne W, Aronson JK, Urquhart J. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73:691–705.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349.
14. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register: a valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46:263–268.
15. The Danish Health Authority. National clinical guideline on cardiac rehabilitation. 2015; sst.dk. https://www.sst.dk/da/udgivelser/2015/~/media/E21E277725B8408698A96502F4BEF472.ashx. Accessed April 4, 2019.
16. Wallach Kildemoes H, Toft Sorensen H, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39:38–41.
17. IOM, International Organization for Migration. Key migration terms: International Organization for Migration. 2015; www.iom.int. https://www.iom.int/key-migration-terms. Accessed April 4, 2019.
18. Statistics Denmark. Indvandrere i Danmark 2017. Copenhagen, Denmark: Statistics Denmark; Report No. 11. 2017; www.dst.dk. https://www.dst.dk/da/Statistik/Publikationer/VisPub?cid=20705. Accessed April 4, 2019.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
20. Gislason GH, Rasmussen JN, Abildstrøm SZ, Gadsbøll N, Buch P, Friberg J, Rasmussen S, Køber L, Stender S, Madsen M, Torp-Pedersen C. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J*. 2006;27:1153–1158.
21. Blackburn DF, Dobson RT, Blackburn JL, Wilson TW, Stang MR, Semchuk WM. Adherence to statins, beta-blockers and angiotensin-converting enzyme inhibitors following a first cardiovascular event: a retrospective cohort study. *Can J Cardiol*. 2005;21:485–488.
22. van der Elst ME, Bouvy ML, de Blaey CJ, de Boer A. Preventive drug use in patients with a history of nonfatal myocardial infarction during 12-year follow-up in The Netherlands: a retrospective analysis. *Clin Ther*. 2005;27:1806–1814.
23. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, Kokia E. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. *Clin Ther*. 2008;30:2167–2179.
24. Ringbäck Weitoft G, Ericsson O, Löfroth E, Rosén M. Equal access to treatment? Population-based follow-up of drugs dispensed to patients after acute myocardial infarction in Sweden. *Eur J Clin Pharmacol*. 2008;64:417–424.
25. Galdas PM, Ratner PA, Oliffe JL. A narrative review of South Asian patients' experiences of cardiac rehabilitation: patients' experiences of cardiac rehabilitation. *J Clin Nurs*. 2012;21:149–159.
26. Ranganathan M, Bhopal R. Exclusion and inclusion of nonwhite ethnic minority groups in 72 North American and European cardiovascular cohort studies. *PLoS Med*. 2006;3:e44.
27. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e01283.
28. Zwisler A-D, Rossau HK, Nakano A, Foghmar S, Eichhorst R, Prescott E, Cerqueira C, Soja AM, Gislason GH, Larsen ML, Andersen UO, Gustafsson I, Thomsen KK, Boye Hansen L, Hammer S, Viggers L, Christensen B, Kvist B, Lindström Egholm C, May O. The Danish Cardiac Rehabilitation Database. *Clin Epidemiol*. 2016;8:451–456.
29. Dhaliwal KK, King-Shier K, Manns BJ, Hemmelgarn BR, Stone JA, Campbell DJT. Exploring the impact of financial barriers on secondary prevention of heart disease. *BMC Cardiovasc Disord*. 2017;17:61.
30. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, Solomon DH. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol*. 2007;166:348–354.