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Control of cardiovascular risk factors and health behaviors in patients post acute coronary syndromes eligible for protein convertase subtilisin/kexin-9 inhibitors

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Keywords Protein convertase subtilisin/kexin-9 inhibitors; low-density lipoprotein cholesterol; acute coronary syndrome; cardiovascular prevention; cardiovascular disease.

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Abstract

Background We aimed to examine cardiovascular risk factors and health behaviors in patients with acute coronary syndromes (ACS) according to potential extension of eligibility criteria for protein convertase subtilisin/kexin-9 inhibitors (PCSK9i) to all patients with low-density lipoprotein cholesterol (LDL-c) equal or above 1.8 mmol/l.

Methods In this prospective cross-sectional study, patients with ACS between 2009 and 2016 and with available LDL-c at one year were considered. We defined three mutually exclusive groups of patients according to eligibility for PCSK9i: “not eligible”, “currently eligible”, and “newly eligible”. We explored the control of cardiovascular risk factors and health behaviors.

Results Out of 3,025 patients who had an ACS one year ago, 1,071 (35.4%) were not eligible for PCSK9i, 415 (13.7%) were currently eligible, and 1,539 (50.9%) were newly eligible. The proportion of patients with uncontrolled hypertension in the not eligible group was lower than in the group currently eligible (27.6% vs 33.6%, *p*=0.02), but similar to the group newly eligible (27.6% vs 28.2%, *p*=0.73). The proportion of smokers in the not eligible group was lower than in the group currently eligible (21.2% vs 28.0%, *p*=0.02), but similar to the group newly eligible (21.2% vs 22.5%, *p*=0.51).

Conclusions More than half of patients with ACS would be additionally eligible for PCSK9i if prescription is extended from current guidelines to all patients with LDL-c equal or above 1.8 mmol/l. Patients currently eligible for PCSK9i one year after an ACS had a worst control of cardiovascular risk factors than patients potentially newly eligible.

Keywords Protein convertase subtilisin/kexin-9 inhibitors; low-density lipoprotein cholesterol; acute coronary syndromes; cardiovascular prevention; cardiovascular disease.

Introduction

Proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i) are a new class of cholesterol lowering drugs that reduce cardiovascular events among patients with atherosclerotic cardiovascular disease and high low-density lipoprotein cholesterol (LDL-c) levels despite statins.[1-4] Because only one third of patients with acute coronary syndromes (ACS) can achieve a level of LDL-c below 1.8 mmol/l with statins, PCSK9i are a real opportunity to improve the management of lipids and cardiovascular risk among patients with ACS.[5] Both the latest European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) and the American Heart Association/American College of Cardiology (ACC/AHA) guidelines for the management of cholesterol recommend using lipid-lowering drugs in an incremental strategy to decrease LDL-c to a target level of <1.8 mmol/l among patients with cardiovascular disease.[6-11] However, with elevated annual costs per patient, PCSK9i reimbursement is limited by healthcare insurances in many countries. In Switzerland, current eligibility criteria for reimbursement are based on the latest ESC/EAS guidelines: patients with LDL-c >3.5 mmol/l in case of a first cardiovascular event, or alternatively >2.6 mmol/l in case of a recurrent cardiovascular event within a 5-year period.[11]

Recent randomized controlled trials showed cardiovascular benefits to further reduce the LDL-c with the addition of a PCSK9i on top of statins.[1, 2] Among patients with atherosclerotic cardiovascular disease, the addition of evolocumab reduced the LDL-c median value from 2.4 mmol/l to 0.8 mmol/l over 2.2 years.[1] Among patients with an acute coronary syndrome, the addition of alirocumbab reduced the LDL-c median value from 2.4 mmol/l to 1.7 mmol/l over 2.8 years.[2] Thus, discussions are now ongoing to extend the current eligibility for PCSK9i prescription and reimbursement to all patients with atherosclerotic cardiovascular disease and a LDL-c equal or above 1.8 mmol/l.

However, only few data exist about how to implement evidence from randomized controlled trials into clinical practice. Particularly, the means put in place to control cardiovascular risk factors other than LDL-c and the health behaviors of patients with ACS can largely influence the risk or recurrence. This is important because PCSK9i may have a larger benefits among patients with higher global cardiovascular risk.[12] The latest 2018 ACC/AHA cholesterol clinical practice guidelines recommend using PCSK9i only

in patients with cardiovascular disease who have additional high-risk conditions.[6] To examine this issue, we aimed to compare the level of control of cardiovascular risk factors and motivation to change health behaviors among a representative sample of patients with ACS, taking into account potential new eligibility criteria for PCSK9i prescription.

Patients and methods

Study population

We studied patients who were part of the Special Program University Medicine-Acute Coronary Syndromes (SPUM-ACS) study, an observational prospective Swiss cohort of consecutive patients hospitalized for ACS.[13] The aim of the SPUM-ACS study is to assess the quality of care after an ACS and identify new biomarkers for coronary heart disease prevention. For this analysis, we considered only the random sample of patients with measured LDL-c performed 12 months after the index ACS (**Supplemental Figure 1**). Inclusion criteria for the index ACS were age ≥18 years and diagnosis of ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina. Exclusion criteria were severe physical disability, inability to give consent due to dementia, or life expectancy of less than one year for non-cardiac reasons. Out of 6,359 ACS patients included from 2009 to 2016 with available follow-up information, a random sample of 3,025 patients had available measurements of LDL-c levels at 12 months.

Eligibility for prescription of PCSK9i

One year after the index ACS, we defined three mutually exclusive groups of patients according to eligibility criteria for PCSK9i based on ESC/EAS guidelines (**Supplemental Table 1**).[11] The first category included “not eligible” patients and was defined as LDL-c <1.8 mmol/l one year after the index ACS. The second category was “currently eligible” patients when their LDL-c was >3.5 mmol/l, or >2.6 mmol/l for those who had several cardiovascular events. The third category was “newly eligible” patients when their LDL-c was between 1.8 and 2.6 mmol/l, or between 2.6 and 3.5 mmol/l for those with only one cardiovascular event. Furthermore, we performed sensitivity analyses to compare the “not eligible” group to all potential eligible patients with a LDL-c of 1.8 mmol/l or above, which correspond to the combination

of the “currently eligible” and “newly eligible” groups. The assessment of cardiovascular events other than the index ACS was determined with the self-reported history of previous cardiovascular disease that occurred any time before the index ACS, or alternatively the occurrence of an adjudicated myocardial infarction, stroke, peripheral artery disease, angina or unplanned revascularization over the year after the index ACS. Self-reported previous cardiovascular disease before the index ACS included coronary heart disease, ischemic cerebrovascular disease or peripheral artery disease. A similar methodology has been used and reported previously to assess eligibility for PCSK9i according to several guidelines in this cohort.[14]

Outcomes assessed one year after the index ACS

One year after the index ACS, clinical information, questionnaires and biologic parameters were measured or collected by trained study nurses and doctors during a face-to-face visit, and gathered using a standardized web-based case report forms available in all participating centers.[15]. Smoking cessation was defined as having stop smoking over the year after the index ACS. Smokers with missing information regarding smoking status at one year were considered as current smokers. Patients with Body Mass Index (BMI) > 30 kg/m^2 were defined as obese. Weight change in kilogrammes was calculated as weight at one-year follow-up minus weight at the index ACS. Weight drop was defined as the ratio of negative weight change over the weight at the index ACS and was dichotomized into less than 5%, and 5% and more. The International Physical Activity Questionnaire (IPAQ)[16] was analyzed to assess the level of physical activity at the time and one year after the index ACS. Volume of physical activity was reported in metabolic equivalent (MET) minutes per week. Patients with ≤ 600 MET minutes per week of physical activity were defined as sedentary. Patients with 0 or more than 2500 MET minutes per week of physical activity were excluded from the analysis to avoid misclassification. Change of physical activity over the year after the index ACS was dichotomized into increased activity, and stabilisation or decreased activity. Motivation scales with ten levels were used to measure motivation to change health behaviors regarding general health, diet, physical exercise, and smoking cessation one year after the index ACS. No motivation was defined as a score of 1, and best motivation as a score of 10.

Definitions of co-variables

Diabetes one year after the index ACS was defined as the use of antidiabetic medication or a hemoglobinA1c of 6.5% or greater measured at the one-year visit, or as having diabetes at the time of the index ACS. High systolic blood pressure was defined has having a systolic blood pressure > 140 mmHg. Alcohol use was reported in units per week. Patients with more than 14 unit per week of alcohol were defined as at risk consumer. High-Intensity statin therapy was defined according to current lipid guidelines.[9] Levels for total cholesterol, high-density lipoprotein cholesterol (HDL-c) and triglycerides were measured locally using standardized dosage methods, and LDL-c was calculated using the Friedewald formula. Familial hypercholesterolemia was defined according to Dutch Lipid Clinic Network score (possible, probable or definite). Anti-hypertensive therapy was defined as the use of angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers, or beta-blockers, or calcium-channel blockers, or diuretics. We defined three categories for number of drugs administrated: between 0 and 5, 6 and 8, and over 8 drugs. Drugs included use of Acetylsalicylic acid, Clopidogrel, Prasugrel, Ticagrelor, anticoagulants, statins, lipid-lowering therapy other than statins, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium-channel blockers, diuretics, nonsteroidal anti-inflammatory drugs, Amiodarone, Digoxin, antidepressants, Dipyridamole, other antiarrhythmic drugs, immunosuppressive therapy, antiretroviral therapy, hormonotherapy. The Center for Epidemiological Studies-Depression (CES-D) self-assed questionnaire was used to screen for depression (score ≥ 16). The EQ-5D with 3 levels of severity for each of the 5 dimensions (EQ-5D-3L) questionnaire was used to measure health-related quality of life. Scores of the 5 dimensions were summed up and total score of 5 was defined as best quality of life, and total score of 15 as worst quality of life. The EQ visual analogue scale (EQ VAS) with a score from 0 (worst imaginable health state) to 100 (best imaginable health state) was used to measure health-related quality of life that reflects the patient's own judgement.

Statistical analysis

We categorized patients according to eligibility criteria for PCSK9i in three groups. We reported clinical characteristics, health care utilization, medication, and cardiovascular risk factors in each three groups. "Newly eligible" and "currently eligible" groups were each compared to the "not eligible" group using

Student's *t*-tests for continuous variables, and Chi-square tests for categorical variables. Continuous variables are reported as mean with standard deviation, whereas categorical variables as actual numbers with percentages. All analyses were conducted in STATA version 14.0® (STATA Corporation, College Station, TX, USA). The significance level was set at 0.05.

Ethics statement

The study was approved by Medical Ethics Committees of each center (Lausanne, Geneva, Bern and Zurich) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients gave written informed consent to participate.

Results

One year after their ACS, 3,025 patients were alive with available LCL-c values. Overall, 1,071 (35.4%) patients had well-controlled LDL-c and were not eligible for PCSK9i, 415 (13.7%) were currently eligible, and 1,539 (50.9%) were newly eligible for PCSK9i. Clinical characteristics of patients with respect to these three categories are reported in **Table 1**. The use of statins in the not eligible group was higher compared to the group currently eligible (99.1% vs 74.3%, $p<0.001$), and to the group newly eligible (99.1% vs 95.3%, $p<0.001$). The use of ezetimibe in the not eligible group was lower compared to the group currently eligible (7.3% vs 7.5%, $p=0.9$), and higher compared to the group newly eligible (7.3% vs 6.2, $p=0.29$). The proportion of patients with only one cardiovascular event in the not eligible group was higher compared to the group currently eligible (73.8% vs 36.9%, $p<0.001$), and lower compared to the group newly eligible (73.8% vs 81.5%, $p=<0.001$). The proportion of patients with diabetes in the not eligible group was higher compared to the group currently eligible (23.4% vs 15.6%, $p=0.001$), and to the group newly eligible (23.4% vs 14.9%, $p<0.001$). Health-related quality of life in the not eligible group was better compared to the group currently eligible (6.2 vs 6.5, $p=0.001$), and similar to the group newly eligible (6.2 vs 6.2, $p=0.77$).

Comparisons of health care and preventive drugs utilizations one year after the index ACS are reported in **Table 2**. The use of anti-hypertensive therapy in the not eligible group was higher compared to the group

currently eligible (95.5% vs 89.2%, *p*<0.001), and similar to the group newly eligible (95.5% vs 93.4%, *p*=0.02). Similarly, the proportion of patients who had attended a follow-up visit with a cardiologist in the not eligible group was higher compared to the group currently eligible (83.5% vs 75.1%, *p*=0.001), and similar compared to the group newly eligible (83.5% vs 84.1%, *p* =0.67).

Control of cardiovascular risks factors one year after the index ACS is reported in **Table 3**. The proportion of patients with systolic blood pressure > 140 mmHg in the not eligible group was lower compared to the group currently eligible (27.6% vs 33.6%, *p*=0.025), and similar to the group newly eligible (27.6% vs 28.2%, *p*=0.73). The proportion of current smokers in the not eligible group was lower compared to the group currently eligible (21.2% vs 28.0%, *p*=0.02), and similar to the group newly eligible (21.2% vs 22.4%, *p*=0.52). The proportion of patients with diabetes and glycated hemoglobin ≥7.5% in the not eligible group was lower compared to the group eligible (25.9% vs 35.7%, *p*=0.2), and similar to the group newly eligible (25.9% vs 24.2%, *p*=0.72). When comparing all potential eligible participants to those not eligible because of a LDL-c < 1.8 mmol/l, there were no differences in the control of cardiovascular risks factors (**Supplemental Table 2)**.

Change in health behaviors over the year after the index ACS according to eligibility for PCSK9i is shown in **Figure 1.** Mean weight change for obese patients was a loss of 1.7 kg for those not eligible, a gain of 0.3 kg for those currently eligible (*p*=0.01), and a loss of 1 kg for those newly eligible (*p*=0.29). However, there were no difference in change in physical activity among sedentary patients across the three groups. Motivation to change health behaviors assessed with motivation scales are shown in **Supplemental Figure 2**. In the three groups, the highest motivation to change concerned general health. There were no differences in motivation to change general health, diet or physical activity between the three groups. Motivation to stop smoking in the not eligible group was higher compared to the group currently eligible (*p*=0.0025), and similar to the group newly eligible (*p*=0.23).

Discussion

In this multicenter observational study of patients post ACS, we found that half of them would be newly eligible for PCSK9i if current prescription criteria were extended to all ACS patients with a persistent LDL-c equal or above 1.8 mmol/l. However, except for LDL-c levels, those patients who were potentially newly eligible for PCSK9i had a similar control of cardiovascular risk factors than patients with well-controlled LDL-c levels below 1.8 mmol/l. Moreover, patients who would be newly eligible for PCSK9i had a better health profile than those who were currently eligible; they were relatively younger and had a better control of cardiovascular risk factors and lifestyle habits, including higher smoking cessation rates, lower high blood pressure rates, higher physical activity rate, or higher optimal weight drop rates. Our data also suggest that those patients who would be newly eligible for PCSK9i had better adherence to preventive drugs than those who were currently eligible, which made their profile more similar to patients with well-controlled LDL-c levels.

The latest European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) consensus statement, as well as Swiss health authorities restrict the use of PCSK9i exclusively to patients with high LDL-c levels above 2.6 or 3.5 mmol/l.[11] This is in discordance to current evidence from randomized controlled trials that included patients with coronary heart disease and LDL-c equal or above 1.8 mmol/l, and that did not show an effect modification of PCSK9i cardiovascular benefit according to LDL-c levels. Eligibility criteria for use of PCSK9i in clinical practice has been already extended to all high-risk patients with cardiovascular disease and LDL-c equal or above 1.8 mmol/l despite maximal use of other lipid-lowering drugs.[6] In our study, we found that those patients who would be newly eligible for PCSK9i have a good medical adherence to drugs and medical visits, better than those who meet current criteria for PSCK9i reimbursement and prescription. Cost-effectiveness analyses of PCSK9i showed that their price needs to be reduced to meet conventional cost-effectiveness thresholds.[17-19] However, these analyses are based on clinical trials that do not always reflect the real world effectiveness of PCSK9i in patients with cardiovascular disease. The safety profile of PSCK9i regarding medium-term adverse effects has been examined and these drugs are generally well tolerated, with limited impact on muscle symptoms,[1-3, 20, 21] without differences between alirocumab and evolocumab.[22] However, long-term adverse effects are

unknown. Genetic PCSK9 deficiency is associated with higher risk of type 2 diabetes mellitus.[23-25] However, PCSK9i drugs may not increase the risk of diabetes, because they target mainly circulating PCSK9 with limited impact on pancreatic cells.[26] Our results suggest that extending the current eligibility for PCSK9i prescription would also mean treating more patients with high cardiovascular risk who would benefit from further lowering of LDL-c levels, although we acknowledge that the absolute benefit would be less significant than for very high-risk patients.

Previous studies have mainly modelled the eligibility for prescribing a PCSK9i treatment in patients with coronary heart disease according to guidelines. However, few previous studies have reported characteristics of patients eligible with PCSK9i outside of randomized controlled trials. Previous modelling studies reported a low proportion of patients that would be eligible for PCSK9i, even after simulation of an oral lipid lowering therapy intensification and assuming full adherence.[27, 28] In a previous report, we compared the eligibility for PCSK9i according to the 2016 American College of Cardiology (ACC) and the 2017 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) consensus statements, and found that more patients would be eligible for PCSK9i using ACC criteria.[14] Saborowski and al. studied 38 patients treated with PCSK9i using eligibility criteria based on their cardiovascular risk and failure of other available lipid-lowering therapy.[29, 30] Zafrir and al. studied 133 patients from a regional lipid clinic, who had submitted an approval for PCSK9i use.[30]

To our knowledge our analysis is among the first ones to report the control of cardiovascular risk factors and health behaviors of patients according to an extension of eligibility criteria for PCSK9i. We aimed especially to describe patients with elevated LDL-c levels, but who did not reach the current guideline criteria for PSCK9i prescription, in order to inform the societal impact of broadening current reimbursement criteria.

Our study has limitations. First, the eligibility for PSCK9i was simulated and not observed, and we cannot exclude misclassification. For example, we were not able to assess the reasons for persistent high LDL-c levels one year after ACS. Particularly, we had no information on statin-associated muscle symptoms,

which could be an explanation for the relatively low proportion of patients using high-intensity statins and the uncontrolled LDL-c levels one year after the index ACS. Thus, the proportion of patients newly or currently eligible for PCSK9 may have been overestimated. However, this misclassification would not differ alter the control of main cardiovascular risk factors and health behaviors in these two groups. Second, our study compares patients at one point of time one year after an ACS, which make it a cross-sectional study.

In conclusion, more than half of patients with ACS would be additionally eligible for PCSK9i if reimbursement is extended from current guidelines to all patients with LDL-c equal or above 1.8 mmol/l. Patients with ACS additionally eligible for PCSK9i had lower cardiovascular risks factors and healthier lifestyle than those currently eligible. Expanding the eligibility for PCSK9i based on LDL-c levels may therefore increase the prescription to patients at lower cardiovascular risk.

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Conflict of interest

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Authors' contributions

AB and DN contributed to the conception and design of the work. All participated to the acquisition, analysis and interpretation of data for the work. AB drafted the manuscript. BG, KK, DC, LR, RK, CM, TL, SW, OM, NR, FM and DN critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1. Characteristics of patients one year after an acute coronary syndrome, according to eligibility for PCSK9i (n=3,025).

	Not eligible[a]	**Currently eligible[b]**	**Newly eligible[c]**	***p*-value** Not eligible vs Currently eligible	***p*-value** Not eligible vs Newly eligible
Number of patients	1,071 (35.4)	415 (13.7)	1,539 (50.9)		
Demographics					
Age, years	64 (12)	64 (12)	62 (12)	0.47	**0.001**
Female	180 (16.8)	81 (19.5)	314 (20.4)	0.22	**0.02**
High education[d] (n=2,856)	361 (35.7)	114 (29.2)	485 (33.4)	**0.020**	0.23
Comorbidities					
Familial hypercholesterolemia[e]	142 (13.3)	93 (22.4)	358 (23.4)	**<0.001**	**<0.001**
Diabetes mellitus[f]	251 (23.4)	65 (15.6)	230 (14.9)	**0.001**	**<0.001**
At risk alcohol consumption[g] (n=2,626)	107 (11.2)	48 (13.5)	168 (12.8)	0.26	0.26
Depression (n=1,661)[h]	149 (26.7)	64 (25.6)	206 (24.2)	0.74	0.28
Objective measures					
Total cholesterol, mmol/l	3.2 (0.5)	5.7 (1.0)	4.2 (0.6)	**<0.001**	**<0.001**
LDL-cholesterol, mmol/l	1.4 (0.3)	3.7 (0.9)	2.4 (0.4)	**<0.001**	**<0.001**
HDL-cholesterol, mmol/l	1.2 (0.4)	1.2 (0.3)	1.3 (0.3)	0.93	**0.05**
Triglycerides, mmol/l	1.3 (0.8)	1.6 (0.7)	1.3 (0.7)	**<0.001**	**0.03**
Lipid-lowering therapy					
Statins (n=3,016)	1,059 (99.1)	304 (74.3)	1,465 (95.3)	**<0.001**	**<0.001**
High-Intensity statins (n=3,016)	627 (58.7)	132 (32.3)	844 (54.9)	**<0.001**	0.06

Ezetimibe (n=3,025)	78 (7.3)	31 (7.5)	96 (6.2)	0.90	0.29
Number of cardiovascular events[i] (n=3,023)				**<0.001**	**<0.001**
One	790 (73.8)	153 (36.9)	1,253 (81.5)		
Two	256 (23.9)	235 (56.6)	261 (17.0)		
Three	24 (2.2)	27 (6.5)	24 (1.6)		
Quality of life					
EQ-5D-3L questionnaire[j] score (n=2,371)	6.2 (1.4)	6.5 (1.4)	6.2 (1.4)	**0.001**	0.77
EQ visual analogue scale[k] score (n=2,387)	76.5 (17.2)	73.2 (17.9)	77.8 (16.3)	**0.004**	0.08

Data are given as number (percentage) or mean (standard deviation).

[a]Defined as low-density lipoprotein cholesterol (LDL-c) <1.8 mmol/l.

[b]Defined as LDL-c >3.5 mmol/l, or >2.6 mmol/l for patients who had several cardiovascular events.

[c]Defined as LDL-c between 1.8 and 2.6 mmol/l, or between 2.6 and 3.5 mmol/l for patients with only one cardiovascular event.

[d]Defined as a high school or university graduation or higher.

[e]Defined as possible or probable familial hypercholesterolemia according to Dutch Lipid Clinic Network score.

[f]Defined as having diabetes at the time of acute coronary syndrome (self-reported or use of antidiabetic medication or a hemoglobinA1c ≥ 6.5% at admission) or as the use of antidiabetic medication or a hemoglobinA1c ≥ 6.5% at one year.

[g]Defined as more than 14 unit per week.

[h]Defined as a score ≥ 16 in the Center for Epidemiological Studies-Depression (CES-D) self-assed questionnaire.

[i]Defined as coronary heart disease, ischemic cerebrovascular disease, peripheral artery disease or unplanned revascularization, including the index ACS.

[j]Based on EQ-5D-3L questionnaire, score from 5 (best quality of life) to 15 (worst quality of life).

[k]Based on EQ visual analogue scale (EQ VAS), score from 0 (worst imaginable health state) to 100 (best imaginable health state).

Table 2. Healthcare and preventive drug utilization one year after an acute coronary syndrome, according to eligibility for PCSK9i (n=3,025).

	Not eligible[a]	**Currently eligible[b]**	**Newly eligible[c]**	***p*-value** Not eligible vs Currently eligible	***p*-value** Not eligible vs Newly eligible
Number of patients	1,071 (35.4)	415 (13.7)	1,539 (50.9)		
Health care utilization over one year					
At least one medical visit (n=2,739)	975 (98.5)	359 (97.6)	1,370 (99.2)	0.25	0.1
At least one primary care visit (n=2,686)	894 (92.4)	324 (91)	1,274 (93.5)	0.42	0.27
At least one cardiologist visit (n=2,678)	807 (83.5)	268 (75.1)	1,139 (84.1)	**0.001**	0.67
Antiplatelet therapy (n=3,017)[d]	1,045 (97.7)	389 (95.1)	1,502 (97.7)	**0.01**	0.99
Antihypertensive therapy[e] (n=3,017)	1,022 (95.5)	365 (89.2)	1,436 (93.4)	**<0.001**	**0.02**
Number of drugs[f] (n=1,617)				0.62	0.06
0-5	348 (53.9)	102 (58)	477 (60)		
6-8	279 (43.2)	69 (39.2)	296 (37.2)		
>8	19 (2.9)	5 (2.8)	22 (2.8)		

Data are given as number (percentage) or mean (standard deviation).

[a]Defined as low-density lipoprotein cholesterol (LDL-c) <1.8 mmol/l.

[b]Defined as LDL-c >3.5 mmol/l, or >2.6 mmol/l for patients who had several cardiovascular events.

[c]Defined as LDL-c between 1.8 and 2.6 mmol/l, or between 2.6 and 3.5 mmol/l for patients with only one cardiovascular event.

[d]Defined as the use of Acetylsalicylic acid.

[e]Include use of angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers, or beta-blockers, or calcium-channel blockers, or diuretics.

[f]Acetylsalicylic acid , Clopidogrel, Prasugrel, Ticagrelor, anticoagulants, statins, lipid-lowering therapy other than statins, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium-channel blockers, diuretics, nonsteroidal anti-inflammatory drugs, Amiodarone, Digoxin, antidepressants, Dipyridamole, other antiarrhythmic drugs, immunosuppressive therapy, antiretroviral therapy, hormonotherapy.

Table 3. Control of cardiovascular risk factors one year after an acute coronary syndrome, according to eligibility for PCSK9i (n=3,025).

	Not eligible[a]	**Currently eligible[b]**	**Newly eligible[c]**	***p*-value** Not eligible vs Currently eligible	***p*-value** Not eligible vs Newly eligible
Number of patients	1,071 (35.4)	415 (13.7)	1,539 (50.9)		
Blood pressure (n=2,921)					
Systolic blood pressure, mmHg	132 (18)	137 (20)	132 (18)	**<0.001**	0.86
Diastolic blood pressure, mmHg	77 (15)	81 (12)	79 (10)	**<0.001**	**0.001**
High systolic blood pressure[d]	284 (27.6)	135 (33.6)	420 (28.2)	**0.02**	0.73
Diabetes					
Diabetic patients with glycated hemoglobin ≥7.5% (n=396)	51 (25.9)	15 (35.7)	38 (24.2)	0.2	0.72
Smoking status (n=3,024)					
Current smokers	227 (21.2)	116 (28)	346 (22.5)	**0.02**	0.51
Weight (n=2,883)					
Body mass index, kg/m^2	27.1 (4.4)	27.2 (4.6)	27.2 (4.4)	0.66	0.48
Obese[e]	206 (20.4)	92 (23.2)	310 (21)	0.24	0.71
Physical activity					

Sedentary[f]	343 (32)	142 (34.2)	468 (30.4)	0.42	0.38

Data are given as number (percentage) or mean (standard deviation).

[a]Defined as low-density lipoprotein cholesterol (LDL-c) <1.8 mmol/l.

[b]Defined as LDL-c >3.5 mmol/l, or >2.6 mmol/l for patients who had several cardiovascular events.

[c]Defined as LDL-c between 1.8 and 2.6 mmol/l, or between 2.6 and 3.5 mmol/l for patients with only one cardiovascular event.

[d]Defined as systolic blood pressure > 140 mmHg.

[e]Defined as Body Mass Index (BMI) > 30 kg/m^2.

[f]Defined as ≤ 600 Metabolic Equivalent of Task *(*MET) minutes per week of physical activity.

Figure 1. Change in health behaviors over the year after an acute coronary syndrome, according to eligibility for PCSK9i (n=3,025).

[a]Current smokers with motivation to quit smoking ≥ 5 on motivation scale.

[b]Defined as ≤ 600 Metabolic Equivalent Task (MET) minutes per week of physical activity.

[c]Defined as the ratio of negative weight change over the weight at the index acute coronary syndrome (ACS).

[d]Defined as Body Mass Index (BMI) > 30 kg/m^2.