Rev Esp Cardiol. 2016;69(2):117–124

Original article

Interhospital Variability in Drug Prescription After Acute Coronary Syndrome: Insights From the ACDC Study

Ignacio Ferreira-González,[a,*] Xavier Carrillo,[b] Victoria Martín,[c] José M. de la Torre Hernández,[d] José Antonio Baz,[e] Josep Navarro Manchón,[f] Mónica Masotti,[g] Ángel Cequier,[h] Mérida Cárdenas,[i] and Fernando Alfonso Manterola[j] on behalf of the ACDC research group[◇]

[a] *Unidad de Epidemiología, Servicio de Cardiología, Hospital Universitari Vall d'Hebron, CIBER de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain*
[b] *Servicio de Cardiología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain*
[c] *Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[d] *Servicio de Cardiología, Hospital Universitario Marqués de Valdecilla, Santander, Spain*
[e] *Servicio de Cardiología, Hospital Meixoeiro, Vigo, Pontevedra, Spain*
[f] *Servicio de Cardiología, Hospital Universitari i Politècnic La Fe, Valencia, Spain*
[g] *Servicio de Cardiología, Hospital Clínic i Provincial de Barcelona, Barcelona, Spain*
[h] *Servicio de Cardiología, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain*
[i] *Servicio de Cardiología, Hospital Universitari Dr. Josep Trueta, Girona, Spain*
[j] *Servicio de Cardiología, Hospital Clínico Universitario San Carlos, Madrid, Spain*

Article history:
Received 23 February 2015
Accepted 20 April 2015
Available online 5 August 2015

Keywords:
Acute coronary syndrome
Polypill
Variability in prescribing

ABSTRACT

Introduction and objectives: To analyze the rate of patients admitted for acute coronary syndrome who concomitantly received acetylsalicylic acid, statins, and angiotensin-converting enzyme inhibitors at discharge, and to analyze interhospital variability in the prescription of these drugs and its potential prognostic impact.

Methods: Interhospital variability in drug prescription was estimated using the intraclass correlation coefficient and median odds ratio (hierarchical analysis). Cox regression analysis was used to estimate the risk of death or myocardial infarction associated with prescription of all 3 agents at 2-years of follow-up.

Results: In total, 489 (53.3%) of 917 patients were prescribed all 3 agents. The rate was similar in patients with hypertension and diabetes (56.8%). There was significant variability among centers in the prescription of the 3 drugs at discharge (from 23% to 77% of patients). Hypertension (odds ratio = 1.93; 95% confidence interval, 1.42-2.61), ejection fraction < 45% (odds ratio = 2.2; 95% confidence interval, 1.44-3.37), being in a clinical trial (odds ratio = 1.89; 95% confidence interval, 1.24-2.88), and renal failure (odds ratio = 0.53; 95% confidence interval, 0.29-0.94) were associated with prescription of the 3 drugs. After adjustment for these factors, residual variability persisted (intraclass correlation coefficient 0.046 [95% credibility interval, 0.007 to 0.192]; median odds ratio = 1.46 [95% credibility interval, 1.16-2.32]). There was no clear association between the prescription of all 3 drugs and the risk of events during follow-up (hazard ratio = 0.81, 95% confidence interval, 0.55-1.18; $P = .27$).

Conclusions: The prescription rate for acetylsalicylic acid, angiotensin-converting enzyme inhibitors, and statins after acute coronary syndrome is suboptimal, varies among centers, and is possibly related to different health care approaches.

Variabilidad interhospitalaria en la prescripción tras un síndrome coronario agudo: hallazgos del estudio ACDC

Palabras clave:
Síndrome coronario agudo
Policomprimido
Variabilidad de prescripción

RESUMEN

Introducción y objetivos: Analizar la tasa de pacientes ingresados por síndrome coronario agudo que recibieron al alta conjuntamente ácido acetilsalicílico, estatinas e inhibidores de la enzima de conversión de la angiotensina, la variabilidad entre hospitales en dicha prescripción y el pronóstico asociado a esta.

Métodos: Se estimó la variabilidad entre hospitales en la prescripción con el coeficiente de correlación intraclase y la *odds ratio* mediana ajustada (análisis jerárquico). El riesgo de muerte o infarto a 2 años se estimó mediante modelos de Cox.

* Corresponding author: Unidad de Epidemiología, Servicio de Cardiología, Hospital Universitari Vall d'Hebron, Paseo Vall d'Hebron 119-129, 08035 Barcelona, Spain.
E-mail address: nacho@ferreiragonzalez.com (I. Ferreira-González).

◇ See the Appendix for the names of the researchers who conducted the ACDC (Adherence to antiplatelet treatment in acute Coronary synDrome patients after Catheterization) study.

http://dx.doi.org/10.1016/j.rec.2015.04.018
1885-5857/

Resultados: De un total de 917 pacientes, 489 (53,3%) tenían prescritos los 3 fármacos, sin apenas variación entre hipertensos y diabéticos (56,8%). Se observó una alta variabilidad entre centros en la prescripción (23-77% de los pacientes). La hipertensión (*odds ratio* = 1,93; intervalo de confianza del 95%, 1,42-2,61), la fracción de eyección < 45% (*odds ratio* = 2,2; intervalo de confianza del 95%, 1,44-3,37), la inclusión en el ensayo clínico (*odds ratio* = 1,89; intervalo de confianza del 95%, 1,24-2,88) y la insuficiencia renal (*odds ratio* = 0,53; intervalo de confianza del 95%, 0,29-0,94) se asociaron con la prescripción. En el análisis ajustado persistió una variabilidad residual (coeficiente de correlación intraclase 0,046 [intervalo de credibilidad del 95%, 0,007 a 0,192]; *odds ratio* mediana =1,46 [intervalo credibilidad del 95%, 1,16-2,32]). No se verificó un mayor riesgo de eventos durante el seguimiento (*hazard ratio* = 0,81; intervalo de confianza del 95%, 0,55-1,18; p = 0,27).
Conclusiones: Tras un síndrome coronario agudo, en casi la mitad de los pacientes no se prescribieron los tres fármacos al alta. La prescripción fue variable entre centros y posiblemente relacionada con hábitos asistenciales diferentes.

Abbreviations

ACS: acute coronary syndrome
ACE: angiotensin-converting enzyme
CrI: credibility interval
ICC: intraclass correlation coefficient
MOR: median odds ratio

INTRODUCTION

Improved survival rates have been observed in patients discharged after an acute coronary syndrome (ACS) with guideline-indicated medications, such as antiplatelet agents, statins, angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers.[1–4] Adherence to these medications has also been associated with improved prognosis.[5]

However, the prescription rate of guideline-indicated medications for patients with ischemic heart disease is far from optimal, and it has been suggested that the underestimation of patient risk and poor adherence to guidelines are potential factors underlying suboptimal prescribing.[6] It has also been suggested that the situation is similar in other contexts, such as heart failure.[7] The use of fixed doses of several drugs in a single pill (known as a polypill) for patients with chronic conditions such as ischemic heart disease could increase patient adherence and adherence to guidelines by physicians.[8,9] Polypills have recently been added to the therapeutic arsenal in Spain.

The ACDC study (Adherence to antiplatelet treatment in acute Coronary synDrome patients after Catheterization) was a prospective registry of patients with at least 1 drug-eluting stent admitted to 29 Spanish hospitals.[10–12] This study used the ACDC database to analyze the proportion of patients admitted with ACS who were prescribed 3 drugs (acetylsalicylic acid, statins, and ACE inhibitors), interhospital variability in the prescription rate of the 3 drugs, and the characteristics of the patients and hospitals associated with this variability. This study also analyzed if there was an association between being discharged with prescriptions for all 3 drugs and the composite event rate of cardiovascular death, ACS, or stroke at 2-years of follow-up.

METHODS

The ACDC study has already been published.[10–12] The study was a prospective multicenter cohort study, which included 29 hospitals. Almost all the public and private hospitals in Catalonia that performed percutaneous procedures were included. It was not logistically possible to include all other Spanish hospitals and thus a representative sample of 12 hospitals from the autonomous communities was selected. The inclusion criterion was a patient with a drug-eluting stent, thus ensuring the comprehensive consecutive inclusion of patients without exclusion criteria. Patients were included in the study from 28th January, 2008 to 28th April, 2008. The study collected information on type of hospital, demographic variables, risk factors, patient history, reason for admission, procedure performed, complications during hospitalization, and treatment at discharge. Most of the variables had standard definitions, which were reviewed with the fieldworkers during the preparatory meetings.

Seven hospitals were excluded from the analysis because they had less than 14 patients; multilevel statistical analysis requires a minimum number of patients per cluster for the estimates to be considered robust.[13]

Statistical Analysis

Of the 1965 patients who were discharged during the ACDC study, 968 patients (49%) had been admitted for ACS; of these patients, 917 (47%) patients were discharged from the 22 hospitals included in the present analysis.

Quantitative variables are expressed as mean and standard deviation or as median and interquartile range. Discrete variables are expressed as proportions. Two groups of patients were analyzed: Those who had been discharged with prescriptions for all 3 drugs, and those who had been discharged with prescriptions for 1 or 2 drugs. Differences between groups were evaluated using the Student *t* test or the Mann-Whitney U test (according to the data distribution), and the chi-square test.

Variability Analysis

The main aim of the analysis was to evaluate interhospital variability in the prescription rate for all 3 drugs at discharge and to analyze if any variability was due to the patients or hospitals having different characteristics, such as the volume of patients treated and the type of funding (public or private). A 3-step multilevel logistic regression model was used for this analysis. Firstly, an empty model was constructed in which the random constant term measured interhospital variability in the ratio of patients treated with 3 drugs. Secondly, several individual patient characteristics were included to analyze the extent to which

interhospital variations in prescriptions could be attributed to differences in the patients treated at each hospital. All the baseline characteristics that differed between groups were included ($P < .2$). Age and sex were included as fixed adjustment variables. Once adjusted for patient characteristics, interhospital variability should be zero if variability in the rate of patients prescribed all 3 drugs depended exclusively on interhospital variability in the number of treated patients. Finally, a third model included hospital characteristics: the number of patients with stents implanted during 1 year, whether the hospital was private or public, and whether it was a university hospital or not. Odds ratios (OR) were estimated as measures of association. The multilevel logistic regression models were estimated by assuming independent covariance using the procedure included in the R statistical software package, version 3.2.0.

The change in variability among hospitals was measured at each step by calculating the percentage change in interhospital variance between the more complex model and the simpler model. The intraclass correlation coefficient (ICC) and median OR (MOR) were estimated to measure the size of interhospital variance. The ICC can be interpreted as the proportion of total variance in the variable considered that could be attributed to interhospital variation. The MOR was defined as the median value of the estimated OR in a "high-risk" hospital vs a "low-risk" hospital after repeatedly and randomly selecting 2 hospitals. The MOR was used to express the association between an individual's likelihood of being discharged with a prescription for all 3 drugs and the hospital discharging the patient. A MOR of 1 indicated that there was no interhospital variation in the prescription rate; however, if the MOR strongly differed from 1, then some characteristic of the hospital was affecting an individual's likelihood of being discharged with a prescription for all 3 drugs (ie, some interhospital variation remained unexplained). Bayesian estimation was used to obtain 95% credibility intervals (95%CrI) for the ICC and MOR.

Model calibration and discrimination were estimated using the Hosmer-Lemeshow test and the receiver operating characteristic curve. In both cases, the hierarchical structure of the data was taken into account when predicting the likelihood of a patient being discharged with prescriptions for all 3 drugs.

The methods and formulas used for the multilevel analysis are presented in Merlo et al.[14]

Survival Analysis

Cox regression models were used to analyze if discharge with a prescription for all 3 drugs was associated with a higher composite event rate of "ACS, cardiovascular death, or stroke" at 2 years of follow-up. Firstly, a model was constructed that included the main predictors of the composite event. Candidate variables were those that were associated with the event in the binary analysis ($P < .2$; see supplementary material). Backward and forward stepwise modeling was used to select the best model and the explanatory variable "3 drugs at discharge" was subsequently included in the model.

RESULTS

Of the 917 patients with ACS discharged from the 22 hospitals during the study period, 55 patients (6%) were prescribed antiplatelet drugs alone, 373 (40.7%) were prescribed 2 drugs, and 489 (53.3%) all 3 drugs. Of the patients prescribed 2 drugs, 100% received antiplatelet therapy, 11.2% of whom received an ACE inhibitor, and 88.8% a statin. When various subgroups of patients were considered depending on the presence of hypertension and diabetes or the absence of kidney failure, defined as a baseline creatinine concentration of less than 1.4 mg/dL (first analysis at admission), there was no significant change in the proportion of prescriptions for all 3 drugs (Figure 1).

Table 1 shows the differences in baseline characteristics between patients prescribed 1 or 2 drugs at discharge vs patients prescribed all 3 drugs. The former group of patients tended to have higher rates of chronic kidney failure, whereas the latter group had higher levels of hypertension. There were no significant differences between patients in socio-cultural characteristics, including their level of depression, which was assessed with the PHQ (Patient Health Questionnaire). Heart failure during admission, ejection fraction < 45%, and being included in a clinical trial were more frequent in patients prescribed all 3 drugs at discharge. Being discharged from a university hospital and a higher hospital activity index was also more frequent among patients discharged with all 3 drugs.

Figure 2 shows interhospital variability in the rate of patients prescribed 1, 2, or 3 drugs at discharge. In the unadjusted multilevel model, interhospital variability was 23%, with an ICC of 0.066 (95%CrI, 0.023 to 0.204) and an MOR of 1.58 (95%CrI, 1.30-2.39) (Table 2). After adjustment for age, sex, and the number of drugs other than the 3 analyzed, an increased prescription rate for all 3 agents was associated with several baseline patient characteristics, especially hypertension (OR = 1.93; 95% confidence interval [95%CI], 1.42-2.61), ejection fraction < 45% (OR = 2.2; 95%CI, 1.44-3.37), and inclusion in a clinical trial (OR = 1.89; 95%CI, 1.24-2.88). On the other hand, chronic kidney failure was associated with a lower prescription rate for all 3 drugs (OR = 0.53; 95%CI, 0.29-0.94). A model adjusted for these variables showed that interhospital variability was reduced by 8%, but residual variability remained (ICC, 0.061 [95%CrI, 0.018-0.186]; MOR = 1.55 [95%CrI, 1.27-2.28]), suggesting that a factor unrelated to the patient profile is associated with different prescription rates for the 3 drugs. Finally, no association was found between the variables of being a university hospital, type of funding, and hospital activity index and an increased prescription rate for all 3 drugs. After inclusion of these variables in the model, significant variability remained among hospitals (ICC, 0.046 [95%CrI: 0.007 to 0.192]; MOR = 1.46 [95%CrI, 1.16-2.32]), suggesting that the care process shows variability that remains unexplained by individual patient characteristics or by the amount of hospital care.

Table 3 shows that the raw event rate was slightly lower in patients prescribed all 3 drugs at 2-years of follow-up, without reaching statistical significance. A multivariate model showed that there was no clear association between being discharged with a prescription for all 3 drugs and the risk of events during follow-up (hazard ratio = 0.81; 95%CI, 0.55-1.18; $P = .27$) (Table 4).

DISCUSSION

This study showed that, at discharge, less than 60% of patients admitted for ACS in the ACDC study were prescribed the 3 drugs recommended by the main scientific societies. This rate remained almost unchanged when we considered the patient subgroup with a strong indication for all 3 drugs, such as those with hypertension and diabetes. In addition, there was significant interhospital variability in the prescription rate for all 3 drugs. Although interhospital variability was associated with certain characteristics of the patients, residual variability remained after adjustment for these factors. This result suggests that there are differences in the healthcare process that are not explained by the distinct characteristics of the patients, but which may be explained by differences in the healthcare practices of each hospital. Finally, although the composite event rate of cardiovascular death, ACS,

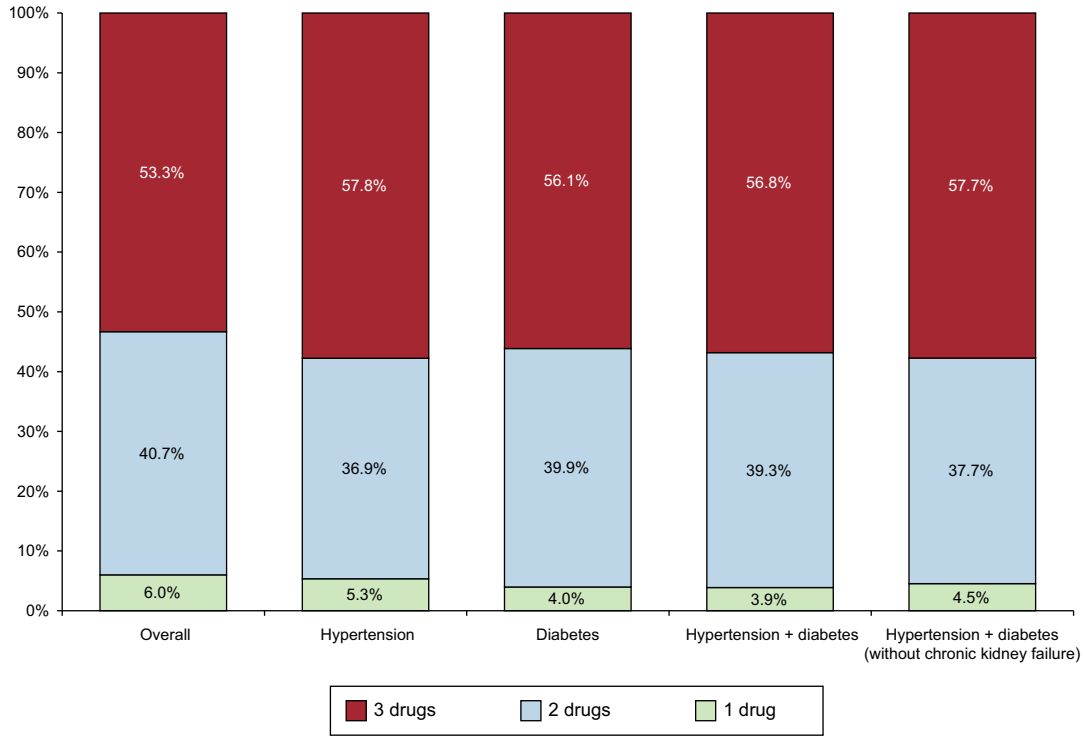

Figure 1. Total rate of patients prescribed 1, 2, or 3 drugs at discharge and rate according to hypertension, diabetes, or kidney failure.

and stroke was slightly lower in patients who had been discharged with a prescription for all 3 drugs, the association was inconclusive.

It has been repeatedly stated that prognosis is improved by physician adherence to guideline-based treatment instructions regarding prescribing drugs of proven efficacy.[1–5] However, "suboptimal" adherence to the guidelines on ischemic heart disease and other chronic diseases is common both in Spain and Europe.[15] In Spain, there has been a recent and progressive increase in the rates of prescribing antiplatelet agents, ACE inhibitors, and statins in patients discharged after an ACS. For example, the PRIAMHO II study (2000) reported an ACE inhibitors prescription rate of around 45%,[16] the MASCARA study (2008) reported a rate of around 55% in a similar population,[17] and the DIOCLES (2015) reported a rate of 79%.[18] Although less marked, a similar situation exists in relation to statins and antiplatelet agents. In the present study, although the overall ACE inhibitors prescription rate at discharge (56.8%) was similar to that in the MASCARA study (around 55%), the prescription rate for all 3 drugs together was 53%. Although previous studies have not addressed the prescription rate for all 3 drugs at discharge, it is assumed that there has been a parallel increase in the rate of prescribing each drug.

Several studies have tried to identify the factors that explain, even partially, suboptimal drug prescribing despite the guideline recommendations. Although risk underestimation by physicians is a factor associated with suboptimal prescribing,[6] there is a strong association between variability in prescribing and, in the final analysis, suboptimal prescribing, and multiple guidelines and recommendations on ACS that often overlap and even differ from each other, and the speed in which innovations or therapeutic variations are incorporated in daily practice.[15]

In the present study, less than 60% of patients who had been admitted with ACS were discharged with a prescription for acetylsalicylic acid, statins, and ACE inhibitors. Although contraindications or poor tolerance cannot be excluded as possible causes of the nonprescription of these drugs, this percentage barely increased in the patient subgroup with more indications, such as hypertension and diabetes, and without contraindications, such as kidney failure. Although the latter disease could deter physicians from prescribing certain drugs, particularly ACE inhibitors, it does not seem to be a determining factor. Significant interhospital variability was found in prescription rates, which ranged from just over 23% to just over 77% in patients discharged with a prescription for all 3 agents. The factors that could explain this variability include different patient characteristics by hospital and different hospital characteristics according to 3 variables: type of funding, being a university hospital, and hospital activity index.

Several patient variables, such as hypertension, low ejection fraction, and kidney failure are associated with a higher rate (the first 2 variables) or a lower rate (the third variable) of prescribing the 3 drugs. However, although expected, this association does not explain the significant interhospital variability. In fact, interhospital variability remained after adjustment for these 3 variables and variables such as age, sex, and the number of drugs prescribed at discharge that differed from the 3 drugs studied. This result suggests that specific patient characteristics alone do not explain the different rates of prescribing 3 drugs at discharge. Although the bivariate analysis showed that being treated at a university hospital and a higher hospital activity index were associated with a higher prescription rate for all 3 drugs, the association did not reach statistical significance after adjustment for individual patient variables. This result may suggest that patient characteristics differ as a function of these 2 hospital characteristics. Regardless, when both characteristics were included, there was still interhospital variability in prescribing all 3 agents. These differences in prescribing behavior deserve further study.

The aim of this study was to describe interhospital variability in prescribing and poor physician adherence to the guideline recommendations, rather than to investigate their causes or the conditions that favor them in the setting of ACS in Spain. Other studies on ACS in Spain have already described interterritorial

Table 1
Baseline Characteristics According to the Number of Drugs Prescribed at Discharge

	1-2 drugs (n = 428)		3 drugs (n = 489)		Total (n = 917)		*P*
	No.	no. (%)	No.	no. (%)	No.	no. (%)	
Demographic and cardiovascular risk factors							
Age, years (mean ± standard deviation)	428	64.09 ± 11.4	489	64.05 ± 11.8	917	64.07 ± 11.6	.92
Women	428	98 (22.9)	489	94 (19.22)	917	192 (20.94)	.17
Active smokers	428	116 (27.1)	489	155 (31.7)	917	271 (29.55)	.13
Hypercholesterolemia	428	243 (56.78)	489	272 (55.62)	917	515 (56.16)	.73
Hypertension	428	245 (57.24)	489	335 (68.51)	917	580 (63.25)	< .001
Diabetes	428	143 (33.41)	489	183 (37.42)	917	326 (35.55)	.20
Cardiovascular history							
Peripheral arterial disease	428	49 (11.45)	489	61 (12.47)	917	110 (12)	.63
Stroke	428	16 (3.74)	489	30 (6.13)	917	46 (5.02)	.10
Heart failure	428	17 (3.97)	489	25 (5.11)	917	42 (4.58)	.41
Pacemaker	428	4 (0.93)	489	6 (1.23)	917	10 (1.09)	.67
Prosthetic valve	428	1 (0.23)	489	3 (0.61)	917	4 (0.44)	.38
Atrial fibrillation	428	17 (3.97)	489	17 (3.48)	917	34 (3.71)	.69
Myocardial infarction	428	110 (25.7)	489	130 (26.58)	917	240 (26.17)	.76
Coronary surgery	428	98 (22.9)	489	120 (24.54)	917	218 (23.77)	.56
Percutaneous revascularization	428	24 (5.61)	489	28 (5.73)	917	52 (5.67)	.94
Other conditions							
Chronic obstructive pulmonary disease	428	46 (10.75)	489	52 (10.63)	917	98 (10.69)	.96
Chronic kidney disease	428	35 (8.18)	489	27 (5.52)	917	62 (6.76)	.11
Chronic liver disease	428	5 (1.17)	489	5 (1.02)	917	10 (1.09)	.83
Oncologic disease	428	6 (1.4)	489	11 (2.25)	917	17 (1.85)	.34
Chronic anticoagulant therapy	423	15 (3.55)	487	17 (3.49)	910	32 (3.52)	.96
Psychosocial characteristics							
Immigrant	428	19 (4.44)	489	17 (3.48)	917	36 (3.93)	.45
Employment status	427		484		911		.17
Active		151 (35.36)		158 (32.64)		309 (33.92)	
Retired		219 (51.29)		265 (54.75)		484 (53.13)	
Unemployed		9 (2.11)		19 (3.93)		28 (3.07)	
Other		48 (11.24)		42 (8.68)		90 (9.88)	
Level of educational	423		472		895		.19
Low		139 (32.86)		137 (29.03)		276 (30.84)	
Average		231 (54.61)		286 (60.59)		517 (57.77)	
High		53 (12.53)		49 (10.38)		102 (11.4)	
Index of depression, PHQ-9 scale	421		476		897		.23
Low-moderate		361 (85.75)		421 (88.45)		782 (87.18)	
Moderate-severe		60 (14.25)		55 (11.55)		115 (12.82)	
Findings during admission							
Heart failure	428	27 (6.31)	489	58 (11.86)	917	85 (9.27)	.004
Major bleeding	428	2 (0.47)	489	3 (0.61)	917	5 (0.55)	.76
Ejection fraction < 45%	428	42 (9.81)	489	85 (17.38)	917	127 (13.85)	.001
Patient included in a clinical trial	428	47 (10.98)	488	91 (18.65)	916	138 (15.07)	.001
Hospital characteristics							
University hospital	428	377 (88.08)	489	457 (93.46)	917	834 (90.95)	.005
Private funding	428	23 (5.37)	489	22 (4.5)	917	45 (4.91)	.54
Number of patients with a stent (2007)	428		489		917		.006
< 500		147 (34.35)		121 (24.74)		268 (29.23)	
500-1000		156 (36.45)		209 (42.74)		365 (39.8)	
> 1000		125 (29.21)		159 (32.52)		284 (30.97)	

Unless otherwise indicated, data are expressed as no. (%).

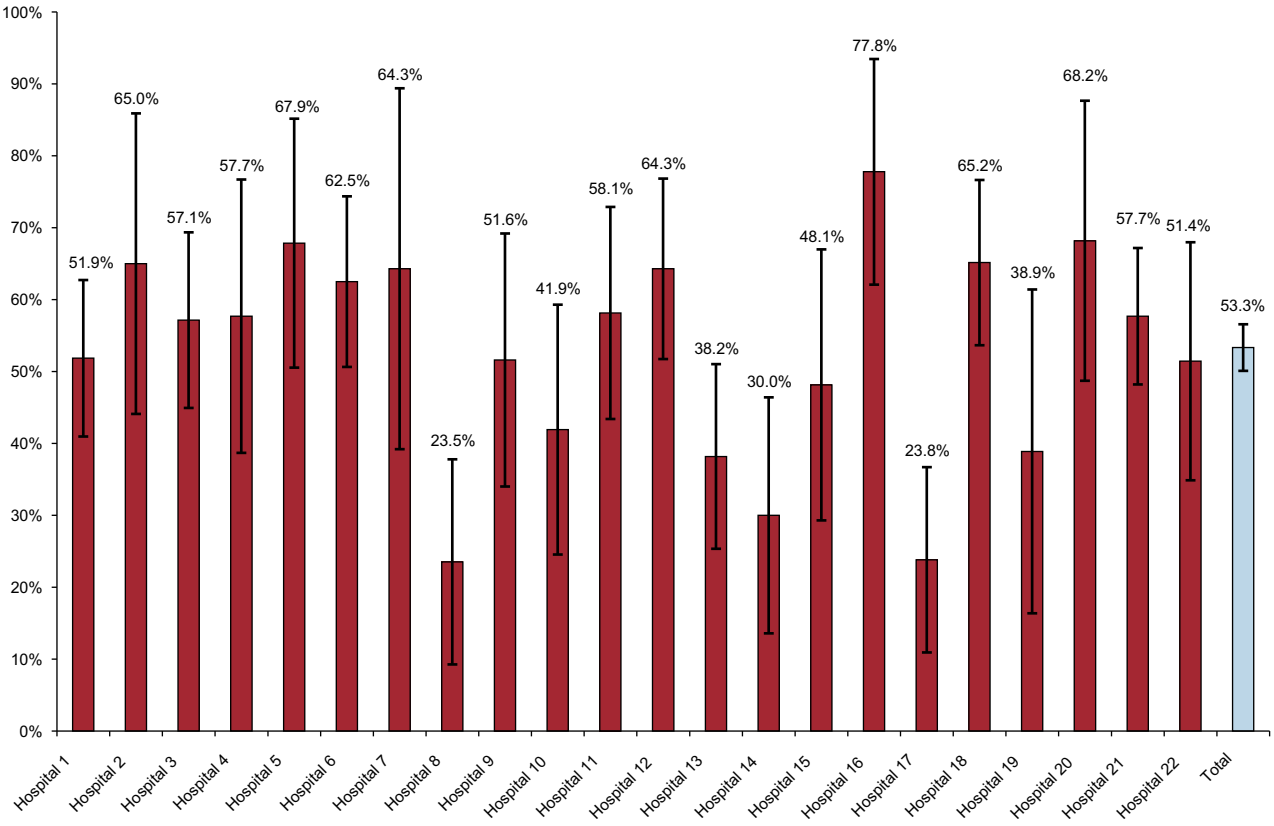

Figure 2. Prescription rate for antiplatelet drugs, statins, and angiotensin-converting enzyme inhibitors after acute coronary syndrome at discharge by hospital.

variability and variability in access to specific tests and the use of specific drugs according to the type of hospital.[19,20] Studies on interterritorial variations in the prognosis of ACS suggest that the rate of use of specific tests and recommended drugs may be an underlying explanatory factor.[21] Although there may be many underlying factors, multidrug regimens have been associated with variability in prescribing and specifically with the low rate of prescribing all 3 drugs. The use of the polypill could increase the rate of prescribing drugs with a class IA recommendation in the guidelines and could be more cost-effective than conventional treatment. For these reasons, some leading researchers have appealed for their inclusion in the model list of essential medicines

Table 2
Factors Associated With Interhospital Variability in the Prescription of 3 Drugs

	Model 0[a]			Model 1[b]			Model 2[c]		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
Patient variables									
Age				1.00	0.99-1.01	.980	1.00	0.99-1.00	.946
Women				0.81	0.57-1.16	.250	0.82	0.58-1.17	.270
Hypertension				1.93	1.42-2.61	<.001	1.92	1.42-2.60	<.001
Chronic kidney disease				0.53	0.29-0.94	.031	0.52	0.29-0.94	.030
Ejection fraction < 45				2.20	1.44-3.37	<.001	2.20	1.44-3.37	<.001
Patient included in a clinical trial				1.89	1.24-2.88	.003	1.88	1.23-2.85	.003
Number of drugs at discharge (no statins, antiplatelet drugs, or ACE inhibitors)				0.91	0.81-1.03	.141	0.91	0.81-1.03	.139
Hospital variables									
University hospital							1.26	0.56-2.79	.577
Private funding							1.43	0.56-3.64	.453
> 500 revascularized patients							1.46	0.84-2.52	.179

95%CI, 95% confidence interval; 95% CrI, 95% credibility interval; ACEI, angiotensin-converting enzyme inhibitors; ICC, intraclass correlation coefficient; MOR, median odds ratio; OR, odds ratio.

[a] Model 0: variance, 0.233; CCI, 0.066 (95% CrI, 0.023-0.204); ORM = 1.58 (95% CrI, 1.30-2.39); calibration, 7.49 (*P* = .48); discrimination, 0.64 (*P* < .001).

[b] Model 1: variance, 0.214; ICC, 0.061 (95% CrI, 0.018-0.186); MOR = 1.55 (95% CrI, 1.27-2.28); calibration, 9.49 (*P* = .28); discrimination, 0.69 (*P* < .001).

[c] Model 2: variance, 0.159; ICC, 0.046 (95% CrI, 0.007-0.192); MOR = 1.46 (95% CrI, 1.16-2.32); calibration, 13.1 (*P* = .11); discrimination, 0.69 (*P* < .001).

Table 3
Raw Event Rate in Each Group After 2 Years of Follow-up

	1-2 drugs (n = 463)	3 drugs (n = 505)	Total (n = 968)	*P*
	n (%)	n (%)	n (%)	
Total mortality or acute coronary syndrome or stroke	58 (12.53)	55 (10.89)	113 (11.67)	.428
Total mortality	31 (6.70)	21 (4.16)	52 (5.37)	.080
Cardiovascular mortality	16 (3.46)	9 (1.78)	25 (2.58)	.101
Acute coronary syndrome	28 (6.05)	32 (6.34)	60 (6.2)	.852
Stroke	7 (1.51)	8 (1.58)	15 (1.55)	.928

developed by the World Health Organization.[9] If they had been included, the possible impact of using the polypill in Spain would have been shown by an increased rate of prescribing the 3 drugs and a decrease in interhospital variability.

Although there was an association between a slightly lower major event rate at 2-years of follow-up and prescription of all 3 drugs at discharge, the association did not reach statistical significance. This finding should be interpreted in the setting of the ACDC study, which included only patients with drug-eluting stents; the risk profile of these patients was more favorable than that of other patients in studies that have shown a clear association.[3,22]

Limitations

The main limitation of this study is that the ACDC study was conducted in 2008 and so extrapolation of the findings to the present time should be undertaken with caution. In terms of changes in healthcare practices or the introduction of therapeutic innovations, there seems to be no compelling reason to suspect that the current situation of prescribing recommended drugs is very different to that of a few years ago. As mentioned, the ACDC study included only patients with at least 1 drug-eluting stent and excluded patients with ACS but without a drug-eluting stent; however, it is unlikely that these criteria introduced a selection bias when we estimated prescribing behavior. On the other hand, selection bias may have been introduced by using convenience sampling methods rather than random sampling methods to select the hospitals. However, any such sampling bias is more likely to have underestimated the magnitude of the findings regarding the low prescription rate for all 3 drugs and interhospital variability in prescribing, given that the participation of hospitals in the study may have led to better clinical practice than normal. The findings of this article should be interpreted in view of the fact that it only analyzed the prescription rates for the 3 drugs in patients discharged after an ACS. It could be hypothesized that, in an outpatient care setting, the prescription rate for all 3 agents might increase soon after discharge. Finally, although no statistically significant association was found between prescription of all 3 agents and the risk of major events at 2 years of follow-up, it should be taken into account that the analysis had relatively low statistical power, which was due to the use of a selected sample of patients with a drug-eluting stent, who had a lower overall risk than patients included in comprehensive registries of ACS.

Table 4
Risk of Major Events Associated With Prescription of 3 Drugs at 2 Years of Follow-up

	HR	95%CI	*P*
Three drugs at discharge	0.81	0.55-1.18	.267
Age	1.03	1.01-1.05	.003
Immigrant	2.71	1.15-6.35	.022
Peripheral arterial disease	1.84	1.18-2.88	.007
Chronic obstructive pulmonary disease	2.42	1.54-3.79	< .001
Chronic kidney disease	3.49	2.18-5.59	< .001
Chronic liver disease	3.08	1.12-8.45	.029
Heart failure during hospitalization	1.82	1.04-3.18	.035
Major bleeding during hospitalization	5.76	1.38-24.1	.016

95%CI, 95% confidence interval; HR, hazard ratio.

FUNDING

The ACDC study was funded with a grant from the Health Research Fund (*Fondo de Investigación Sanitaria* PI07/90031), an unconditional grant from Bristol-Myers-Squibb, and an unconditional grant from Laboratorios Ferrer. These organizations and institutions were not involved in the design of the study, data collection, analysis, and interpretation, or in the preparation of the manuscript.

CONFLICTS OF INTEREST

None declared.

APPENDIX. RESEARCHERS AND HOSPITALS PARTICIPATING IN THE ACDC STUDY

A. Ribera-Solé, P. Cascant-Castelló, J.R. Marsal-Mora, G. Permanyer-Miralda, B. García del Blanco, G. Martí, V. Serra, I. Otaegui, B. Serra, J.F. Muñoz, O. Abdul Jawad-Altisent, S. Valdivieso, I. Roca, and D. García-Dorado (H.U. Vall d'Hebron, Barcelona); J. Mauri-Ferré, E. Nofrerías, O. Rodríguez-Leor, C. Olliete, and N. Salvatella (H.U. Germans Trias i Pujol, Badalona, Barcelona); M.C. López-Pérez (C. Sagrada Familia, Barcelona); M. Sabaté, and S. Brugaletta (H. de la Sta. Creu i Sant Pau, Barcelona); J. Casanova-Sandoval, F. Worner-Diz, L. Barta, and E. Piñol (H.U. Arnau de Vilanova, Lleida); J.A. Gómez-Hospital (H.U. de Bellvitge, L'Hospitalet Llobregat, Barcelona); B. Pujol-Iglesias, J. Bassaganyas, and M. Puigfel (H.U. Dr. Josep Trueta, Girona); M. Jiménez-Kockar, T. Martorell, X. Freixa, and S. Federico (H. Clinic, Barcelona); M.A. Cepas (C. Quirón, Barcelona); N. Batalla-Sahún, and J. Bureba-Sancho (H.U. Sagrat Cor, Barcelona); E. Blanco-Monteseirín, and E. Larrousse (C. Corachán, Barcelona); J. Guarinos, M. Bono-Más, J. Massoni, J. Mateo, A. Minguella, J. Vidal, and A. Comiñas (H.U. Joan XXIII, Tarragona); E. Martín, M.J. Fernández de Muniain-Comajuncosa, and M. Rugat-Fernández (C.C. Sant Jordi, Barcelona); A. Serra-Peñaranda, F. Miranda-Guardiola, G. Sierra, J.L. Triano, and B. Vaquerizo (H. del Mar, and C. Teknon, Barcelona); T. Ber-Muñoz,

and G. Otero-Soriano (H. De Barcelona, Barcelona); D. Sanmiguel-Cervera (H.U. Dr. Peset, Valencia); R. Raso-Raso (H.U.P. La Fe, Valencia); A. Iñiguez-Romo, E.M. Sánchez-Hernández, and M.A. Martínez (H. Meixoeiro, Vigo, Pontevedra); J.R. Rumoroso-Cuevas, A. Subinas-Elorriaga, J. Onaindia, and M. Sábada (H. Galdakao, Galdakao, Bizkaia); R. Trillo-Nouche, M. Gutierrez-Feijoo, and E. González-Babarro (H.U. Santiago, A Coruña); M.L. Capote-Toledo (H.C. San Carlos, Madrid); L. Goicolea, J. Goicolea, A. Blasco, and M. Pérez-Requena (H.U. Puerta de Hierro, Majadahonda, Madrid); L. Iñigo-García, O. Sanz-Vázquez, J.F. Muñoz-Bellido, C. García-Jarillo, and M. Pombo (H. Costa del Sol, Marbella, Málaga); R. Ruiz-Salmerón, M.J. Álamo-López, A. Romero-González, J.C. Dorado, C. Márquez, J.A. Muñoz-Campos, F. Reina, S. Santos, N. García-Fernández, and M. Madueño (H.U. Virgen Macarena, Sevilla); J. Sánchez-Gila, J.A. Herrador, J.C. Fernández-Guerrero, M. Guzmán, A. Bracero, and J. Blanca-Castillo (C.H. Jaén, Jaén); M. Ruiz-Lera e I. Madrazo (H.U. Marqués de Valdecilla, Santander).

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rec.2015.04.018.

REFERENCES

1. Granger CB, Steg PG, Peterson E, López-Bescós J, Van de WF, Kline-Rogers E, et al. Medication performance measures and mortality following acute coronary syndromes. Am J Med. 2005;118:858–65.
2. Setoguchi S, Glynn RJ, Avorn J, Mittleman MA, Levin R, Winkelmayer WC. Improvements in long-term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge: a 10-year trend analysis. J Am Coll Cardiol. 2008;51:1247–54.
3. Mukherjee D, Fang J, Chetcuti S, Moscucci M, Kline-Rogers E, Eagle KA. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. Circulation. 2004;109:745–9.
4. Rogers AM, Ramanath VS, Grzybowski M, Riba AL, Jani SM, Mehta R, et al. The association between guideline-based treatment instructions at the point of discharge and lower 1-year mortality in Medicare patients after acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) initiative in Michigan. Am Heart J. 2007;154:461–9.
5. Zeymer U, Junger C, Zahn R, Bauer T, Bestehorn K, Senges J, et al. Effects of a secondary prevention combination therapy with an aspirin, an ACE inhibitor and a statin on 1-year mortality of patients with acute myocardial infarction treated with a beta-blocker. Support for a polypill approach. Curr Med Res Opin. 2011;27:1563–70.
6. Bagnall AJ, Yan AT, Yan RT, Lee CH, Tan M, Baer C, et al. Optimal medical therapy for non–ST-segment-elevation acute coronary syndromes: exploring why physicians do not prescribe evidence-based treatment and why patients discontinue medications after discharge. Circ Cardiovasc Qual Outcomes. 2010;3:530–7.
7. Komajda M, Lapuerta P, Hermans N, Gonzalez-Juanatey JR, Van Veldhuisen DJ, Erdmann E, et al. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. Eur Heart J. 2005;26:1653–9.
8. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120:713–9.
9. Huffman MD, Yusuf S. Polypills: essential medicines for cardiovascular disease secondary prevention? J Am Coll Cardiol. 2014;63:1368–70.
10. Ferreira-González I, Marsal JR, Ribera A, Permanyer-Miralda G, García-Del Blanco B, Martí G, et al. Background, incidence, and predictors of antiplatelet therapy discontinuation during the first year after drug-eluting stent implantation. Circulation. 2010;122:1017–25.
11. Ferreira-González I, Marsal JR, Ribera A, Permanyer-Miralda G, García-Del Blanco B, Martí G, et al. Double antiplatelet therapy after drug-eluting stent implantation: risk associated with discontinuation within the first year. J Am Coll Cardiol. 2012;60:1333–9.
12. Ribera A, Ferreira-González I, García del Blanco B, Marsal JR, Cascant P, Martí G, et al. Drug-eluting stents for off-label indications in real clinical world: evidence based or 'intuition' based clinical practice? Int J Cardiol. 2013;164:116–22.
13. Austin PC. Estimating multilevel logistic regression models when the number of clusters is low: a comparison of different statistical software procedures. Int J Biostat. 2010;6:Article 16.
14. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health. 2006;60:290–7.
15. Van de WF, Ardissino D, Bueno H, Collet JP, Gershlick A, Kolh P, et al. Acute coronary syndromes: considerations for improved acceptance and implementation of management guidelines. Expert Rev Cardiovasc Ther. 2012;10:489–503.
16. Bosch X, Sambola A, Arós F, López-Bescós L, Mancisidor X, Illa J, et al. Utilización de la trombólisis en los pacientes con infarto agudo de miocardio en España: observaciones del estudio PRIAMHO. Rev Esp Cardiol. 2000;53:490–501.
17. Ferreira-González I, Permanyer-Miralda G, Marrugat J, Heras M, Cuñat J, Civeira E, et al. Estudio MASCARA (Manejo del Síndrome Coronario Agudo. Registro Actualizado). Resultados globales. Rev Esp Cardiol. 2008;61:803–16.
18. Barrabés JA, Bardají A, Jiménez-Candil J, Del Nogal Sáez F, Bodí V, Basterra N, et al. Pronóstico y manejo del síndrome coronario agudo en España en 2012: estudio DIOCLES. Rev Esp Cardiol. 2015;68:98–106.
19. Fiol M, Cabadés A, Sala J, Marrugat J, Elosua R, Vega G, et al. Variabilidad en el manejo hospitalario del infarto agudo de miocardio en España. Estudio IBERICA (Investigación, Búsqueda Específica y Registro de Isquemia Coronaria Aguda). Rev Esp Cardiol. 2001;54:443–52.
20. Ruiz-Nodar JM, Cequier A, Lozano T, Fernández Vázquez F, Möller I, Abán S, et al. Impacto del tipo de hospital en el tratamiento y evolución de los pacientes con síndrome coronario agudo sin elevación del ST. Rev Esp Cardiol. 2010;63:390–9.
21. Bertomeu V, Cequier A, Bernal JL, Alfonso F, Anguita MP, Muñiz J, et al. Mortalidad intrahospitalaria por infarto agudo de miocardio. Relevancia del tipo de hospital y la atención dispensada. Estudio RECALCAR. Rev Esp Cardiol. 2013;66:935–42.
22. Oliveras Vilà T, Ferrer Massot M, Curós Abadal A, Rueda Sobella F, Serra Flores J, Carrillo Suárez X, et al. Real-life use of the polypill components (ASA + ACEI + statins) after an acute coronary syndrome and long-term mortality. Int J Cardiol. 2014;177:209–10.