ORIGINAL ARTICLE

Differences in outcomes in patients with stable coronary artery disease managed by cardiologists versus noncardiologists

Results from the international prospective CLARIFY registry

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KEY WORDS

coronary artery disease, outcome, registry, specialist care, stable angina

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ABSTRACT

INTRODUCTION Clinical outcomes of patients with stable coronary artery disease (CAD) may differ between those primarily managed by cardiologists versus noncardiologists.

OBJECTIVES Our main objective was to analyze the clinical outcomes of outpatients with stable CAD in relation to the specialty of the managing physicians.

PATIENTS AND METHODS We studied 32 468 outpatients with stable CAD included in the CLARIFY registry, with up to 4 years of follow-up data. Cardiologists provided medical care in 84.1% and noncardiologists in 15.9% of the patients. Primary outcome was the composite of cardiovascular death, nonfatal myocardial infarction (MI), or stroke.

RESULTS Important differences in management as well as demographic and clinical characteristics were observed between the groups at baseline. Patients treated by cardiologists were younger and more of them had dyslipidemia, hypertension, and diabetes. The use of β-blockers and thienopyridines, as well as history of percutaneous coronary intervention were more frequent in this group. More patients treated by noncardiologists had a history of MI as well as concomitant peripheral artery disease and asthma or chronic obstructive pulmonary disease. They also had lower left ventricular ejection fraction and more often received lipid-lowering drugs. After adjustment for baseline differences, patients treated by cardiologists had a lower risk of the primary outcome (adjusted hazard ratio, 0.80; 95% confidence interval, 0.68–0.94; $P = 0.0067$) and of most secondary outcomes, but greater risk of bleeding.

CONCLUSIONS Outpatients with stable CAD managed by cardiologists had a lower rate of cardiovascular outcomes than those managed by noncardiologists. We did not find clear evidence that cardiologists provided superior guideline-based treatment, so the differences in outcome were most likely due to unquantifiable differences in patient characteristics.

INTRODUCTION

Coronary artery disease (CAD) is responsible for over half of all major cardiovascular events.[1-3] Patients with established stable CAD are generally at a relatively low risk of cardiovascular events. However, these patients form a nonuniform group and their prognosis may differ depending on demographic, clinical, geographic, and socioeconomic factors.

For a broad range of diseases, there is evidence to suggest differences between specialists and generalists in terms of knowledge and patterns of care. Nevertheless, the effect of these differences on patient outcome is not well established.[4] Although the effect of specialty care has been relatively well addressed for patients with heart failure and indicates that involvement of a cardiologist is associated with improved clinical outcome,[5-7] data in patients with stable CAD are scant.[8-10] It is therefore unclear whether there are any differences in outcomes between patients primarily managed by cardiologists versus those managed by noncardiologists, and if so, whether they are related to different patient characteristics or practice patterns. The global CLARIFY registry[11] (ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) provided the opportunity to explore these questions.

We hypothesized that patients with stable CAD managed by cardiologists may receive medical care better reflecting the current knowledge, and thus may have better clinical outcomes than those treated by nonspecialists. Our objective was to analyze the demographic and clinical characteristics, management, and clinical outcomes of outpatients with stable CAD primarily managed by cardiologists versus those managed by noncardiologists in the CLARIFY registry.

PATIENTS AND METHODS

Study design

Detailed descriptions of the CLARIFY study have been published elsewhere.[11,12] Briefly, CLARIFY is a prospective, observational, longitudinal registry including over 33 000 consecutive outpatients with stable CAD from 45 countries in Europe, the Americas, Africa, the Middle East, and Asia/Pacific, enrolled between November 2009 and July 2010. The planned follow-up time is 5 years.

Medical care was provided primarily by cardiologists or by internists/general practitioners, depending on the local health care system and patient preferences. The definition of cardiologist vs noncardiologist was self-defined by the recruiting physician. Each physician was asked to recruit 10 to 15 consecutive patients. The same physician took care of the patient for the entire duration of the study.

Study sites were selected with the aim of best reflecting care patterns in each country, taking into consideration the geographic distribution and location (ie, urban, suburban, or rural). Except for China, each country had a predefined national target of 25 patients per million population.

Participants had to fulfil at least one of the following criteria: 1) documented previous myocardial infarction (MI); 2) significant (>50%) stenosis on coronary arteriography; 3) chest pain with evidence of myocardial ischemia; and 4) percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) more than 3 months before inclusion. Patients hospitalized for cardiovascular disease within the past 3 months, awaiting a planned revascularization, or with a condition hampering 5-year follow-up were excluded from the study.

Data were collected by managing physicians at baseline and at annual visits, using standardized electronic case report forms. Detailed information on data captured at baseline and during follow-up are presented in Supplementary material online, *Table S1*. All data were transferred to the independent academic Robertson Centre for Biostatistics at the University of Glasgow, United Kingdom (UK), where they were stored and analyzed. To ensure data quality, on-site audits of 100% of the data were performed in 5% of randomly selected centers; regular telephone contact was maintained with investigators; and electronic case report forms underwent centralized verification for completeness, consistency, and accuracy.

The CLARIFY registry is registered in the ISRCTN registry of clinical trials with the number ISRCTN43 070 564 (http://www.controlled-trials.com/ISRCTN43 070 564).

Clinical outcomes

For the purpose of this analysis, the primary clinical outcome of interest was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke within 4 years. The secondary outcomes included all-cause death, cardiovascular death, fatal or nonfatal MI, fatal or nonfatal stroke, unstable angina, and major bleeding within the same period.

Statistical analysis

Baseline characteristics according to the pattern of care (cardiologists versus noncardiologists) were presented by means of descriptive statistics, using mean (SD) or median (interquartile range) for continuous values, depending on data distribution, and number (%) for categorical data. Accordingly, the *t* test or the Kruskal-Wallis test was used for between-group comparisons for continuous variables, and the χ^2 or Fisher exact test was used for categorical variables, as appropriate. Individual and composite clinical outcomes were analyzed based on the time to the first event. The risk of outcomes was compared between the groups using Cox proportional hazards regression models to calculate hazard ratios (HRs), corresponding 95% confidence intervals (CIs), and *P* values. Data were presented as unadjusted values and after adjustment for age, geographic region, sex, MI, CABG, PCI, blood pressure, left ventricular ejection fraction, congestive heart failure, diabetes mellitus, peripheral artery disease (PAD), and asthma or chronic obstructive pulmonary disease (COPD).

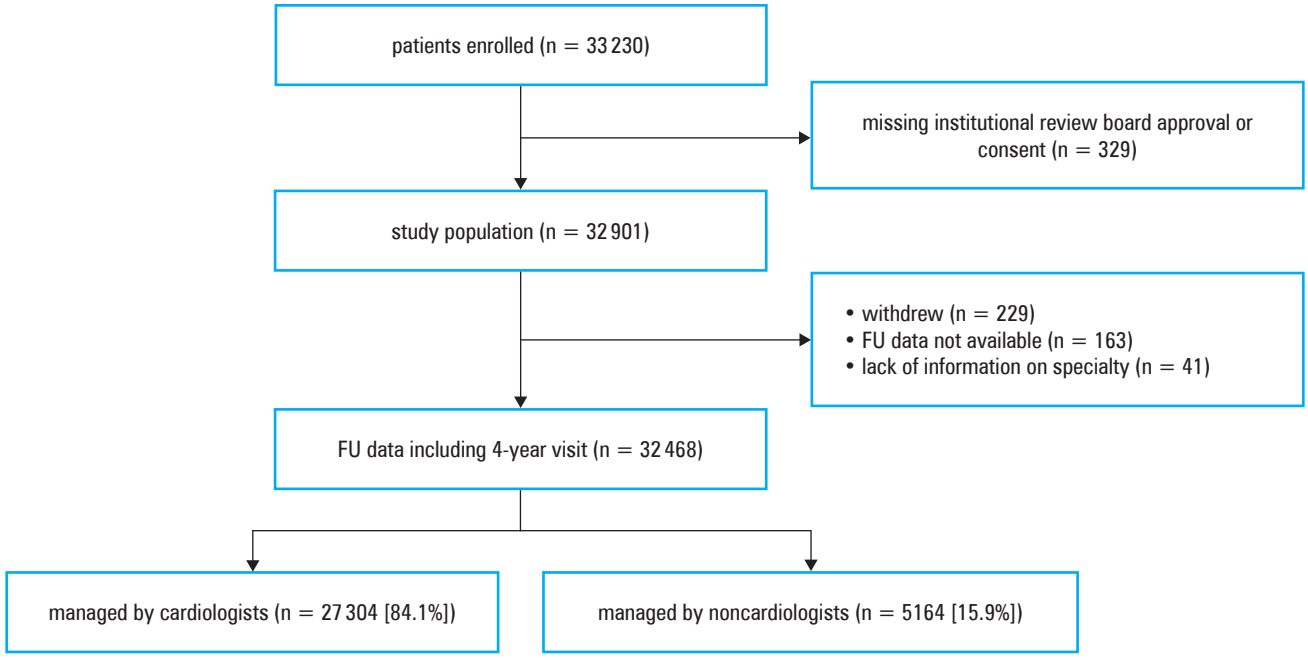

FIGURE 1 Patient disposition
Abbreviations: FU, follow-up

Ethics statement The study was approved by the appropriate Ethics Committees, and performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their written informed consent prior to inclusion in the study, in accordance with national and local guidelines.

RESULTS

Patient disposition The study enrolled 33 230 participants. After exclusion of patients with missing institutional review board approval or consent, the study population comprised 32 901 participants. Up to 4 years of follow-up data were available for 32 468 patients (98.7%). The information on the number of patients included in this analysis by country and region is included the Supplementary material online, *Table S2*.

Medical care was provided primarily by cardiologists in 27 304 patients (84.1%) and by noncardiologists in 5164 patients (15.9%) (FIGURE 1).

Baseline characteristics of the patients There were important differences between the patient groups (TABLE 1). Notably, patients managed by cardiologists were marginally younger, less likely to have a history of MI and CABG, but more likely to have a history of PCI. Of note, less than one-quarter of the patients had symptoms of angina, but the prevalence of Canadian Cardiac Society angina class II or III/IV was higher among patients treated by cardiologists. A higher proportion of cardiologist-treated patients had a history of hospitalization for heart failure; a higher proportion of noncardiologist-treated patients were without heart failure symptoms. Both groups had a mean heart rate below 70 bpm. Blood pressure control was adequate, with slight (<2 mmHg) between-group differences (systolic blood pressure lower and diastolic blood pressure higher in the cardiologist-treated group). The mean left ventricular ejection fraction in the whole study population was over 50%, but was lower in the group managed by noncardiologists. Coronary angiography was performed more often in cardiologist-treated patients, and a higher proportion of these patients had multivessel disease.

Among patients managed by cardiologists, there was a higher prevalence of dyslipidemia, hypertension, and diabetes mellitus, and those patients had a lower median body mass index. Comorbidities, such as PAD and asthma or COPD, were more common in patients treated by noncardiologists.

Treatment At baseline, the use of aspirin and calcium antagonists was similar in both groups. Cardiologists more frequently used thienopyridines (mostly clopidogrel), β-blockers, ivabradine, and long-acting nitrates, but less often used lipid-lowering agents and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (TABLE 2). The use of different drug classes and the dosage of most commonly prescribed β-blockers in both groups at 4-year follow-up are presented in Supplementary material online, *Tables S3 and S4*.

Lipid and blood pressure control were more effective in patients treated by noncardiologists. Control of glycated hemoglobin in patients with diabetes mellitus was better in the cardiologist-managed group (FIGURE 2).

Clinical outcomes The risk of the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke, in both the unadjusted and adjusted analyses, was lower among patients managed primarily by cardiologists compared with those managed by noncardiologists: unadjusted HR, 0.78; 95% CI, 0.69–0.87 (P <0.0001) and

TABLE 1 Baseline characteristics according to cardiologist or noncardiologist care

Characteristics		Cardiologist care (n = 27 304)	Noncardiologist care (n = 5164)	*P* value
age, y, mean (SD)		63.9 (10.5)	65.3 (10.0)	<0.0001
men, n (%)		21 224 (77.7)	3942 (76.3)	0.026
body mass index, kg/m^2, median (IQR)		27.1 (24.7–30.1)	28.4 (25.5–31.6)	<0.0001
ethnicity, n (%)	Caucasian	16 775 (61.4)	4224 (81.8)	<0.0001
	South Asian	2056 (7.5)	375 (7.3)	
	Chinese	2763 (10.1)	33 (0.6)	
	Japanese/Korean	1031 (3.8)	4 (0.1)	
	Hispanic	1525 (5.6)	5 (0.1)	
	Black/African	248 (0.9)	90 (1.7)	
	unknown	2906 (10.6)	433 (8.4)	
time since CAD diagnosis, y, median (IQR)		4 (2–9)	7 (3–12)	<0.0001
medical history, n (%)	MI	16 090 (58.9)	3329 (64.5)	<0.0001
	PCI	16 563 (60.7)	2424 (46.9)	<0.0001
	CABG	6236 (22.8)	1391 (26.9)	<0.0001
	hospitalization for heart failure	1314 (4.8)	201 (3.9)	0.0040
	stroke	1105 (4.0)	197 (3.8)	0.43
	asthma/COPD	1823 (6.7)	583 (11.3)	<0.0001
	family history of premature CAD	7307 (26.8)	1945 (37.7)	<0.0001
	treated hypertension	19 675 (72.1)	3394 (65.7)	<0.0001
	diabetes mellitus	8085 (29.6)	1352 (26.2)	<0.0001
	dyslipidemia	20 512 (75.1)	3782 (73.2)	0.0039
	PAD	2644 (9.7)	556 (10.8)	0.017
angina status, n (%)	no angina	21 211 (77.7)	4039 (78.2)	<0.0001
	CCS I	1575 (5.8)	486 (9.4)	
	CCS II	3372 (12.4)	470 (9.1)	
	CCS III/IV	1140 (4.2)	169 (3.3)	
coronary angiography performed, n (%)		23.697 (86.8)	3993 (77.3)	<0.0001
number of vessels with >50% stenosis, n (%)	0	684 (2.9)	317 (8.0)	<0.0001
	1	9773 (41.3)	1599 (40.1)	
	≥2	13.209 (55.8)	2070 (51.9)	
no heart failure symptoms, n (%)		22.809 (83.5)	4745 (91.9)	<0.0001
laboratory test results	creatinine, mmol/l, median (IQR)	0.088 (0.076–0.101)	0.088 (0.077–0.102)	0.019
	fasting glucose, mmol/l, median (IQR)	5.7 (5.1–6.7)	5.6 (5.0–6.4)	<0.0001
	total cholesterol, mmol/l, median (IQR)	4.3 (3.7–5.1)	4.1 (3.6–4.8)	<0.0001
	LDL cholesterol, mmol/l, median (IQR)	2.4 (1.9–3.0)	2.2 (1.8–2.8)	<0.0001
	ECG heart rate, bpm, mean (SD)	67 (11)	67 (12)	0.74
	ECG sinus rhythm, median (IQR)	20 768 (95.1)	2209 (94.1)	0.091
	SBP, mmHg, mean (SD)	130.9 (16.7)	131.8 (16.6)	0.0007
	DBP, mmHg, mean (SD)	77.6 (9.9)	75.8 (10.1)	<0.0001
	LVEF, %, mean (SD)	56.3 (11.0)	54.3 (11.2)	<0.0001

Abbreviations: CABG, coronary artery bypass surgery; CAD, coronary artery disease; CCS, Canadian Cardiac Society; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ECG, electrocardiogram; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure

adjusted HR, 0.80; 95% CI, 0.68–0.94 (P = 0.0067) (FIGURE 3). Likewise, the risk of fatal or nonfatal MI (adjusted HR, 0.79; 95% CI, 0.63–0.99; P = 0.045) was lower among patients treated primarily by cardiologists. Similarly, after adjustment, stroke and unstable angina were significantly less likely among patients treated by cardiologists: adjusted HR, 0.73; 95% CI, 0.54–0.99; P = 0.040 and adjusted HR, 0.77; 95% CI, 0.67–0.88; P = 0.0001, respectively. Conversely, major bleeds—although rare—occurred more frequently in patients treated by cardiologists (adjusted HR, 1.62; 95% CI, 1.10–2.38; P = 0.012) (FIGURE 3).

TABLE 2 Medical treatment at baseline according to primary cardiologist or noncardiologist care

Treatment	Cardiologist care (n = 27 304)	Noncardiologist care (n = 5164)	*P* value
aspirin	23 965 (87.8)	4500 (87.2)	0.21
thienopyridines	8112 (29.7)	638 (12.4)	<0.0001
lipid-lowering agents	25 137 (92.1)	4843 (93.8)	<0.0001
β-blockers	20 790 (76.2)	3651 (70.7)	<0.0001
calcium antagonists	7491 (27.4)	1373 (26.6)	0.21
long-acting nitrates	6188 (22.7)	952 (18.4)	<0.0001
ivabradine	3060 (11.2)	154 (3.0)	<0.0001
ACEI or ARB	20 749 (76.0)	4006 (77.6)	0.013

Data are presented as n (%) and are based on the number of patients with data available.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Because of the unique pattern of care in the UK, where all patients with a cardiac condition are treated by primary care physicians after an initial cardiology consultation, we preformed sensitivity analysis on the outcome results after exclusion of those patients. The results were consistent with those in the entire study group (Supplementary material online, *Table S5*).

DISCUSSION Our main finding is that patients with stable CAD who were primarily cared for by cardiologists had a lower rate of the composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke than patients attended by noncardiologists. This difference was robust and persisted after adjustment for multiple factors. Similar results were seen for fatal or nonfatal MI, fatal or nonfatal stroke, and unstable angina. Conversely, major bleeds were more common among patients treated by cardiologists.

Our findings are consistent with those reported by Go et al,[9] who analyzed the effects of physician specialty on knowledge, treatment, and outcomes of patients with CAD or heart failure. They found that patients treated by cardiologists were more likely to receive evidence-based care and probably had better outcomes. However, their analysis involved a mixed population of patients with CAD, including those with acute coronary syndromes.

In the current study, the differences in outcomes between cardiologist-treated and noncardiologist-treated patients may have resulted from differences in baseline risk (even though there was adjustment for the main differences), or differences in management.

Diabetes mellitus was better controlled in patients managed primarily by cardiologists. Interestingly, however, blood pressure and lipid targets were more frequently met in the nonspecialist group. This, paradoxically, could be due to the fact that cardiovascular risk in individual patients may be perceived as higher by generalists than by cardiologists.[13] In contrast to our findings, in previous studies[8,10] a higher proportion of patients with cardiologist involvement achieved adequate lipid and blood pressure control versus those without cardiologist involvement. There were important differences in the use of evidence-based secondary prevention treatments, such as β-blockers (greater use by cardiologists) and lipid-lowering drugs (greater use by noncardiologists). While aspirin use did not differ, the greater proportion of patients receiving thienopyridines in the cardiologist-managed group was most likely a reflection of the more frequent history of PCI in this group.

It needs to be emphasized that patients in our study received adequate guideline-recommended medical treatment, regardless of the specialty involved. In comparison, in the Euro Heart Survey,[14] which included almost 3800 patients with stable CAD enrolled by cardiologists, 78% were treated with aspirin, 48% with a statin, 67% with a β-blocker, and 37% with an angiotensin-converting enzyme inhibitor after their initial assessment. Revascularization rates were low, with only 13% of patients having PCI or CABG performed or planned.[14]

Thus, in our study we did not find clear evidence that patients primarily treated by cardiologists receive better guideline-based treatment than those managed by noncardiologists.

Previous studies (CLARIFY and others) have indicated that the prevalence and control of major cardiovascular risk factors may vary markedly by geographic region, age, sex, and other factors.[15-19] Thus, the differences in management patterns in our study, both recorded and unrecorded, might have been responsible for the better outcomes in patients managed by cardiologists. The second potential explanation is intrinsic differences between the groups. Indeed, significant differences were observed between the 2 groups in terms of demographics and medical history. Importantly, patients treated by noncardiologists had more comorbidities, such as PAD and asthma or COPD, while in the specialist-treated group, CAD was a dominant problem.

There are important sex-related differences in clinical characteristics and management in all age groups of outpatients with stable CAD.[15,20] Also, patient preferences and their sociodemographic status may play an important role in their ability to receive specialist care.[19] Differences in health care systems between countries may be responsible for the availability of specialist care. For example, in the UK outpatient care for patients with stable CAD is provided by primary care physicians. In our study, about half of the patients managed by noncardiologists came from the UK, which might have confounded our observations. However, sensitivity analyses excluding UK patients found consistent results.

Although outcomes were corrected for some identified intergroup differences at baseline in the current study, we may not have captured all relevant factors. It is possible that residual confounding, unmeasured selection biases, such as

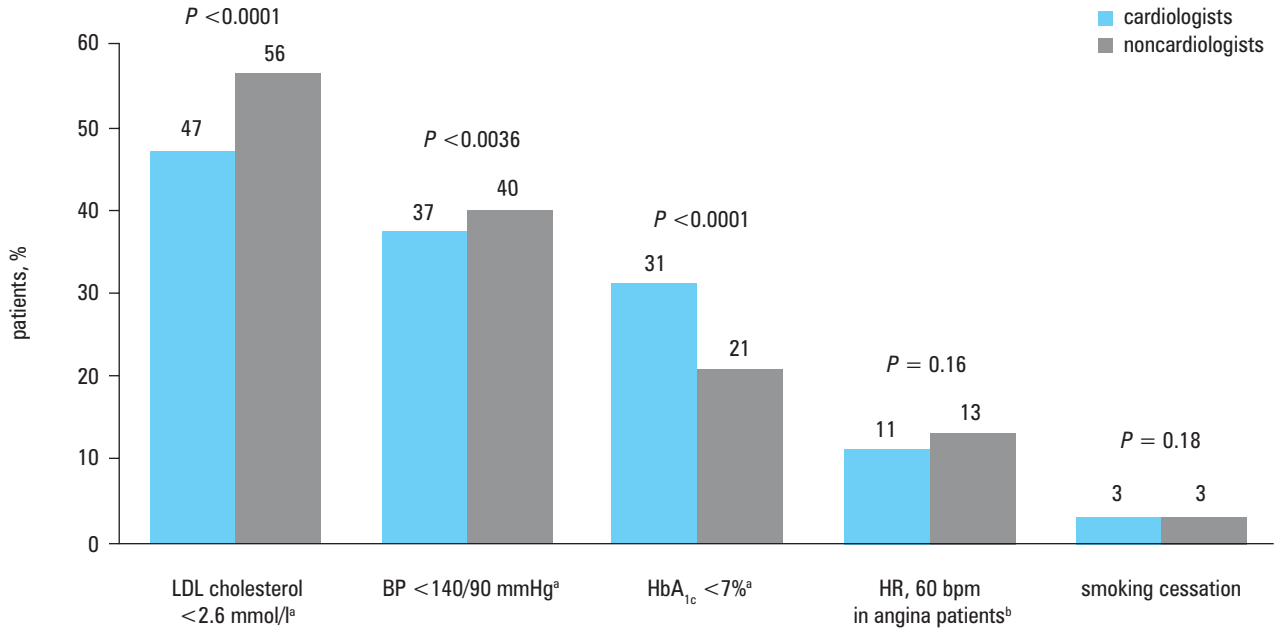

FIGURE 2 Proportions of patients reaching therapeutic targets. Because of poor lipid control described in registry data, for the low-density lipoprotein cholesterol we used a threshold less stringent than that indicated by the current guidelines.

a among those with the risk factor at baseline

b patients with angina at baseline and at follow-up

Abbreviations: BP, blood pressure; HbA_{1c}, hemoglobin A_{1c}; HR, heart rate; LDL, low-density lipoprotein

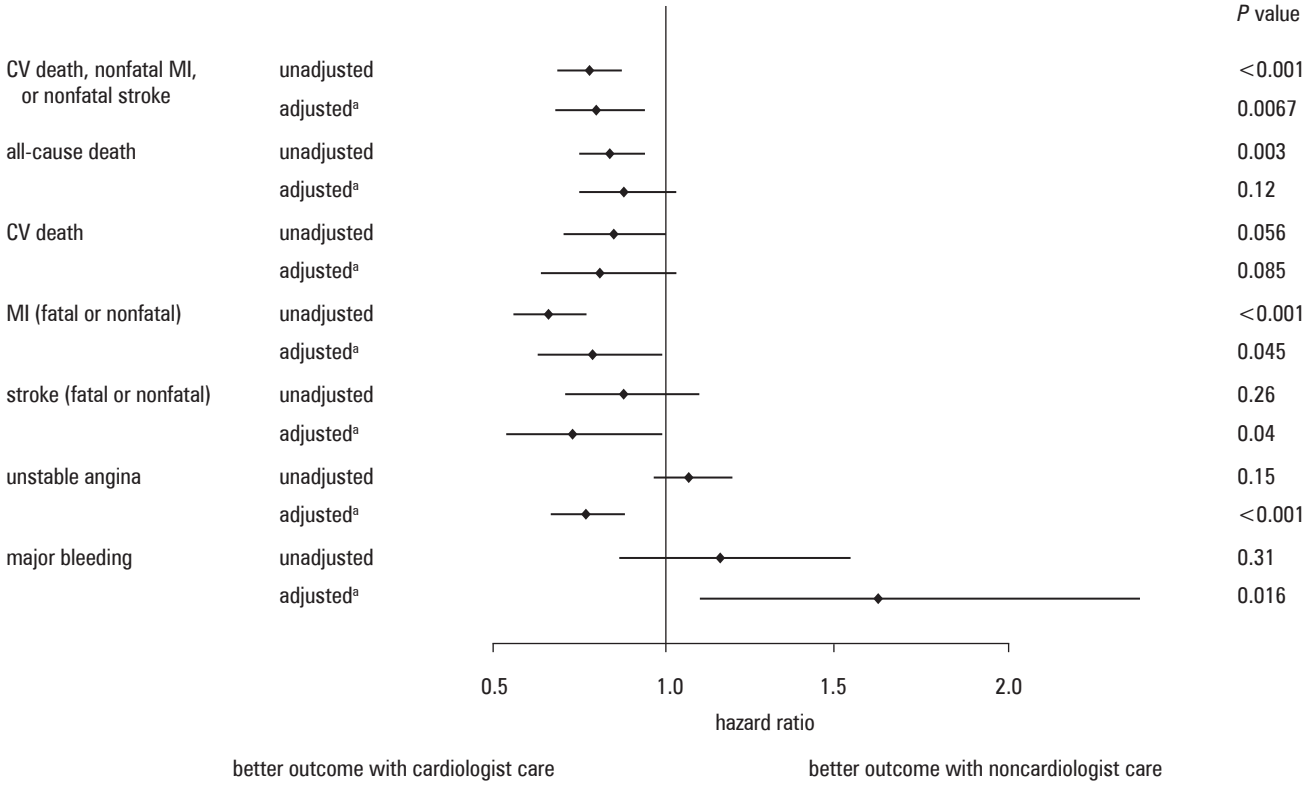

FIGURE 3 Comparison of clinical outcomes between patients primarily managed by cardiologists versus noncardiologists

a adjusted for age, geographic region, sex, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, blood pressure, left ventricular ejection fraction, congestive heart failure, diabetes mellitus, peripheral artery disease, and asthma/chronic obstructive pulmonary disease

Abbreviations: CV, cardiovascular; MI, myocardial infarction

social and demographic factors, patient preferences in receiving specialty care, and differences in patient lifestyles and behaviors might have contributed to our findings.

Finally, among patients primarily managed by noncardiologists, the degree of collaboration with specialists may differ. Such interaction has been shown to have a positive effect on outcome in patients with heart failure,[21] and is also likely to play a role in patients with stable CAD, but its degree is difficult to capture.

Our study has several limitations: the data were observational; center selection was made on a voluntary basis; the outcome events were not adjudicated, but were based on investigators' reporting; and unmeasured confounders might have contributed to our findings.

In conclusion, in the contemporary global CLARIFY registry, outpatients with stable CAD managed by cardiologists had a lower rate of cardiovascular events than those managed by noncardiologists. These differences were most likely due to unknown and unquantifiable characteristics of the type of patients managed by cardiologists compared with noncardiologists, as opposed to differences in the quality of care provided by cardiologists and noncardiologists.

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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Contribution statement ZP, PGS, and MT conceived and designed the paper. NG and IF analyzed the data. ZP wrote the paper. JM, MAG, and SK recruited the patients. PGS, MT, NG, RF, IF, KF, JCT, JM, MAG, and SK provided a critical review of the manuscript. All authors contributed to this work and approved the manuscript for submission.

Conflict of interest ZP has received consultation fees related to the CLARIFY study. PGS has received research grants from Merck, Sanofi, and Servier, and speaking or consulting fees from Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, CSL-Behring, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, Servier, and the Medicines Company. RF reported that he received honorarium from Servier for steering committee membership consulting and speaking, and support for travel to study meetings from Servier. In addition, he received personal fees from Boehringer-Ingelheim, Novartis, Merck Serono, and Irbtech. Finally, he is a stockholder in Medical Trials Analyis. IF has received research grants and honoraria from Servier and Amgen. KF has received fees, honoraria, and travel expenses from Servier. JCT has received research grants from Amarin, AstraZeneca, Cymabay, DalCor, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi, and Servier, and fees from DalCor, Pfizer, and Servier. He holds the Canada Research Chair in translational and personalized medicine and the Université de Montréal endowed research chair in atherosclerosis. JM received consultation fees and honoraria from Servier, Bayer Healthcare, BMS, Novartis, Boehringer Ingelheim, and Daiichi-Sankyo. MAG has received honoraria and consultation fees from Servier, AstraZeneca, Amgen, Bayer, Sanofi, Lilly, and Pfizer. SK has received an honorarium from Servier for national steering committee membership consulting auditing and speaking, and support for travel to study meetings from Servier. MT has received honoraria and consultation fees from Servier, Bayer, Pfizer, Janssen-Cilag, TIMI Group, and Celyad.

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