Original Research

Clinical Presentation and Management of Stable Coronary Artery Disease: Insights from the International Prospective CLARIFY Registry – Results from the Greek National Cohort

Eftihia Sbarouni[1], Vassilis Voudris[1], Panagiota Georgiadou[1], Michalis Hamilos[2], P. Gabriel Steg[3,4,5], Kim M. Fox[5], Nicola Greenlaw[6], Roberto Ferrari[7], Panos E. Vardas[2]; on behalf of the Greek CLARIFY investigators (see Appendix)

[1]Second Division of Interventional Cardiology, Onassis Cardiac Surgery Center, Athens, [2]Department of Cardiology, Heraklion University Hospital, Crete, Greece; [3]Université Paris-Diderot, Sorbonne Paris-Cité, [4]Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Assistance Publique – Hôpitaux de Paris, Paris, France; [5]NHLI Imperial College, ICMS, Royal Brompton Hospital, London, [6]University of Glasgow, Glasgow, UK; [7]Department of Cardiology, University Hospital of Ferrara and Maria Cecilia Hospital, GVM Care & Research, E.S. Health Science Foundation, Cotignola, Italy

Introduction: Coronary artery disease (CAD) is highly prevalent worldwide, yet there is a paucity of data regarding the clinical characteristics and management of outpatients with stable CAD. In this paper, we report the baseline data of the Greek cohort and we compare our national data with the global results of the entire registry, as well as the results from the western European countries.

Methods: CLARIFY is an international, prospective, observational, longitudinal registry of outpatients with stable CAD, defined as prior myocardial infarction or revascularization procedure, evidence of coronary stenosis >50%, or chest pain associated with proven myocardial ischemia. A total of 33,283 patients from 45 countries in 4 continents were enrolled between November 2009 and July 2010; of these, 14,726 were from western European countries (Austria, Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Portugal, Spain, Switzerland and the United Kingdom) and 559 patients were enrolled in Greece.

Results: Compared to their counterparts in western Europe and the entire cohort, Greeks were younger ($p<0.0001$, $p<0.0001$, respectively), more predominantly male ($p<0.0039$, $p<0.0001$), with a higher body mass index ($p<0.0002$, $p<0.0001$) and a larger waist circumference ($p<0.0001$, $p<0.0001$), as well as a higher prevalence of family history of CAD ($p<0.0008$, 0.0005), hyperlipidemia ($p<0.0001$, $p<0.0001$) and smoking ($p<0.0001$, $p<0.0001$). Noninvasive testing ($p<0.0001$, $p<0.0001$, respectively) and coronary angiography ($p<0.0001$, 0.0013) along with surgical revascularization (CABG) ($p<0.0001$, 0.0088) were performed more often in Greece. Antiplatelets, b-blockers and lipid lowering medications were used to an equal extent in Greece as in the other two cohorts.

Conclusion: There are substantial differences in demographics, clinical profiles and treatment in patients with stable CAD within the data set, which are also observed for Greek data. Interestingly, these differences are consistent in relation to the global as well as the western European data.

Coronary artery disease (CAD) is the leading cause of death worldwide.[1-4] Most available data regarding CAD are from patients with acute coronary syndromes and little is known about those with stable CAD who are managed as outpatients. CLARIFY (ProspeCtive observational LongtudinAl Reg-

Istry oF patients with stable coronary arterY disease) is an international prospective observational longitudinal registry of more than 33,000 patients with CAD who are receiving standard management in 45 countries on 4 continents.[5-8] The objectives of the registry are to delineate the demographics, risk factors, clinical profiles, management and outcome of contemporary stable CAD patients of various origins.

In this paper, we report the baseline data of the Greek cohort and we compare our national data with the global results of the entire registry, as well as the results from the western European countries.

Methods

The rationale and design of CLARIFY have been published previously.[5] Eligible patients had at least one of the following: documented myocardial infarction (MI) >3 months before enrolment; coronary artery stenosis >50% on angiography; chest pain with positive stress electrocardiogram; coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) performed >3 months before enrolment. Exclusion criteria were hospital admission for cardiovascular reasons (including revascularization) in the past 3 months, planned revascularization, noncardiovascular diseases hampering the 5-year follow-up (i.e. serious comorbidities interfering with life expectancy), and other severe cardiovascular diseases (advanced heart failure, severe valve disease, valve repair/replacement). Patients' enrolment was restricted to a brief period between November 2009 and July 2010. The study was approved by national ethical committees and all patients gave informed consent. The study is registered (ISRRCTN43070564) and the website is www.clarify-registry.com.

The investigators completed standardized electronic case report forms at baseline. Data were collected regarding baseline demographics, risk factors and life style, physical condition, medical history, physical signs, current symptoms and treatments. Results of noninvasive and invasive procedures were recorded but were not mandatory for inclusion.

Statistical analysis

Summary data are expressed as mean (standard deviation) or median (lower quartile, upper quartile) for continuous variables, depending on whether the data were normally distributed or skewed, and number (percentage) for categorical variables. Differ-

ences between the Greek data and other global/geographical data were tested using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables, depending on the distribution of the data, and Pearson's chi-square test for the categorical variables. Statistical analysis was performed using the SAS statistical program (version 9.2). The accepted significance level was $p < 0.05$.

Results

A total of 33,283 patients were included at baseline. Of these, 14,726 were from western European countries (Austria, Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Portugal, Spain, Switzerland and United Kingdom); 559 patients were enrolled in Greece.

The major baseline characteristics of the Greek patients in comparison to global data and western European data are presented in Table 1. The cardiovascular medications received by the study populations are shown in Figure 1.

In relation to the entire registry, Greek patients were younger, more predominantly male, with a higher body mass index (BMI) and a larger waist circumference; the sample was extremely homogeneous regarding ethnic origin, unlike the rest of the globe. At the time of enrolment, Greek patients had higher employment rates: employed full time 163 (29.16) vs. 7961 (24.35), $p < 0.0001$. In terms of risk factors for CAD, Greeks were more likely to have a positive family history for CAD and were more often hyperlipidemic and smokers, whereas they were less often physically inactive. Noninvasive testing and coronary angiography were performed more often in Greece; regarding revascularization procedures, CABG occurred more often and PCI marginally less often. In Greece, patients presented less often with angina or heart failure symptoms. On angiography, no significant stenosis was found more often in the Greek cohort; significant left main disease was also found more often. As expected, the total and low-density lipoprotein (LDL) cholesterol were higher and, although there was no difference in fasting blood glucose, glycated hemoglobin ($HbA1_C$) was lower in the Greek population. Importantly, there was no significant difference in the use of aspirin, clopidogrel, b-blockers, or lipid lowering medications (Figure 1). However, angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) were prescribed more often, as were ivabradine, calci-

Table 1. Baseline characteristics: Greece vs. the globe and Greece vs. western Europe.

Parameter	Greece (n=559)	Globe (n=32,724)	p	Western Europe (n=14,167)	p
Age, years*	62.34 (10.59)	64.18 (10.48)	<0.0001	66.34 (10.11)	<0.0001
Male[†]	472 (84)	25289 (77)	<0.0001	11234 (79)	0.0039
BMI, kg/m^{2‡}	28.2 (25.7,31.1)	27.3 (24.8,30.3)	<0.0001	27.5 (25.2,30.4)	0.0002
Waist circumference, cm median[‡]	102.00 (92.00,110.00)	96.52 (88.00,105.00)	<0.0001	99 (90,107)	<0.0001
Caucasian[†]	558 (100)	20779 (63)	§	10685 (75)	§
RISK FACTORS					
Family history of premature CAD[†]	196 (35)	9265 (28)	0.0005	4038 (29)	0.0008
Treated hypertension[†]	400 (72)	23191 (71)	0.75	9578 (68)	0.056
Diabetes[†]	156 (28)	9540 (29)	0.51	3735 (26)	0.43
Dyslipidemia[†]	499 (89)	24390 (75)	<0.0001	10764 (76)	<0.0001
Smoking[†]					
Current	91 (16)	4035 (12)	<0.0001	1587 (11)	<0.0001
Former	299 (53)	14794 (45)		7129 (50)	
Never	169 (30)	13860 (42)		5433 (38)	
PHYSICAL ACTIVITY					
No physical activity[†]	72 (13)	5347 (16)	0.0017	2475 (17)	<0.0001
Light most weeks[†]	319 (57)	16738 (51)		6776 (48)	
20 min vigorous 1-2/week[†]	104 (19)	5474 (17)		2595 (18)	
20 min >2/week[†]	64 (11)	5123 (16)		2298 (16)	
Alcohol intake (drinks/week)					
0	171 (31)	15911 (49)	<0.0001	4743 (34)	0.28
1-20	359 (64)	15618 (48)		8638 (61)	
>20	29 (5)	1155 (4)		726 (5)	
MEDICAL HISTORY					
AMI[†]	319 (57)	19530 (60)	0.20	8099 (57)	0.9318
Coronary angiography not done[†]	27 (5)	4840 (15)	<0.0001	1235 (9)	0.0013
Noninvasive test for ischaemia[†]	488 (87)	20093 (61)	<0.0001	11204 (79)	<0.0001
Evidence of ischaemia[†]	162 (29)	5207 (16)	<0.0001	2415 (17)	<0.0001
PCI[†]	305 (55)	19201 (59)	0.047	8775 (62)	0.0004
CABG[†]	172 (31)	7612 (23)	<0.0001	3652 (26)	0.0088
TIA[†]	31 (6)	986 (3)	0.0006	457 (3)	0.0027
Stroke[†]	13 (2)	1314 (4)	0.043	474 (3)	0.18
PVD[†]	61 (11)	3194 (10)	0.37	1773 (13)	0.25
Hospitalization for CHF[†]	14 (2)	1538 (5)	0.015	561 (4)	0.081
Asthma/COPD[†]	36 (6)	2417 (7)	0.39	1366 (10)	0.011
SYMPTOMS					
Any angina[†]	89 (16)	7226 (22)	0.0005	1965 (14)	0.17
Angina and CCS Class[†]					
No angina	470 (84)	25460 (78)	0.0005	12182 (86)	0.20
CCS class I[†]	38 (7)	2053 (6)		684 (5)	
CCS class II[†]	42 (7)	3846 (12)		1001 (7)	
CCS class III[†]	9 (2)	1245 (4)		245 (2)	
CCS class IV[†]	0 (0)	78 (0.2)		34 (0.2)	
CHF symptoms[†]			<0.0001		0.32
No	528 (94)	27770 (85)		13137 (93)	
NYHA II	27 (5)	4108 (13)		839 (6)	
NYHA III	4 (1)	804 (2)		169 (1)	
ANGIOGRAPHY					
No stenosis[†]	32 (6)	1038 (3)	0.0007	559 (4)	0.036
LM>50%[†]	67 (12)	2798 (9)	0.0041	1639 (12)	0.76
LAD>50%[†]	331 (59)	18990 (58)	0.57	8378 (59)	0.97
Cx>50%[†]	237 (42)	11687 (36)	0.0011	5427 (38)	0.051
RCA>50%[†]	250 (45)	14118 (43)	0.45	6529 (46)	0.53
Graft>50%[†]	21 (4)	2636 (8)	0.0002	1380 (10)	<0.0001

CARDIAC PARAMETERS					
Heart rate (palpation)*	68.24 (10.15)	68.29 (10.63)	0.92	66.13 (10.56)	<0.0001
ECG heart rate*	67.55 (10.88)	67.17 (11.45)	0.51	65.39 (11.12)	0.0001
SBP (mmHg)*	127.85 (14.19)	131.05 (16.69)	<0.0001	131.58 (16.07)	<0.0001
DBP (mmHg)*	78.10 (9.23)	77.23 (9.98)	0.040	76.38 (9.35)	<0.0001
LVEF (%)*	55.98 (9.14)	56.11 (11.13)	0.79	57.49 (10.82)	0.0019
ECG rhythm[†]					
Sinus	388 (95.80)	22994 (94.93)	0.36	10435 (93.65)	0.11
AF	14 (3.46)	827 (3.41)		468 (4.20)	
Paced	3 (0.74)	401 (1.66)		239 (2.15)	
LABORATORY RESULTS, mmol/L					
Glucose[‡]	5.7 (5.3,6.6)	5.7 (5.1,6.6)	0.13	5.7 (5.1,6.6)	0.096
Creatinine[‡]	0.088 (0.080,0.097)	0.088 (0.076,0.102)	0.0029	0.088 (0.077,0.102)	0.0029
TC[‡]	4.6 (4.1,5.1)	4.3 (3.7,50)	<0.0001	4.3 (3.7,4.9)	<0.0001
HDL[‡]	1.17 (1.04,1.35)	1.14 (0.96,1.37)	0.015	1.20 (1.00,1.40)	0.25
LDL[‡]	2.60 (2.24,3.12)	2.37 (1.88,2.94)	<0.0001	2.35 (1.90,2.86)	<0.0001
TG[‡]	1.5 (1.1,1.9)	1.4 (1.0,1.9)	0.16	1.3 (1.0,1.8)	0.0001
HbA1C (%)*	6.37 (0.87)	6.85 (2.05)	0.0007	6.68 (1.23)	0.0004
Hb[‡]	8.69 (8.19,9.25)	8.69 (8.07,9.31)	0.91	8.75 (8.19,9.31)	0.17

*Mean (SD); [†]n (%); [‡]median (Q1,Q3); [§]p-value not computable.

BMI – body mass index; CAD – coronary artery disease; AMI – acute myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery by-pass grafting ; TIA – transient ischemic attack; PVD – peripheral vascular disease ; CHF – chronic heart failure; COPD – chronic obstructive pulmonary disease; NYHA – New York Heart Association; LM – left main; LAD – left anterior descending; Cx –circumflex; RCA – right coronary artery; SBP – systolic blood pressure; DBP – diastolic blood pressure; LVEF – left ventricular ejection fraction; ECG – electrocardiogram; AF – atrial fibrillation; TC – total cholesterol; HDL – high density lipoprotein; LDL – low density lipoprotein; TG – triglycerides; Hb – hemoglobin.
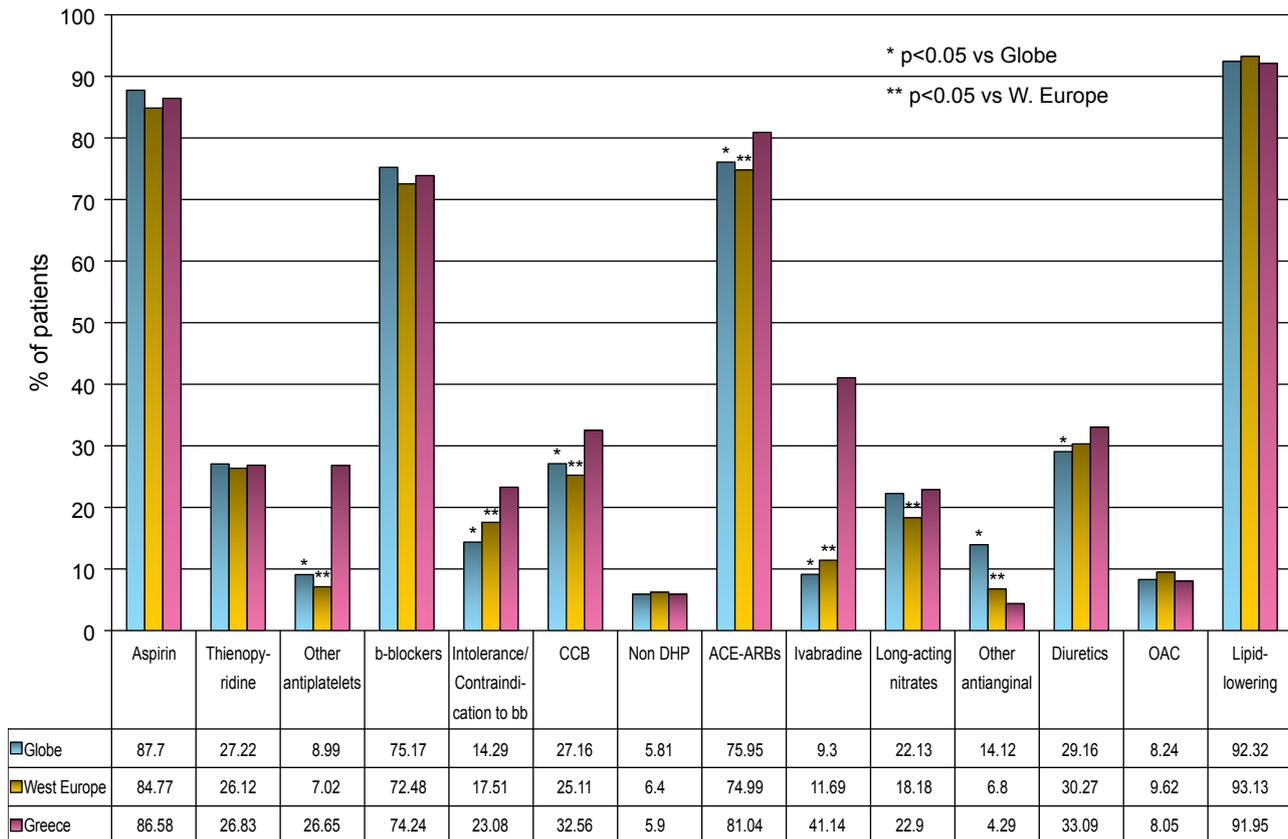

	Aspirin	Thienopy-ridine	Other antiplatelets	b-blockers	Intolerance/ Contraindi-cation to bb	CCB	Non DHP	ACE-ARBs	Ivabradine	Long-acting nitrates	Other antianginal	Diuretics	OAC	Lipid-lowering
Globe	87.7	27.22	8.99	75.17	14.29	27.16	5.81	75.95	9.3	22.13	14.12	29.16	8.24	92.32
West Europe	84.77	26.12	7.02	72.48	17.51	25.11	6.4	74.99	11.69	18.18	6.8	30.27	9.62	93.13
Greece	86.58	26.83	26.65	74.24	23.08	32.56	5.9	81.04	41.14	22.9	4.29	33.09	8.05	91.95

Figure 1. Medications used by the study population. CCB – calcium channel blockers; non DHP – non-dihydropyridine; OAC – oral anti-coagulants.

um channel blockers (CCB), diuretics, and antiplatelets other than aspirin and clopidogrel, whereas antianginals other than the 3 known groups of agents (b-blockers, CCBs and nitrates) were prescribed less often (Figure 1).

The comparison of the Greek sample with the western European data presented associations similar to those of the entire registry, apart from the incidence of left main disease, angina or heart failure symptoms, and the use of diuretics. Proton-pump inhibitors were prescribed less often in Greece (Figure 1). In addition, symptoms indicative of intolerance to b-blockers were recorded more often in the Greek sample.

Discussion

This is a registry of patients with stable CAD, most of whom had a previous MI or revascularization, enrolled in our country between November 2009 and June 2010. Five hundred fifty-nine patients were enrolled at 42 investigational sites (private cardiology offices) based in cities (60%), but also in rural (40%) areas of Greece. The baseline data are reported in this paper and compared with the global as well as the western European data. One-year follow up has been completed and will be published shortly.

The main findings of this study are: Greeks with stable CAD are younger compared to their counterparts in west Europe and the entire cohort; this may be associated with the higher prevalence of a family history of CAD, hyperlipidemia and smoking, as well as the higher BMI and larger waist circumference. A similar relatively young population (mean age of 61), with a high prevalence of modifiable cardiovascular risk factors, has also been documented by the Euro Heart Survey on stable angina pectoris, including 3779 ambulatory patients from 36 countries.[9] Subsequently, higher values of total and LDL cholesterol were recorded. Women were considerably underrepresented in this registry.

CAD is investigated more often in Greece, with both noninvasive testing and coronary angiography, and it is more common for no significant stenosis to be found on angiography, possibly implying unnecessary diagnostic procedures. Regarding revascularization, CABG was more frequently performed in Greek patients; this may be partly due to an increased incidence of significant left main disease, although this has not been observed in the western European data.[10]

Evidence-based medicines for stable CAD—antiplatelets, b-blockers and lipid lowering—were used equally as much in Greece as elsewhere. However, ACEi and/or ARB were prescribed more often, even though ejection fraction was well preserved and no different to the rest of the world. Systolic blood pressure levels, as well as the incidence of transient ischemic attacks or stroke and symptoms or hospitalizations due to heart failure were lower compared to the rest of the world, while the prevalence of diabetes was similar.[6,9,11,12] Ivabradine, CCB, and antiplatelets other than aspirin and clopidogrel were also given more frequently in Greece than in Western Europe, without there being any significant difference in the incidence of angina, hypertension or diabetes. Despite a high rate of use of these heart-rate lowering medications, Greek patients have higher heart rate than other Europeans.

In conclusion, there are differences in demographics, risk factors, life style, medical history, physical signs, current symptoms and treatments in patients with established but stable CAD. Notably, these differences are consistent in both comparisons, in relation to both the global and the western European data; whether these differences are associated with different outcomes remains to be seen.

Appendix

Greek CLARIFY investigators: Elias Alexopoulos, Evaggelia Anastasiou, Vasilios Arfaras, Christos Avgerinos, Sokratis Avlonitis, Polixeni Boboti, Ioannis Bourazanis, Paraskevas Boutsikos, Emmanouil Chalkiadakis, Georgios Chatziioakim, Christos Christoforidis, Panagiotis Dalabiras, Simeon Gavriilidis, Thomas Gkinis, Olga Gouli, Andreas Kalabalikis, Panagiotis Kalaras, Marilena Karachaliou, Georgios Kolios, Elias Konstantinidis, Andreas Kotsalos, Georgios Koutsibanis, Ioannis Leontaridis, Christos Liatas, Dimitrios Mitropoulos, Ioannis Orestis, Konstantinos Panisois, Anna Papathanasiou, Christos Pappas, Elias Petropoulos, Vasilios Plastiras, Nikolaos Pontikakis, Georgios Pournaras, Christos Priftis, Andreas Samothrakitis, Dimitrios Stergiou, Konstantinos Svolis, Panagiotis Tarenidis, Georgios Theodorakis, Ioannis Tsamopoulos, Vasilios Zachos, Charilaos Zakopoulos.

References

1. Murray CJ, Lopez AD. Mortality by cause in eight regions of the world: Global Burden of Disease Study. Lancet. 1997; 349: 1269-1276.

2. Anderson GF, Chu E. Expanding priorities--confronting chronic disease in countries with low income. N Engl J Med. 2007; 356: 209-211.

3. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012; 60: e44-e164.

4. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003; 24: 1601-1610.

5. Steg PG. Heart rate management in coronary artery disease: the CLARIFY registry. Eur Heart J. 2009; 11 (Supplement D): D13-D18.

6. Steg PG, Ferrari R, Ford I, et al; CLARIFY Investigators. Heart rate and use of beta-blockers in stable outpatients with coronary artery disease. PLoS One 2012; 7: e36284.

7. Steg PG, Greenlaw N, Tardif JC, et al. Women and men with stable coronary artery disease have similar clinical outcomes: insights from the international prospective CLARIFY registry. Eur Heart J. 2012; 33: 2831-2840.

8. Ferrari R, Abergel H, Ford I, et al. Gender- and age-related differences in clinical presentation and management of outpatients with stable coronary artery disease. Int J Cardiol. 2013; 167: 2938-2943.

9. Daly CA, Clemens F, Sendon JL, et al. The initial management of stable angina in Europe, from the Euro Heart Survey: a description of pharmacological management and revascularization strategies initiated within the first month of presentation to a cardiologist in the Euro Heart Survey of Stable Angina. Eur Heart J. 2005; 26: 1011-1022.

10. Boden WE. Surgery, angioplasty, or medical therapy for symptomatic multivessel coronary artery disease: is there an indisputable "winning strategy" from evidence-based clinical trials? J Am Coll Cardiol. 2004; 43: 1752-1754.

11. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366: 1267-1278.

12. Yusuf S, Pogue J. ACE inhibition in stable coronary artery disease. N Engl J Med. 2005; 352: 937-939.