Clinical Outcomes, Pharmacologic Treatment and Quality of Life of Patients with Stable Coronary Artery Diseases Managed by Cardiologists: 1-Year Results of the START Study

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ABSTRACT

Aims. We evaluated the 1-year clinical events, pharmacologic management and quality of life in a contemporary cohort of stable coronary artery disease (CAD) patients managed by cardiologists.

Methods and Results. START (STable Coronary Artery Diseases RegisTry) was a prospective, observational, nationwide study that enrolled 5070 stable CAD patients over 3 months in 183 cardiology centers in Italy.

At 1 year, 4790 (94.5%) patients had data on vital status. Death occurred in 107 (2.2%) patients and the cause of death was cardiovascular in 41 (38.3%) of cases. Among the 4775 patients with follow-up data on clinical events available, a hospitalization due to cardiovascular and non-cardiovascular causes occurred in 523 (11.0%) and in 231 (4.8%) of cases, respectively. Over 60% of patients reported as "no problems" in all domains (61.4-84.5%) of the EuroQoL quality of life 5D-5L questionnaire.

Among the 3239 patients with clinical visit/telephone interview at follow-up, in whom optimal medical therapy (OMT; aspirin or thienopyridine, β-blocker, and statin) was prescribed at enrollment, 2971 (91.7%) were still receiving OMT at follow-up. At multivariable analysis, only increasing age (OR 0.98; 95% CI 0.97-0.99; p=0.04) resulted as independent negative predictor of OMT persistence at 1 year from enrolment.

Conclusions. In this large, contemporary registry, stable CAD patients managed by cardiologists presented a high rate of clinical events at 1 year. Nevertheless, the persistence to OMT and quality of life appeared reasonable.

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Key words: stable coronary artery disease; treatment; quality of life; outcome.

INTRODUCTION

In the last decades, major progresses have been made in the diagnosis and treatment of patients with stable coronary artery disease (CAD) (1-3). A suitable myocardial revascularization and a concomitant use of optimal pharmacological treatment have been demonstrated to improve the outcomes of stable CAD (1-3). Nevertheless, these patients still present a high event rate at long-term follow-up that probably depends on their suboptimal medical management (4-7). Indeed, it is well-known that adherence to medical therapy in chronic diseases, especially in asymptomatic patients, is a major health problem (1,2). There is a fairly extensive, but heterogeneous body of evidence on this topic, particularly in the first 12 months following an acute coronary syndrome (8-10). On the other hand, relatively poor data are available on adherence to evidence-based medications and related long-term outcomes of stable CAD patients in a real-world setting (9).

The aim of this study was to report the rate of clinical events, pharmacological management, independent predictors of optimal medical therapy persistence and quality of life at 1-year from the START (STable Coronary Artery Diseases RegisTry) study (11) that enrolled a large cohort of stable CAD patients managed by cardiologists.

METHODS

The design and baseline data of the START registry have been published previously (8). Briefly, the START was a prospective, observational, nationwide study on stable CAD patients as seen by cardiologists in clinical practice in Italy (11). Patients with stable CAD presenting to a cardiologist during an outpatient visit or those discharged from a cardiology ward were eligible if they had at least 1 of the following clinical conditions: 1) typical stable angina and/or non-anginal symptoms (1,2); 2) documented ischemia at stress test with or without symptoms; 3) previous revascularization, such as percutaneous coronary intervention (PCI) or coronary bypass grafting (CABG); 4) prior episode (occurred at least 30 days from enrolment) of acute coronary syndrome (ACS); 5) elective admission for coronary revascularization (including staged procedures). We excluded patients aged <18 years old, those with Canadian Cardiovascular Society (CCS) IV angina or with atypical chest pain that in all probability was not related to CAD (11).

All patients were informed of the nature and aims of the study and asked to sign an informed consent for the anonymous management of their individual data. Local Institutional Review Boards (IRB) of the participating centers (see appendix) approved the study, according to the current Italian rules.

Data were collected using a web-based, electronic CRF with the central database located at the Italian Association of Hospital Cardiologists (ANMCO) Research Center. By using a validation plan, integrated in the data entry software, data were checked for missing or contradictory entries and values out of the normal range.

ANMCO invited to participate all Italian cardiology wards, including those without intensive cardiac care units (CCUs), university teaching hospitals, general and regional hospitals, and private clinics receiving stable CAD patients. No specific protocols or recommendations for evaluation, management, and/or treatment have been put forth during

this observational study. However, current guidelines for the management of patients with stable CAD (1,2) have been discussed during the investigator meetings.

One-hundred eighty-three cardiology centers included 5070 consecutive patients in different periods of 3 months between March 2016 and February 2017 (11).

Follow-up

Patients were followed up by visits or telephone interviews by investigators at 1 year after enrolment. Interviews included questions related to the occurrence of events (cardiac, vascular or others), planned and unplanned hospitalizations, quality of life measurement and pharmacological treatment.

Optimal medical therapy (OMT) was defined as patients being prescribed aspirin or thienopyridine, β-blocker, and a statin, at the maximum tolerated dosage. To be categorized as receiving OMT, individual patients must have been either prescribed or had reported contraindications to all medications in each category. The composite percentages of OMT persistence were calculated using the number of patients receiving OMT, as defined above, at follow-up as the numerator and the total number of patients receiving OMT at enrolment as the denominator.

All patients in the study were asked to complete the self-administered EuroQoL 5D-5L (12) quality of life questionnaire at enrolment and at 1-year follow-up. The EQ 5D-5L is a simple, generic health-related quality of life instrument comprising a visual analogue scale (VAS) of self-rated general health and 5 domains (mobility, self-care, daily activities, pain/worry, and anxiety/depression). Each domain consists of 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems (12). In order to compare the baseline and follow-up EQ 5D-5L questionnaires, in the present analysis we combined the last 2 levels of each domain and defined them as severe/extreme problems.

Statistical analysis

Categorical variables are presented as number and percentages. Continuous variables are presented as mean and standard deviation (SD), except for follow-up duration and VAS score of self-rated general health status assessment, which are reported as median and interquartile range (IQR).

Changes in drug prescriptions and level of EQ 5D-5L questionnaire between enrolment and follow-up were analysed by Mc Nemar test for paired binary variables.

Clinically relevant variables were included in a a hierarchical multivariable logistic regression, with the type of hospital (no CCU; CCU; CCU+cath lab; CCU+cath lab+cardiac surgery) as random effect, and the other covariates as fixed effect, to identify the independent predictors of OMT persistence at follow-up (considering as persistence the prescription of OMT at follow-up visit (yes vs no) in patients treated with OMT at enrolment). The variables included in the model were: age, systolic blood pressure and heart rate (as continuous variables), gender, hypertension, hypercholesterolemia, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, ejection fraction (≥40%, as reference group; <40%; missing), history of heart failure, prior revascularization, prior ST-elevation myocardial infarction, prior stroke/transient ischemic attack, prior angina, and hospitalization for cardiac and/or vascular reasons (no, as reference group; yes; unknown) occurred from enrolment to follow-up. When more than two categories were present, dummy variables were introduced to define a reference group. Finally, a hierarchical multivariable logistic regression (with the type of hospital as stated above) on death and/or hospitalization for cardiovascular causes at follow-up was performed, including in the model the same variables of the logistic on OMT persistence at follow-up, considering the latter as a covariate.

A p value < 0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with SAS system software, version 9.4.

RESULTS

From the original cohort of 5070 patients enrolled in the START registry, 4790 (94.5%) had data on vital status at 1 year; among this latter group, 4654 (97.2%) received a formal follow-up (2475 with clinical visit and 2179 with telephonic contact), 14 (0.3%) were hospitalized, 15 (0.3%) withdrew consent and 107 (2.2%) died (**Figure 1**). The median follow-up duration was 369 [362-378] days.

Baseline characteristics of the population with data on vital status at 1 year are shown in **Table 1**. The mean age was 68±11 years, 3837 (80%) were male, 1468 (31%) diabetics, 3594 (75%) had hypercholesterolemia and an atrial fibrillation was present in 661 (14%) of cases.

The cause of death was cardiovascular in 41 patients (38.3%),cardiac in 36 (33.6%) and vascular in 5 (4.7%), non-cardiovascular in 36 patients (33.6%) and unknown in the remaining 30 (28.1%) patients. The main cause of cardiovascular death was heart failure (21 patients, 51.2%), followed by myocardial infarction (7 patients, 17.1%), arrhythmias (5 patients, 12.2%) and haemorrhagic stroke (3 patients, 7.3%).

Among the 4775 patients with follow-up data on clinical events available, a hospitalization occurred in 523 (11.0%) and in 231 (4.8%) patients, for cardiovascular and non-cardiovascular causes, respectively. The single reasons for hospitalization from enrollment to follow-up are shown in **Figure 2**. The main established causes of hospital admission were myocardial revascularization [223 patients, 4.7% of cases: 186 (3.9%) PCI and 37 (0.8%) CABG], stable angina (81 patients, 1.7%), and heart failure (80 patients, 1.7%) followed by arrhythmias (65 patients, 1.4%).

Pharmacologic treatment

Among the 4654 patients with follow-up visit, the majority of patients were prescribed on statins (4318, 93%), aspirin (3999, 86%), beta-blockers (3604, 77%) or angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) (3533, 76%),

while drugs for angina relief were used in a minority of cases (**Figure 3**). Changes in drugs prescriptions from enrollment to follow-up are depicted on **Figure 4**. The rate of patients with novel prescriptions of aspirin, dual antiplatelet therapy (DAPT), ACE-inhibitors, nitrates (all $p<0.0001$) and statins ($p=0.0004$) significantly decreased from enrollment to follow-up, while oral anticoagulation therapies were *de novo* prescribed more frequently ($p=0.005$) at follow-up.

Out of the 3239 patients with clinical visit/telephone interview at follow-up in whom OMT (aspirin or thienopyridine, β-blocker, and statin) was prescribed at enrollment, 2971 (91.7%) were still receiving OMT at follow-up. At multivariable analysis, only increasing age (OR 0.98; 95% CI 0.97-0.99; $p=0.04$) resulted as independent negative predictors of OMT persistence at 1 year from enrolment (Table 2).

Notably, several variables resulted as independent predictors of death and/or hospitalization for cardiovascular causes at follow-up on multivariable analysis (Table 3).

Quality of Life Assessment

The EQ 5D-5L questionnaire was completed at follow-up by 3838 patients. The median (IQR) VAS score of self-rated general health status was 80 (65-90).

Over 60% of patients reported as "no problems" in all EQ-5D-5L domains (61.4-84.5%). The single domains with the 5 levels of severity on each domain are represented in **Figure 5**.

Among the 3735 patients with EQ 5D-5L questionnaires available at both enrolment and follow-up, the rate of severe/extreme problems at 1 year significantly increased for movement ability (2.1% vs 1.5%, $p=0.04$), and for body care (1.1% vs 0.6%, $p=0.04$), and decreased for pain/warry (1.0% vs 1.6%, $p=0.03$), and for anxiety/depression (1.2% vs 1.9%, $p=0.01$) domains, compared to the time of enrolment.

DISCUSSION

The 1-year follow-up of this nationwide, contemporary, prospective registry of unselected stable CAD patients enrolled in 183 cardiology centers in Italy suggested that: 1. the rate of clinical events was high and mainly driven by cardiovascular death or hospitalizations; 2. the number of prescriptions of OMT slightly declined in 1 year and was negatively associated with the occurrence of cardiovascular hospitalizations, renal dysfunction and advanced age; 3. the quality of life of this high risk population appeared reasonable and fairly stable over time.

In our cohort, we observed a high rate of clinical events at 1-year follow-up: 2.2% of our patients died of any cause, approximately 40% due to cardiovascular causes, and 16% of patients was hospitalized, mainly for cardiac reasons. These rates should probably be ascribed to the high prevalence of prior MI patients in our population, as in other contemporary observational studies. In the REACH (REduction of Atherothrombosis for Continued Health) registry, the rate of all-cause mortality was 2.8%/year in patients with established cardiovascular disease and the annual rate of cardiovascular events or hospitalization was 15% (4). Accordingly, the rate of all-cause death at 2 years in patients with stable CAD was approximately 3.5% in the CLARIFY (prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) registry (5). Recently, in the CICD (Chronic Ischaemic Cardiovascular Disease) Pilot Registry that enrolled 2420 stable CAD patients in 100 centers across 10 European countries, the rate of mortality and hospitalization at 6 months was 2.6% and 22%, respectively (10). Our data therefore confirm that a population with a broad spectrum of stable CAD is at very high cardiovascular risk and should be carefully followed up.

One of the reasons supposed for explaining this high rate of cardiovascular events in both short- and long-term follow-up may be ascribed to the poor adherence to pharmacological therapies recommended by the current international guidelines (1,2). These guidelines suggest the use of pharmacological strategies that have proven to improve the quality of life and/or survival in stable

CAD and define a common OMT comprising oral antiplatelets, β-blockers and statins (1,2). In our cohort, although the rate of OMT at enrollment was suboptimal (11), an OMT persistence was observed in about 92% of patients at 1 year, a high rate compared to other contemporary international registries (4-7,14,15). A reason for this high percentage of OMT at follow-up may be ascribed to the fact that our patients have all been managed by a cardiologist, possibly increasing patient awareness to the importance of each prescribed drug. Furthermore, in our study the adherence was directly ascertained by investigators, as opposed to use of administrative data sets which is a limitation of prior studies.

In our analysis, increasing age resulted as independent negative predictor of OMT persistence, a variable associated with medications withdrawal over time (1-3). For elderly patients, educational programmes to improve adherence to recommended therapies and follow-up procedures should be promoted by scientific societies and/or healthcare systems. We observed a decrease in the rate of patients on nitrates, statins, ACE inhibitors and antiplatelet agents (especially DAPT) at follow-up, respect to the enrollment. This finding could be ascribed to several factors such as costs of medication, access to healthcare, insufficient patient education or the reduction in the rate of angina at follow-up, as documented on EQ 5D-5L questionnaire. This latter may explain the lower use of long-acting nitrates, emerged as not evidence-based for the prolonged angina prophylaxis (2). In addition, the benefit of ACE inhibitors on clinical outcomes has recently been questioned in stable CAD without heart failure and outside post-myocardial infarction (16). In contrast to the recently published European registry (13), we did not find a significant decrease in the rate of prescription of beta-blockers although their role has also been recently disputed in stable CAD (17). On the other hand, we noted a reduction in the rate of prescription of statins that have shown a protective effect on cardiovascular events (18). Finally, the reduction in DAPT prescription over time may be partly due to the fact that we included

patients with recent ACS in whom DAPT was progressively withdrawn, in accordance with current guidelines (19) and contemporary real-world studies (20).

Quality of life assessment has been recognized as an essential measure in stable CAD. In the Euro Heart Survey, that enrolled 3779 consecutive patients with stable angina, around 60% of patients were moderately/severely limited in their daily activities at the time of diagnosis (6). Our study population included patients with or without angina, that exerts a significant impact on quality of life assessment (21). The quality of life profile of our patients improved after 1 year in terms of angina and depression, two important features in this subgroup of patients that have been demonstrated to reduce drug adherence and to worsen clinical outcomes during follow-up (22-24).

Study Limitations

Our study must be evaluated in the light of the known limitations of observational, cross-sectional studies. Although the participating centers were asked to include in the registry all consecutive patients with stable CAD, we were not able to verify the enrolment process, due to the absence of administrative auditing. However, we believe that it is unlikely that selective enrolment in few sites may have substantially changed the study results.

In addition, we did not collect data on vital status at follow-up in 5.5% of patients enrolled in our registry. Loss of these patients might have led to an overestimation of adherence in the study since those who completed the follow-up could have been more adherent to prescribed therapies.

Finally, we did not collect data on lifestyle modifications and the dosage of all prescribed drugs. For this reason, we only assessed the adherence to therapies recommended by guidelines and its persistence at follow-up, but we could not evaluate the intensity of treatment or the achievement of therapeutic targets.

CONCLUSIONS

In this nationwide, contemporary registry, stable CAD patients managed by cardiologists presented a high rate of clinical events at 1-year follow-up. Although the pharmacological management remains suboptimal, the persistence to OMT and quality of life appeared reasonable and stable over time.

The present data confirm the high residual risk of this population and should stimulate efforts to better identify and manage patients at higher hazard for cardiovascular events within the large spectrum of stable CAD.

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Conflicts of interest

Dr. De Luca and Dr. Temporelli report personal fees from Menarini, outside the submitted work; All other authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Gonzini is an employ of Heart Care Foundation, which conducted the study with an unresctricted grant of research from Menarini, Italy.

Contributors

LDL and PLT drafted the manuscript; CR, LM, ST, PC, MS, MSe, FC and MMG revised it critically; LG analysed the data. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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FIGURE LEGEND

Figure 1. Patient flow chart.

Figure 2. Main causes of hospitalizations during follow-up.

ACS: acute heart failure; HF: heart failure; ICH: intracranial hemorrhage

Figure 3. Pharmacological therapies[†] at follow-up, among the 4654 patients with clinical visit/telephone interview at follow-up.

[†]Drugs not reported have been used in less than 1% of cases.

ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; MRA: mineralocorticoid receptor antagonist; OAT: oral anticoagulation therapy

Figure 4. Rates of pharmacological therapies[†] prescribed at enrollment but not at follow-up (heavenly bars) or prescribed at follow-up but not at enrollment (white bars), among the 4654 patients with clinical visit/telephone interview at follow-up.

[†]Drugs not reported have been used in less than 1% of cases.

Figure 5. Single domains of EQ 5D-5L questionnaire at follow-up, among the 3838 patients with questionnaire completed at follow-up (clinical visit/telephone interview).

Appendix

Steering Committee

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Table 1. Baseline clinical characteristics and haemodynamic parameters of stable CAD patients at follow-up.

	n=4790
Age, years (mean±SD)	68±11
Age >75 years, n (%)	1205 (25.2)
Females, n (%)	953 (19.9)
BMI, kg/m^2 (mean±SD)[#]	27.3±4.0
Active smokers, n (%)	833 (17.4)
Hypercholesterolemia, n (%)	3594 (75.0)
Diabetes mellitus, n (%)	1468 (30.7)
Hypertension, n (%)	3811 (79.6)
Chronic renal dysfunction, n (%)	569 (11.9)
Peripheral artery disease, n (%)	432 (9.0)
COPD, n (%)	561 (11.7)
Malignancy, n (%)	313 (6.5)
Depression, n (%)	487 (10.2)
Previous stroke/TIA, n (%)	264 (5.5)
History of major bleeding events, n (%)	89 (1.9)
History of heart failure, n (%)	642 (13.4)
Prior STEMI, n (%)	1725 (36.0)

Prior NSTE-ACS, n (%)	1720 (35.9)
Previous myocadial revascularization, n (%)	3746 (78.2)
SBP, mmHg (mean±SD)[§]	130±16
HR, bpm (mean±SD)	66±11
Atrial fibrillation, n (%)	661 (13.8)

[#] available for 4784 patients; [§]available for 4788 patients

BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; HR: heart rate; MI: myocardial infarction; NYHA: New York Heart Association; SBP: systolic blood pressure; NSTE-ACS: Non ST-elevation ACS; STEMI: ST-elevation myocardial infarction; TIA: transient ischemic attack.

Table 2. Multivariable analysis on OMT persistence at follow-up

Variable	P	OR	95% ci
Female gender	0.411	1.173	0.689 - 1.996
Age (continuous)	**0.038**	**0.986**	**0.973 - 0.999**
SBP (continuous)	0.429	1.003	0.995 - 1.011
HR (continuous)	0.527	0.996	0.984 - 1.008
hypertension	0.820	0.958	0.551 - 1.665
hypercholesterolemia	0.216	1.262	0.786 - 2.028
diabetes mellitus	0.407	1.150	0.724 - 1.827
renal insufficiency	0.126	0.655	0.346 - 1.241
chronic obstructive pulmonary disease	0.703	1.098	0.540 - 2.234
peripheral artery disease	0.492	0.840	0.411 - 1.713
ejection fraction <40% vs ≥40%	0.476	0.817	0.426 - 1.567
ejection missing vs ≥40%	0.886	1.034	0.595 - 1.799
history of heart failure	0.597	1.147	0.547 - 2.407
prior revascularization	0.215	1.298	0.765 - 2.204
prior ST-elevation myocardial infarction	0.982	1.003	0.642 - 1.568
prior stroke/transient ischemic attack	0.629	1.176	0.450 - 3.071
prior angina	0.578	0.909	0.557 - 1.482
hospitalization for cardiac and/or vascular reasons occurred from enrolment to follow-up: yes vs no	0.066	0.657	0.415 - 1.039
hospitalization for cardiac and/or vascular reasons occurred from enrolment to follow-up: unknown vs no	0.494	1.465	0.406 - 5.293

HR= heart rate (bpm); SBP=systolic blood pressure (mmHg)

Table 3. Multivariable analysis on death and/or hospitalization for cardiovascular causes at follow-up.

Variable	P	OR	95% ci
Female gender	0.854	1.024	0.699 - 1.501
Age (continuous)	0.891	0.999	0.989 - 1.009
SBP (continuous)	0.583	0.998	0.993 - 1.004
HR (continuous)	0.058	0.992	0.983 - 1.000
hypertension	0.537	1.095	0.723 - 1.658
hypercholesterolemia	0.999	1.000	0.699 - 1.429
diabetes mellitus	0.953	1.007	0.726 - 1.396
renal insufficiency	**0.017**	**1.869**	**1.233 - 2.832**
chronic obstructive pulmonary disease	0.681	1.064	0.687 - 1.650
peripheral artery disease	**0.036**	**1.659**	**1.066 - 2.583**
ejection fraction <40% vs ≥40%	**0.015**	**1.714**	**1.158 - 2.536**
ejection missing vs ≥40%	0.152	0.737	0.467 - 1.162
history of heart failure	**0.014**	2.**059**	**1.318 - 3.215**
prior revascularization	0.372	1.145	0.759 - 1.726
prior ST-elevation myocardial infarction	0.741	0.963	0.690 - 1.344
prior stroke/transient ischemic attack	0.737	1.071	0.592 - 1.938
prior angina	**0.016**	**1.719**	**1.216 - 2.430**
OMT persistence at follow-up	0.069	0.764	0.561 - 1.040

HR=heart Rate (bpm); OMT=optimal medical therapy; SBP=systolic blood pressure (mmHg);

Figure 1

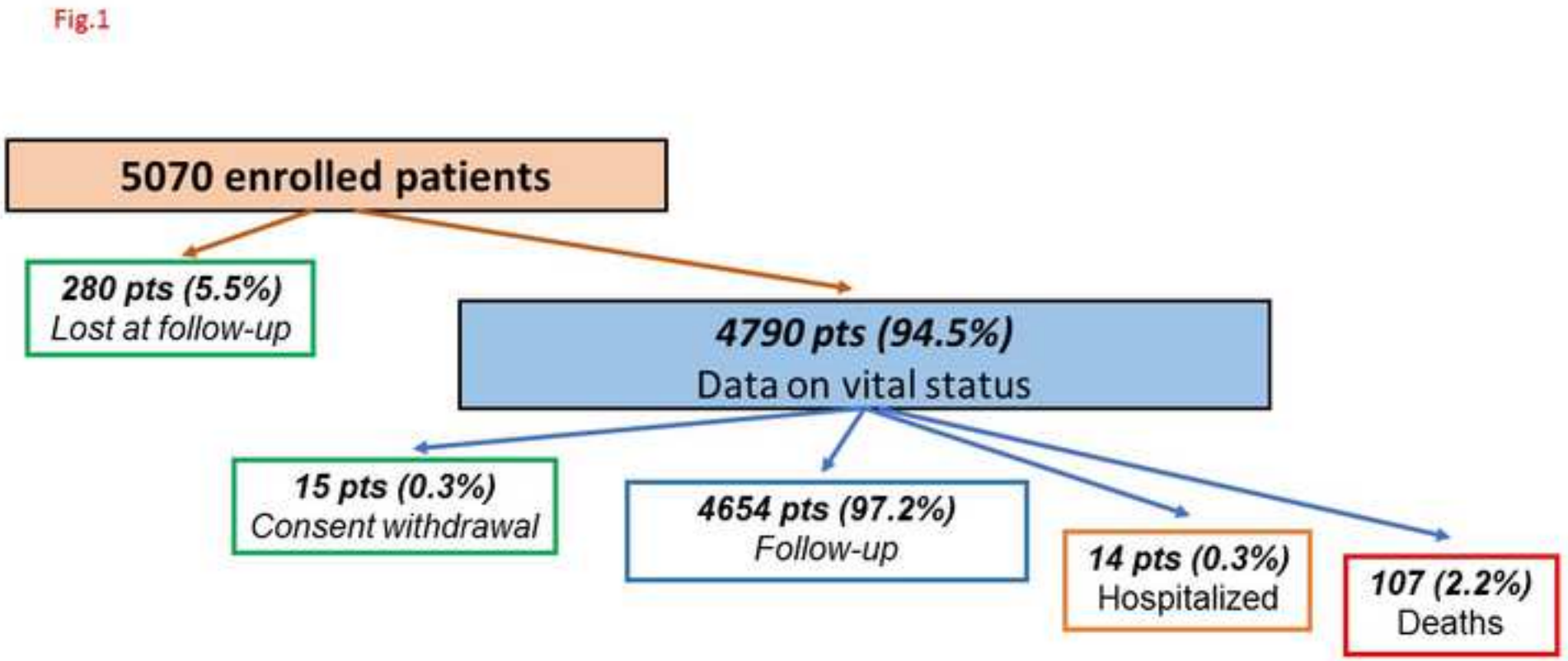

Figure 2

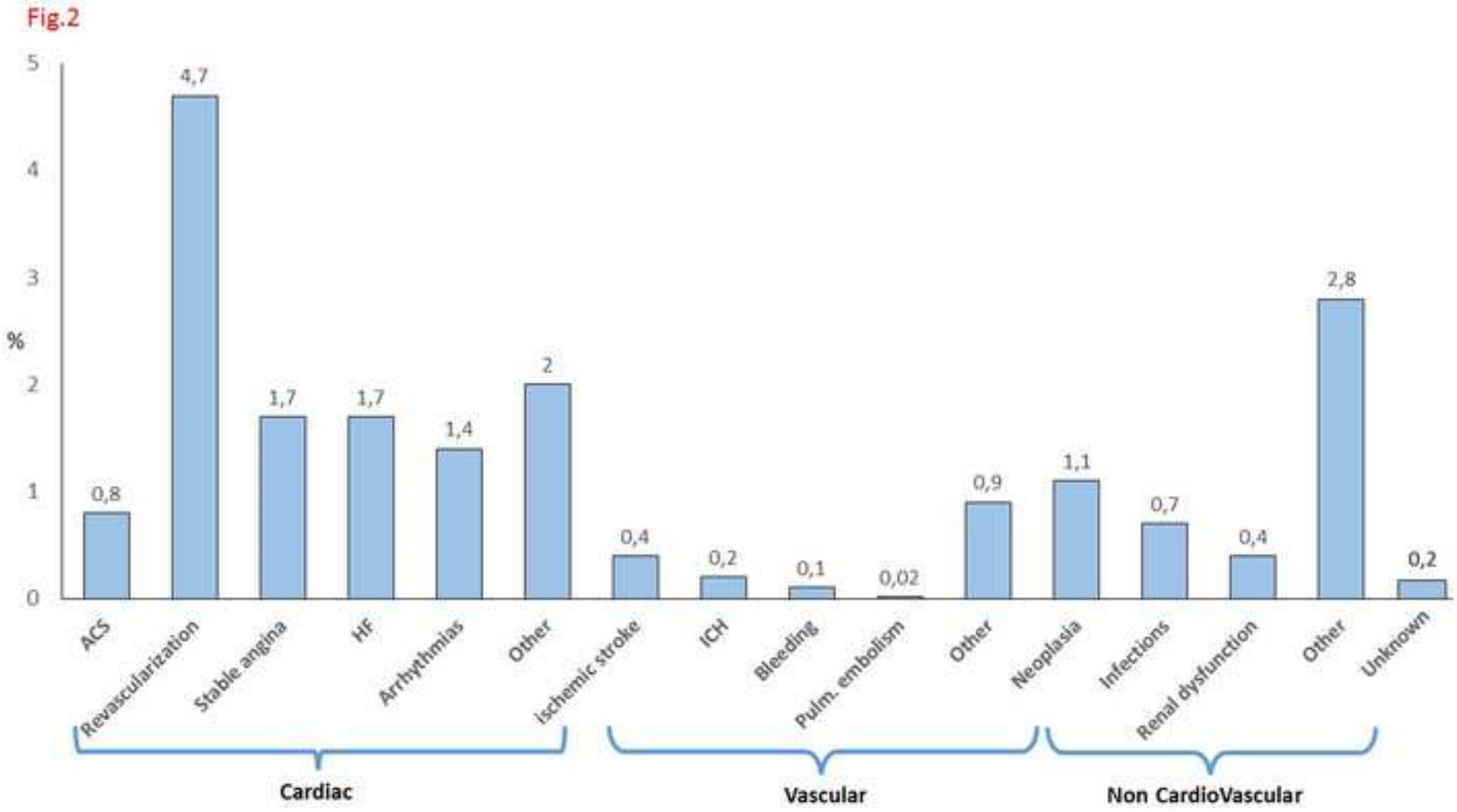

Figure 3

Fig.3

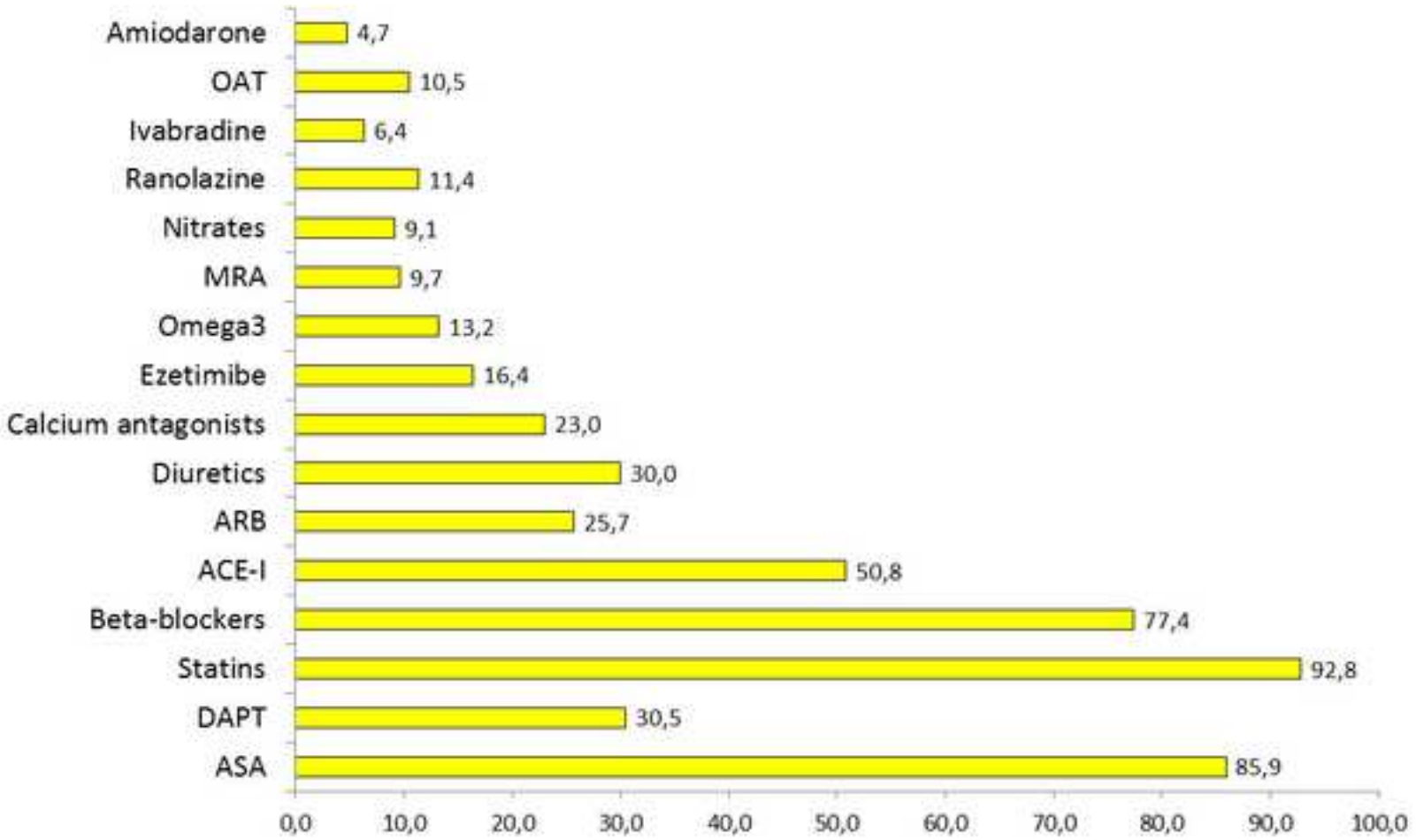

Figure 4

Fig.4

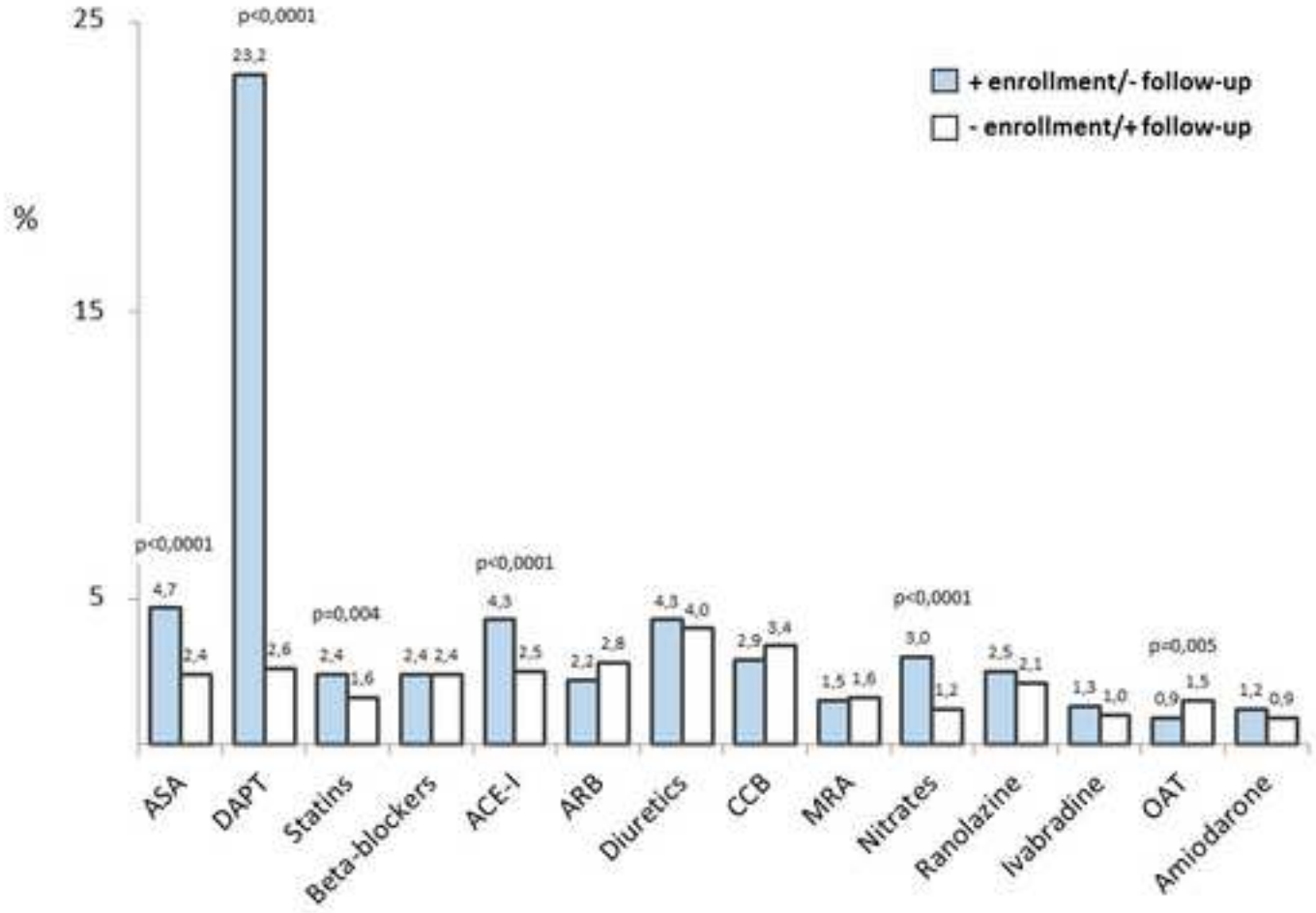

Figure 5