FIRST-LINE ANTI-ISCHEMIC AGENTS FOR STABLE CORONARY ARTERY DISEASE: INSIGHTS FROM CLARIFY

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Over the last decades, with the advent of primary reperfusion therapy, evidence-based secondary prevention medication, and new diagnostic tools, the profile of patients with coronary artery disease and their prognosis have changed considerably. However, little is known about the demographics, characteristics, and prognosis of contemporary patients with stable coronary artery disease.

The CLARIFY registry (ISRCTN43070564) was built to be a useful resource for understanding the current epidemiology of stable coronary artery disease. Some results were presented at the 2018 ESC congress in Munich, especially an analysis on "First-line anti-ischemic agents use and long-term clinical outcomes in stable coronary artery disease. Insights from the CLARIFY study," which was presented by Sorbets E for Steg PG, Young R, et al.

THE CLARIFY REGISTRY

The rationale and methods were described previously.[1] Briefly, between November 2009 and June 2010, 32703 patients with stable coronary artery disease were enrolled in 45 countries by 2898 practitioners (general practitioners and specialists) from rural, suburban, and urban areas. Each physician screened consecutive outpatients in order to enroll 10 to 15 participants.

In order to enroll patients representative of several aspects of contemporary stable coronary artery disease, participants had to meet at least one of the following inclusion criteria: prior MI >3 months, prior revascularization by percutaneous coronary angioplasty or coronary artery bypass graft >3 months, chest pain with proven myocardial ischemia, or coronary angiography showing at least one coronary stenosis >50%. Exclusion criteria were conditions that could interfere with follow-up or life expectancy, including cancer or severe heart failure. Follow-up was done by clinicians yearly up to 5 years. Medical care was at the discretion of each physician. To ensure data quality, every year, 1% of the sites were randomly

selected for onsite audits. At these sites, 100% of the data for all patients were audited for source documentation and accuracy. All patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and local ethical approval was obtained in each country.

The CLARIFY registry was supported by Servier. The sponsor had no role in the study design, data analysis, and interpretation, or in the decision to submit the manuscript for publication, but assisted with the set-up, data collection, and management of the study in each country. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

ASSESSMENT OF THE USE OF FIRST-LINE, ANTI-ISCHEMIC AGENTS

This study was a post-hoc analysis of CLARIFY that was designed to assess the association between β-blockers or calcium antagonists and outcomes in patients with contemporary stable coronary artery disease. Indeed, there is still uncertainty about the benefit of β-blockers in such patients without an impaired left ventricular ejection fraction: the use of β-blockers in patients with stable coronary artery disease is only derived from old randomized clinical trials performed in the acute MI or postacute MI phase, mainly before the start of primary reperfusion therapy. Recently, some registries raised the question of their benefit is patients with stable coronary artery disease. Regarding calcium antagonists, randomized clinical trials that did not enroll contemporary patients failed to demonstrate a beneficial effect on mortality and there is no large registry investigating this drug class in patients with stable coronary artery disease.

Considering this need for contemporary data, two nonmutually exclusive analyses were performed over the CLARIFY registry: one according to β-blocker use at baseline and one according to calcium antagonist use at baseline. Analyses were restricted to patients where all available data were entered in a large, multivariable, adjustment model accounting for cardiovascular risk factors, burden of the cardiovascular disease (including left ventricular ejection fraction, history of heart failure, atrial fibrillation or coronary revascularization, number of involved vascular beds, etc), treatments (aspirin and statins), geographical zones, and pulmonary comorbidities. Some of these potential confounders were summarized by the REACH cardiovascular event risk score entered in the model.[2]

The primary outcome was all-cause death and the secondary outcomes were cardiovascular death and the composite of cardiovascular death or MI. Some sensitivity analyses assessed the use of anti-ischemic agents over time, considering the last available data from the yearly follow-up. Other sensitivity analyses assessed the daily doses of β-blockers.

BASELINE CHARACTERISTICS

β-Blocker users

The analysis of β-blocker use could be performed after multivariable adjustment with no missing data in 22 004 patients from the 32 703 enrolled in CLARIFY. At baseline, more than three-quarters received a β-blocker, mainly bisoprolol (35.6%), metoprolol (27.2%), carvedilol (12.6%), atenolol (12.3%), and nebivolol (6.5%), but only 13.3% received the full β-blocker dose. Among patients not receiving a β-blocker, 39.6% did not receive them due to symptoms of intolerance or contraindication, mainly asthma/chronic obstructive pulmonary disease or bradycardia. Compared with those not receiving a β-blocker, those receiving a β-blocker were younger, with more cardiovascular risk factors, a larger history of prior MI, less peripheral artery disease, less asthma, and more angina symptoms. They had a lower left ventricular ejection fraction and received more secondary prevention therapies. Despite these differences in baseline characteristics, these groups had a similar theoretical cardiovascular risk as assessed by the REACH cardiovascular risk score.

Calcium antagonist users

The analysis of calcium antagonist use could be performed in 22 006 patients from the 32 703 enrolled in CLARIFY. At baseline, nearly one-quarter received calcium antagonists, mainly dihydropyridines (79.8%). Compared with those not receiving a calcium antagonist, those receiving calcium antagonists were older, with more cardiovascular risk factors, a lower history of prior MI, more peripheral artery disease, and more angina symptoms. They had a higher left ventricular ejection fraction and did not receive more secondary prevention therapies. Despite these differences in baseline characteristics, these two groups had a similar REACH cardiovascular risk score, which was comparable with the β-blocker study cohorts.

CLINICAL OUTCOMES

β-Blocker use

According to β-blocker use at baseline and after multivariable adjustment, there was no difference in the risk of all-cause death (HR for use, 0.94; 95% CI, 0.84-1.06), cardiovascular death (HR, 0.91; 95% CI, 0.79-1.05), or cardiovascular death and MI (HR, 1.03; 95% CI, 0.91-1.16). In the subset of patients with a history of MI ≤1 year prior to enrollment, β-blocker use at baseline was associated with a risk reduction in all-cause death (205 events [7.0%] for users vs 59 [10.3%] for nonusers; HR, 0.68; 95% CI, 0.50-0.91; *P*=0.01), driven by a risk reduction in cardiovascular death (132 events [4.5%] for users vs 49 [8.5%] for nonusers; HR, 0.52; 95% CI, 0.37-0.73; *P*=0.0001) and a risk reduction in cardiovascular death and MI (212 events [7.2%] for users vs 59 [10.3%] for nonusers; HR, 0.69; 95% CI, 0.52-0.93; *P*=0.01). In patients

enrolled beyond 1 year after a MI, between 1 and 3 years as well as over 3 years, there was no difference in the risk of all outcomes.

For the sensitivity analyses, regarding treatment use over time, the results were consistent with no difference in the risk of outcomes. Regarding doses at baseline and after categorization by less than a half dose, half to less than a full dose, and a full dose, the event risks were not modified by dose levels, regardless of the outcomes.

Calcium antagonist use

According to calcium antagonist use at baseline and after multivariable adjustment, there was no difference in the risk of all-cause death (HR for use, 1.02; 95% CI, 0.91-1.13), cardiovascular death (HR, 1.01; 95% CI, 0.88-1.16), or cardiovascular death and MI (HR, 1.05; 95% CI, 0.94-1.17). There was no difference in the risk of all outcomes, regardless of the time elapsed since the MI prior to enrollment, by 1 year, between 1 and 3 years, and over 3 years.

DISCUSSION

In this large, international, contemporary registry of patients with stable coronary artery disease, with a high level of evidence-based secondary prevention therapies, and after a large multivariable adjustment, including left ventricular ejection fraction, β-blocker use was associated with a reduction in 5-year mortality, which was driven by a reduction in cardiovascular mortality, but only in patients with a prior MI ≤1 year. In stable patients without a history of MI or with a prior MI >1 year, β-blocker use was not associated with a reduction in mortality. Calcium antagonist use was not associated with a better prognosis regardless of the clinical profile and the history of MI.

These results are consistent with prior registries (REACH,[3] FAST MI,[4] Kaiser Permanente database,[5] and the French health care database[6]) that had some limitations addressed in the present study. CLARIFY was not restricted to a single area, collected left ventricular ejection fraction value, and, for β-blockers, the daily doses and the reasons for not using them. Of course, there were some limitations to this study. Outcomes were not adjudicated. However, it is interesting to highlight that the results were consistent for nonadjudicated outcomes and for all-cause mortality. Even after a large multivariable adjustment, residual confounding data from measured or unmeasured variables cannot be excluded (in particular as relates to indication bias). Thus, randomized controlled trials are needed to confirm these results. A large, powered randomized trial would be required to settle the issue of whether first-line anti-ischemic agents affect prognosis and outcomes in patients with stable coronary artery disease. However, it is uncertain whether it would be feasible to mobilize the resources and obtain the patient numbers that are to address this question adequately.

CONCLUSION

Combined with the previous literature, the present analysis suggests that, in contemporary coronary artery disease, β-blockers should be preferentially used in the year following the MI. Beyond 1 year after the MI or in patients with stable coronary artery disease without a previous MI, both β-blockers and calcium antagonists may be used for symptom relief, but do not appear to be associated with a survival benefit. ■

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