Special Article

Evidence-Based Therapy Prescription in High-Cardiovascular Risk Patients: The REACT Study

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Abstract

Background: **Data on outpatient care provided to patients at high cardiovascular risk in Brazil are insufficient.**

Objective: **To describe the profile and document the clinical practice of outpatient care in patients at high cardiovascular risk in Brazil, regarding the prescription of evidence-based therapies.**

Methods: **Prospective registry that documented the ambulatory clinical practice in individuals at high cardiovascular risk, which was defined as the presence of the following factors: coronary artery disease, cerebrovascular and peripheral vascular diseases, diabetes, or those with at least three of the following factors: hypertension, smoking, dyslipidemia, age > 70 years, family history of coronary artery disease, chronic kidney disease or asymptomatic carotid artery disease. Basal characteristics were assessed and the rate of prescription of pharmacological and non-pharmacological interventions was analyzed.**

Results: **A total of 2364 consecutive patients were included, of which 52.2% were males, with a mean age of 66.0 years (± 10.1). Of these, 78.3% used antiplatelet agents, 77.0% used statins and of patients with a history of myocardial infarction, 58.0% received beta-blockers. Concomitant use of these three classes of drugs was 34%; 50.9% of hypertensive, 67% of diabetic and 25.7% of dyslipidemic patients did not achieve the goals recommended by guidelines. The main predictors of prescription therapies with proven benefit were centers with a cardiologist and history of coronary artery disease.**

Conclusion: **This national and representative registry identified important gaps in the incorporation of therapies with proven benefit, offering a realistic outlook of patients at high cardiovascular risk (Arq Bras Cardiol. 2013;100(3):212-220).**

Keywords: **Cardiovascular Diseases / mortality; Review, Cross-Sectional Studies; Risk Factors; Drug Prescriptions; Randomized Controlled Trials as Topic.**

Introduction

The projection of the Global Burden of Diseases study[1] for 2020 indicates that cardiovascular diseases remain the leading cause of death and disability, particularly in developing countries. In Brazil, the incidence has been increasing over the years and, in parallel, the expenses devoted to treatment have been progressively increasing, both in the setting of public assistance, as well as private health care[2-4].

Several large randomized trials and systematic reviews have shown that in patients with high cardiovascular risk, the benefit of drugs such as statins extends even to patients with normal cholesterol levels[5]; antiplatelets are capable of reducing major cardiovascular events, even in individuals with no clinical manifestations of atherosclerosis[6] and many antihypertensive drugs, mainly angiotensin-converting enzyme inhibitors (ACEI), have the potential to reduce cardiovascular events, even in patients with no diagnostic criteria for systemic arterial hypertension[7]. Additionally, non-pharmacological interventions, such as cardioprotective diets, smoking cessation and regular physical activity, although the data are less robust than those in studies with pharmacological therapies, are also associated with a reduction in clinically relevant outcomes[8-22].

In view of the importance of using evidence-based therapies for cardiovascular risk reduction, it is essential to assess daily clinical practice. International registries have shown significant gaps in the incorporation of guideline recommendations into the real world. To date, no registry has fully documented Brazilian clinical practice in relation

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to the care of individuals at high cardiovascular risk in a large and representative sample, which contemplated both public and private centers from all regions of Brazil. Thus, the objective of this study was to document the current clinical practice through patterns of prescription of evidence-based interventions in patients at high cardiovascular risk in Brazil.

Methods

The complete methodology of REACT has been previously published[23]. Briefly, this is a cross-sectional observational and prospective registry with longitudinal follow-up of patients, with blinded assessment of outcomes. This project was conceived and coordinated by the Brazilian Cardiology Society (SBC), with the participation of public and private centers from all regions of Brazil, respecting the distribution of population according to data from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística - IBGE). Public and private centers, university and non-university ones, were invited to participate in the study, from both large cities and small towns, which met the minimum requirements of Good Clinical Research Practice.

Study population (eligibility criteria)

We included consecutive individuals of both genders, aged 45 years and older that met at least one of the criteria for high cardiovascular risk classification: coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral vascular disease and diabetes mellitus. It also included patients with at least three risk factors for atherosclerosis: hypertension, smoking, dyslipidemia, age > 70 years, family history of CAD, chronic kidney disease or asymptomatic carotid artery disease. All included patients were outpatients.

We excluded patients with neurocognitive or psychiatric conditions that prevented obtaining reliable clinical data (defined by the investigators' clinical decisions), as well as patients with tumors of unfavorable clinical course.

Outcomes of interest

The primary outcome referring to this analysis was the proportion of patients using evidence-based therapies (defined as concurrent use of antiplatelet agents, statins and ACE inhibitors) during the baseline consultation of the REACT study, considering a minimum prescription rate of 90%.

Other outcomes included: the proportion of patients who received recommendations regarding measures of lifestyle changes (smoking cessation, physical activity and nutrition guidelines) and proportion of patients who received each of the following medications individually during the baseline consultation: statins, antiplatelet agents, ACE inhibitors, beta-blockers (analysis restricted to patients with a history of myocardial infarction) and thiazide diuretics (in hypertensive patients).

Additionally, we calculated the rate of hypertensive and dyslipidemic patients with controlled levels within the recommended therapeutic goals, as recommended by SBC.

Data quality control

The participating centers were trained regarding the study procedures and electronic systems, either in person or by phone, by the coordination team. Data quality control was performed through different strategies, such as use of electronic data capture system, central statistical monitoring of collected variables, sporadic sending of reports containing the status of patients at participating centers and direct check of 10% of the records in five centers with higher recruitment. Additionally 20% of the medical records from 20% of the remaining centers were checked after being chosen randomly within each national demographic region.

Finally, biannual meetings were held in order to update their status and discuss, among participating researchers, relevant points of the registry.

Sample size calculation

In order to detect a proportion of 40% for the occurrence of the primary outcome, considering a sampling error of 2%, a two-sided alpha of 5% and a statistical power of 90% were required, thus resulting in the inclusion of at least 2,305 patients.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation, whereas qualitative variables were expressed as absolute and relative frequencies. The primary and secondary outcomes were described by estimates weighted by the number of patients at each center, which ranged from 3 to 213. The assessment of the association between concomitant use of antiplatelet agents, statins and ACE inhibitors and factors such as gender, age, region, specialty and type of center was performed using a multiple logistic regression model. The results of model adjustment were shown as odds ratios (OR) and 95% confidence intervals (95%CI). All analyses were performed with the statistical software Statistical Package for Social Science (SPSS), release 16.0 (SPSS Inc., Chicago, IL, USA) and R 2.13 (R Development Core Team, 2011, http://www.R-project.org/.), considering two-tailed significance level of 5%.

Ethical and good clinical practice aspects

The protocol was approved by the Research Ethics Committee (REC) of Hospital do Coração de São Paulo, in São Paulo (SP), on June 22, 2010 under registration number 118/2010 and subsequently, each participating center also had its local approval. All patients signed a free and informed consent form, and the trial was carried out according to the principles of the current review of the Declaration of Helsinki and Good Clinical Practice Guidelines, in its latest version, as well as Edict 196/96.

Results

A total of 2,403 patients were enrolled at 45 centers between July 2010 and December 2011 and this analysis included only patients with complete baseline data, totaling 2,364 patients. Of this sample, 60.3% were from the Southeast, 26.1% from the South, 9.3% from the Northeast, 2.7% from the North and 1.6% from the Midwest.

The care profile of these patients showed a predominance of mixed institutions (40.5%), followed by Supplemental Health Institutions (31%) and, finally, 28.6% that belonged to the Brazilian Unified Health System (SUS), as shown in Figure 1. Most patients were recruited from centers specialized in cardiology (84.6%); patients were also recruited from primary care centers (6.8%), endocrinology (2.3%), nephrology (2.3%) and internal medicine (2.3%) departments.

Sociodemographic characteristics

Table 1 shows the sample sociodemographic characteristics. In this sense, of the 2,364 patients studied, mean age was 66.0 ± 10.1 years, 55.2% were males, 68.4% self-reported as being Caucasian, 7.8% were illiterate and 73.9% had a body mass index (BMI) ≥ 25. Among the cardiovascular risk factors, the most prevalent was hypertension (92.1%), followed by dyslipidemia (75.3%).

Prescription of lifestyle change measures

Figure 2 shows the frequency of recommendations regarding changes in lifestyle. Of the patients included, 83% received formal recommendations about diet, 77.5% on the benefits of physical activity and 77.1% on the risks of smoking.

Evidence-based drug-therapy prescription

Of the 2,364 patients analyzed, 78.3% received antiplatelet agents, 77.0% statins and 53.0% ACE inhibitors. Among the 681 patients with a history of myocardial infarction, 79.4% received beta-blockers (Figure 3).

The combined use of antiplatelet agents, statins and ACE inhibitors was observed in 34% of patients, with a higher frequency of use (40.1%) in 1,249 patients with CAD, when compared to other categories of high cardiovascular risk (Figure 4).

Cardiovascular risk factor control according to guideline-established goals

Regarding the attainment of goals determined by SBC guidelines, we observed that in 51.2% of 1,328 diabetic patients, blood glucose levels were higher than the recommended ones. In relation to hypertension control, 50.9% of 2,180 patients were hypertensive, with blood pressure levels higher than a usual blood pressure of 140/90 mmHg. Finally, regarding lipid goals recommended for patients at high cardiovascular risk, about 20% to 30% of the sample had LDL levels ≥ 100 mg/dL (Figure 5).

Predictors of evidence-based pharmacological therapy prescription

A multivariate logistic regression was performed to assess independent factors associated with increased likelihood of prescription of evidence-based therapies (defined for this analysis as the combined use of aspirin, statins and ACE inhibitors). Accordingly, among the independent predictors, we highlight the service performed by a cardiologist (OR = 1.42, 95% CI: 1.10 - 1.82) and CAD diagnosis (OR = 1.91, 95% CI: = 1.59 - 2.30) (Figure 6).

Discussion

Main findings

The REACT study represents the largest and most recent national registry, coordinated by a medical society and involving patients at high cardiovascular risk treated in an outpatient setting, from all regions of the country. The main finding of this study refers to the fact that risk factor control (according to guideline goals for LDL, blood pressure and blood glucose levels) is lower than the expected and that there are opportunities for improvement in clinical practice,

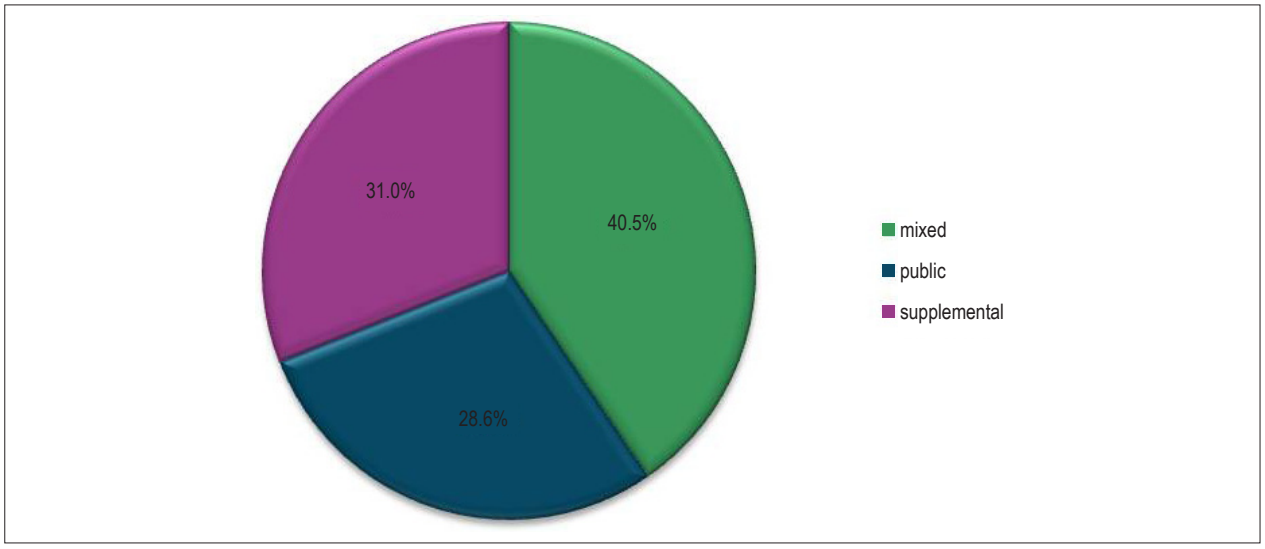

Figure 1 - *Assistance care profile. Analysis considering a total of 2,364 patients.*

Table 1 - Basal characteristics

Basal characteristics	All (n = 2.364) n (%)
Age (years)	66.0 ± 10.1
Male gender	1.234 (52.2)
Ethnicity	
White	1.616 (68.4)
Black	294 (12.4)
Mulatto	424 (17.9)
Body mass index	
≥ 25	1.747 (73.9)
Eligibility criteria	
CAD	1.248 (52.2)
Previous acute myocardial infarction	681 (28.8)
Cerebrovascular accident	295 (12.5)
Diabetes	1.327 (56.1)
Peripheral disease	268 (11.3)
Multiple risk factors	1.342 (56.8)
Hypertension	2.178 (92.1)
Dyslipidemia	1.781 (75.3)
Diabetic nephropathy	167 (7.0)
Age > 70 years	856 (36.2)
Smoking	236 (10.0)
Family history of CAD	975 (41.2)
Asymptomatic carotid disease	229 (9.7)
BP	
Systolic	132.3 ± 21.2
Diastolic	78.9 ± 12.4
Laboratory assessment	
Total cholesterol (mg/dL)	176.6 ± 46.6
LDL (mg/dL)	100.5 ± 49.7
HDL (mg/dL)	47.3 ± 24.8
Triglycerides (mg/dL)	158.7 ± 118.9
Glycemia (mg/dL)	124.5 ± 50.9
Glycated hemoglobin (%)	7.1 ± 3.5
Creatinine (mg/dL)	1.1 ± 0.7

CAD: coronary artery disease; BP: blood pressure.

especially concerning the prescription of evidence-based interventions and mainly the combined use of statins, antiplatelets and ACEI. Among the factors independently associated with the prescription of evidence-based therapies, we highlight treatment by cardiologists and CAD diagnosis.

Comparison with previous literature

The findings of this study showed that patients at high cardiovascular risk treated at Brazilian centers of excellence have a demographic pattern and are receive treatment similar to those seen in recent registries carried out in North America and Western Europe. In this sense, the most prevalent risk factors in the Brazilian population were hypertension and dyslipidemia, which is consistent with literature. The multicenter REACH study, for instance, reported a prevalence of hypertension and dyslipidemia of 81.3% and 70.4%, respectively, similar to that found in this registry, as well as in similar publications[24].

The adequate control of diabetes mellitus in the REACT study was unsatisfactory, as only 23% of diabetics maintained levels of glycated hemoglobin < 7%, even though these patients have greater cardiovascular risk than non-diabetic ones[25]. The IV Brazilian Guidelines on Dyslipidemia and Atherosclerosis Prevention of the Brazilian Society of Cardiology[26] recommends, for high-risk individuals, the simultaneous start of nonpharmacological measures and treatment with lipid-lowering drugs. The REACT study showed that 88% of patients were instructed on cardioprotective diets and 77% were taking lipid-lowering drugs; however, a minority of dyslipidemic patients undergoing secondary prevention, diabetics, patients with CAD, CVD, or PAD reached levels <100 mg/dL of LDL cholesterol. The L-TAP 2 study, which assessed between 2006 and 2007 approximately 10,000 patients from nine countries with dyslipidemia who used statins, found that 73% had achieved their goals of LDL cholesterol, as defined by national guidelines, with greater control found among low-risk patients (86%), when compared to those at high risk (67%)[26].

Recent international and national studies have shown a gap between guidelines and clinical practice, particularly for those patients at higher risk for the development of cardiovascular events. Data from the PREMISE study[27], carried out by the World Health Organization (WHO) in 2005, which included 10,000 patients in developing countries (one thousand patients from Brazil) showed that only about 30% of patients with high cardiovascular risk who had indication for drug therapy were taking statins and ACE inhibitors and only 80% received antiplatelet agents. These findings are consistent with those from the REACT study, considering that antiplatelet agents, statins and ACE inhibitor prescription rates were 78.3%, 72.6% and 53.0%, respectively. The REACT adds additional information to the findings of the PREMISE study[27] as the latter, in Brazil, was carried out exclusively in the South region. Other observational studies have also demonstrated findings consistent with those from the REACT study in relation to the prescription of evidence-based therapies in the real world. Thus, in the REACH study[24] of 31,195 patients assessed, 72.6% were using statins, 43.3% used ACEI and 69% used antiplatelets. As it included a larger number of Brazilian centers, including non-university centers and centers located in small towns, the REACT study added additional important information regarding the findings of the REACH study. In communities located in developing countries, the gaps are even more significant. The PURE study, which included 153,662 patients from 18 countries (both developed and developing ones), aged between 35 and 75 years, living in urban and rural areas, between January 2003 and December 2009, found even more disturbing numbers. Among the population with CAD, only 25.8% used antiplatelets and 16.7% used statins. When we evaluated only the developed countries, these rates increased to 64.1% and 70.9%, respectively[28].

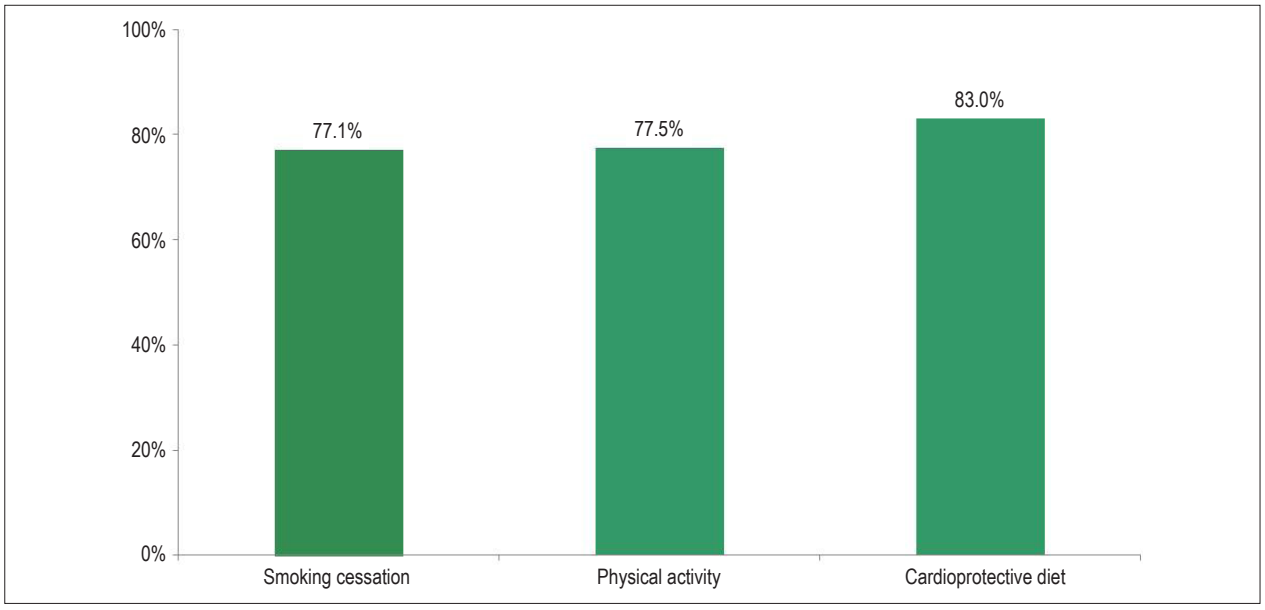

Figure 2 - *Nonpharmacological measures. Analysis considering a total of 2,364 patients.*

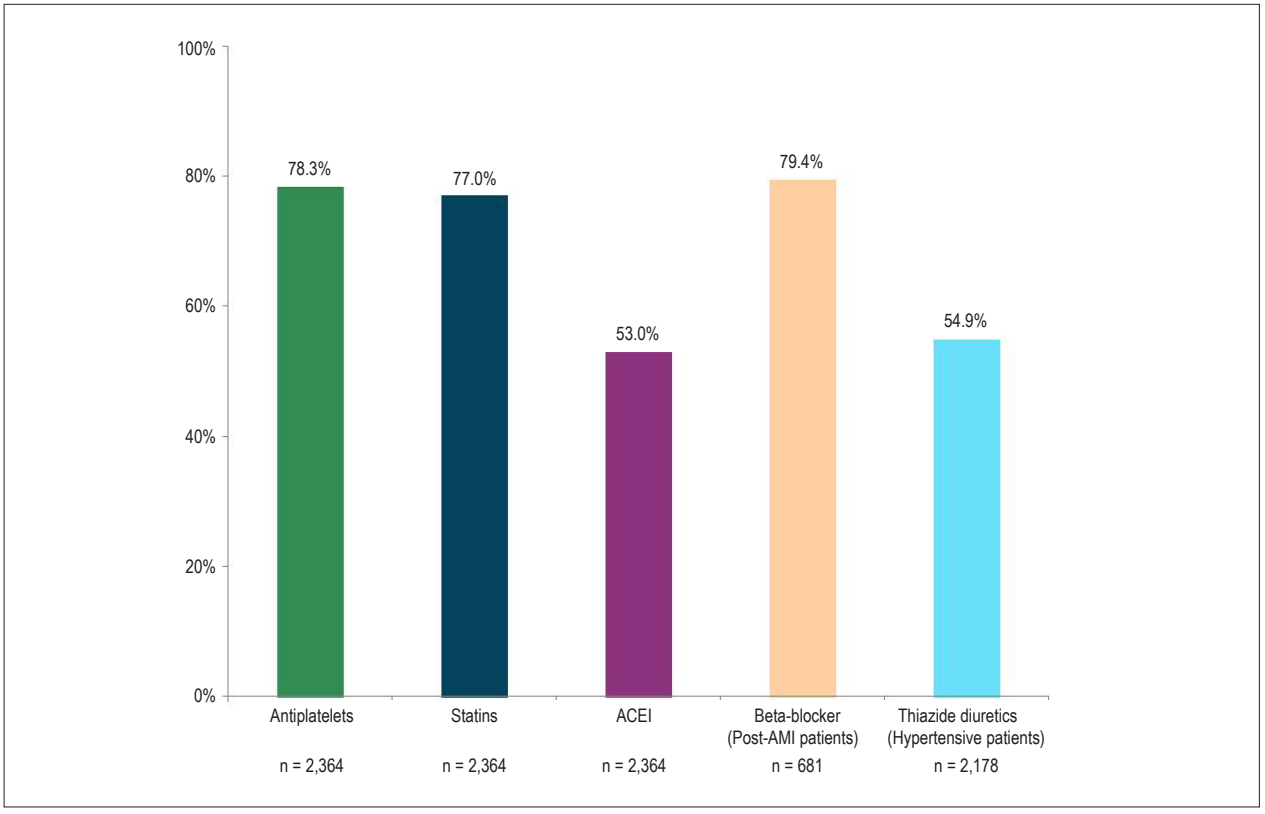

Figure 3 – *Evidence-based drug use. ACEI: angiotensin-converting enzyme inhibitors; AMI: acute myocardial infarction.*

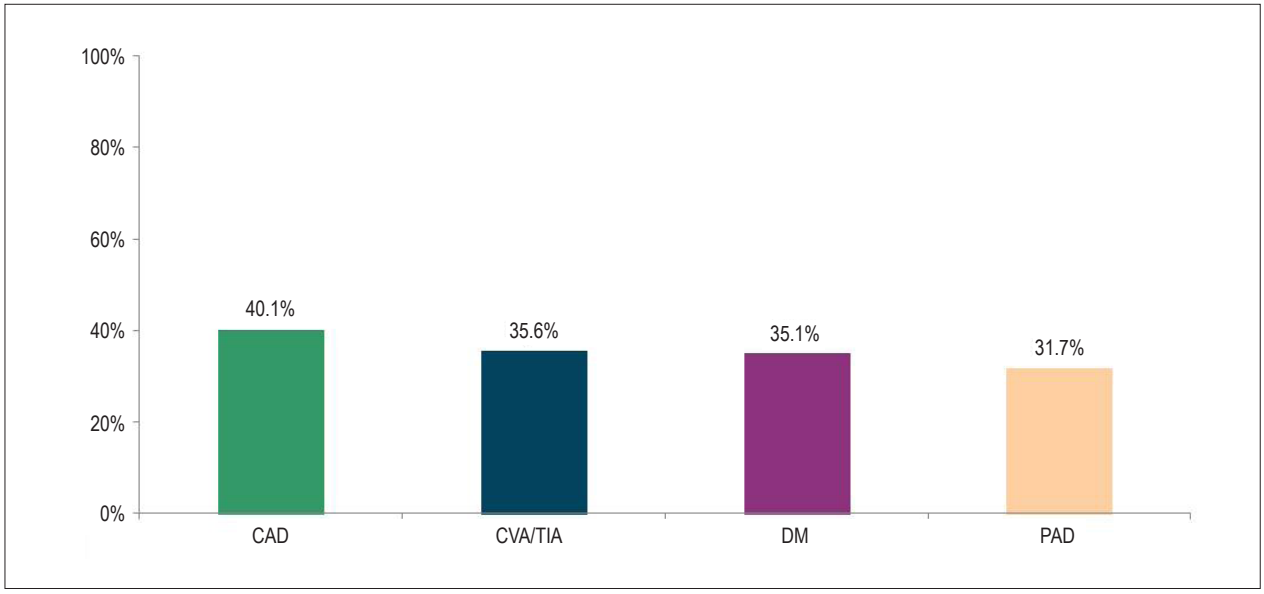

Figure 4 - *Use of evidence-based drugs (antiplatelet agents, statins and angiotensin-converting enzyme inhibitors), according to the clinical history. Analysis considering a total of 2,364 patients. CAD: coronary artery disease; CVA/TIA: cerebrovascular accident / transient ischemic attack; DM: diabetes mellitus; PAD: peripheral arterial disease.*

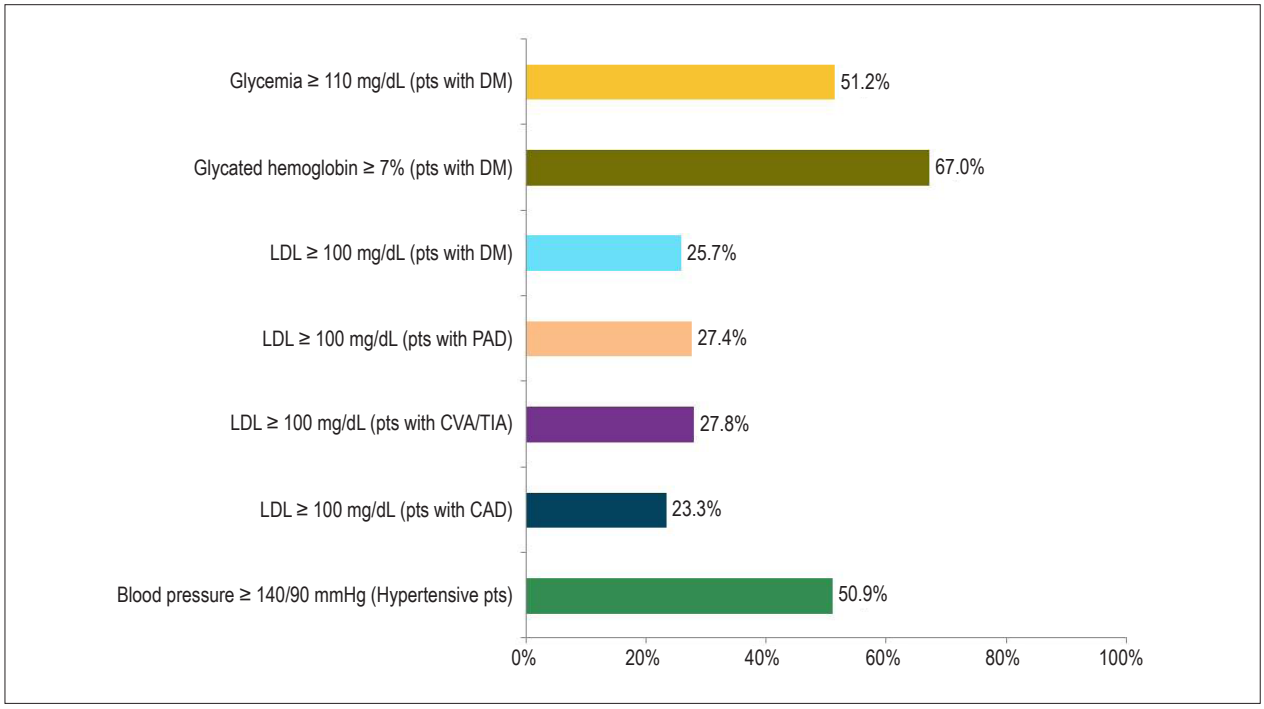

Figure 5 - *Control of risk factors according to the goals determined by the guidelines. DM: diabetes mellitus; PAD: peripheral arterial disease, CVA/TIA: cerebrovascular accident / transient ischemic attack, CAD: coronary artery disease; pts: patients.*

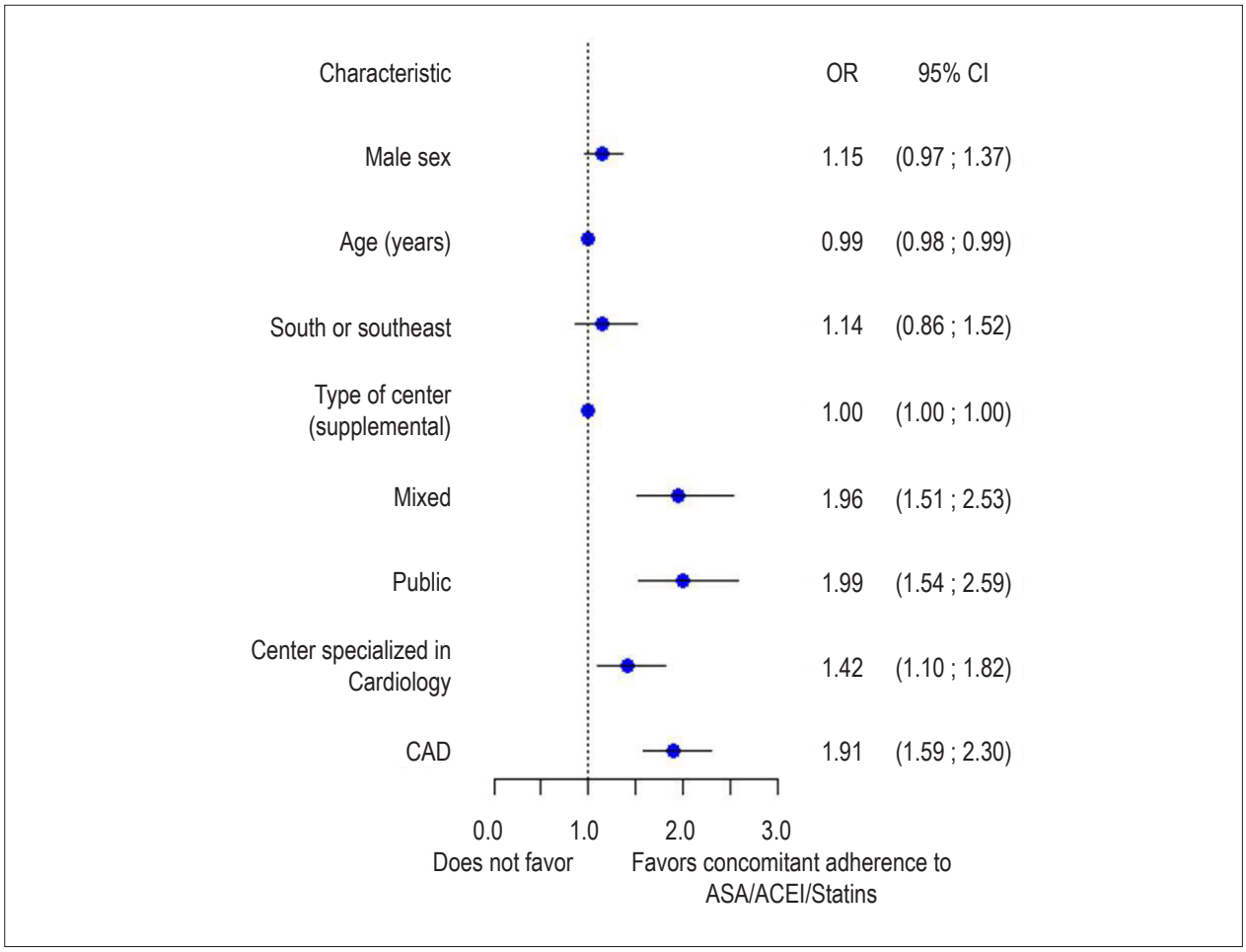

Figure 6 - *Factors associated with adherence to evidence-based drugs. Analysis considering a total of 2,364 patients. CAD: coronary artery disease, ASA: acetylsalicylic Acid; ACEI: angiotensin-converting enzyme inhibitors.*

Among the factors independently associated with prescription of evidence-based therapies, treatment by cardiologists and diagnosis of CAD are highlighted. The findings of the present study are consistent with recent cross-sectional study carried out in ten European countries that analyzed quality indicators in 8928 patients, showing that risk factor control was better in the group with known coronary artery disease, when compared to those with high risk and no cardiovascular disease, for both rates of uncontrolled blood pressure (34.2 vs. 49.3%, $p < 0.001$) and uncontrolled cholesterol (32.4 *versus* 64.5%, $p < 0.001$), which may reproduce drug prescription[29].

Strength and limitations

The main strengths of the REACT study are the fact that it represents the largest and most recent national registry that documents care of patients at high cardiovascular risk, its supra-institutional characteristic (as it was carried out by SBC), the participation of centers from all Brazilian regions, including public (university and non-university), private and mixed hospitals, both from capital and large cities, as well as from smaller towns. The latter aspect represents a differential of the REACT study in relation to international registries with the participation of Brazilian centers, which are usually carried out in large university centers only, which have academic tradition. Additionally, robust methodology was used regarding the observational study design of the registry type, namely: minimization of selection bias by including a consecutive sample of patients, adequate control of random error through satisfactory sample size and robust statistical methods, minimizing measurement bias by central adjudication of outcomes, and finally, the use of several strategies validated for data quality control and fraud prevention system (electronic capture of data, central statistical consistency checking, as well as local and at-distance monitoring centers).

On the other hand there are limitations that must be mentioned. It is noteworthy that, although it included primary care center units and other specialty centers, most centers included were specialized in Cardiology. Thus, potentially, the inclusion of a greater number of patients from Basic Health Units and communities with less access to specialized services could disclose an even greater gap in the incorporation of evidence-based therapies and satisfactory control of risk factors, according to guideline targets. However,

from a qualitative point of view (i.e., presence of gaps in the incorporation of evidence), the results would remain similar, even with the inclusion of those centers.

Additionally, although we have tried to respect the geographical distribution of the population according to the last census of the Brazilian Institute of Geography and Statistics (IBGE), the number of centers in the North, Northeast and Midwest was lower than the representativeness of centers in the South and Southeast regions. Finally, this analysis shows baseline data only, with no description of longitudinal follow-up of patients that might allow measurement of the incidence and predictors of cardiovascular events. Regarding this latter point, it is important to mention that new analyses of the REACT study, regarding the longitudinal follow-up, are in progress and will probably bring relevant information on the incidence of clinically relevant outcomes in this population.

Conclusion and main implications

The goals of cardiovascular risk factor control, drug prescriptions and recommendations for lifestyle change for patients at high cardiovascular risk in Brazil, were outside of those recommended by the Brazilian guidelines. Given the abovementioned facts and based on the results of the REACT study, it is necessary to develop Clinical Practice Improvement Programs under the coordination of the SBC, including research (cluster randomized trials) and professional training, also involving non-specialists.

Although the analysis did not include only patients eligible for pharmacologic intervention, considering that the rate of contraindication to antiplatelet therapy, statins and ACE inhibitors is below 5%, an optimal rate of prescription would be around 95%. Thus, the REACT results showed that the prescription of cardiovascular drugs is lower than the expected.

Finally, it is necessary to carry out similar studies in patients in the community with less access to specialists' services, where larger gaps are expected regarding the incorporation of therapies with proven benefit.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis, Obtaining funding and Critical revision of the manuscript for intellectual content: Berwanger O, Piva e Mattos LA, Guimarães JI, Andrade JP; Acquisition of data: Martin JFV, Lopes RD, Figueiredo EL, Magnoni D, Precoma DB, Machado CA; Writing of the manuscript: Berwanger O, Piva e Mattos LA, Martin JFV, Lopes RD, Figueiredo EL, Magnoni D, Precoma DB, Machado CA, Guimarães JI, Andrade JP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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