Inadequate heart rate control despite widespread use of beta-blockers in outpatients with stable CAD.

Findings from the international prospective CLARIFY registry

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Abstract (249 words)

Background Beta-blockers are recommended in stable coronary artery disease (CAD) to improve symptoms and survival, and reduce heart rate (HR), but their administration is limited due to contraindications or intolerability.

Objective To use CLARIFY, a prospective registry of patients with stable CAD (45 countries), to explore HR control and beta-blocker use.

Methods We analyzed the CLARIFY population according to beta-blocker use.

Results Data on beta-blocker use was available for 33 243 patients, in whom HR was 68±11 bpm; patients with angina, previous myocardial infarction, and heart failure had HRs of 69±12, 68±11, and 70±12 bpm, respectively. 75% of these patients were receiving beta-blockers. Bisoprolol (34%), metoprolol tartrate (15%) or succinate (13%), atenolol (15%), and carvedilol (12%) were mostly used; mean dosages were 49%, 76%, 35%, 53%, and 45% of maximum recommended doses, respectively. Patients aged <65 years were more likely to receive beta-blockers than patients ≥75 years (P<0.0001). Gender had no effect. Subjects with HR≤60 bpm were more likely to use beta-blockers than patients with HR≥70 bpm (P<0.0001). Patients with angina, previous myocardial infarction, heart failure, and hypertension were more frequently receiving beta-blockers (all P<0.0001), and those with PAD and asthma/COPD less frequently (both P<0.0001). Beta-blocker use varied according to geographical region (from 87% to 67%).

Conclusion Three-quarters of patients with stable CAD receive beta-blockers. Even so, HR is insufficiently controlled in many patients, despite recent ACCF/AHA guidelines for the management of CAD. There is still much room for improvement in HR control in the management of stable CAD.

Keywords: CLARIFY; stable CAD; beta-blocker; heart rate

Introduction

Elevated heart rate is known to have a detrimental effect on the occurrence of myocardial ischemia and is a well-established risk factor in patients with coronary artery disease (CAD) (1-5). This is recognized in the recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for the management of stable CAD, which stress the prognostic importance of elevated heart rate and recommend that beta-blocker dose be adjusted to limit resting heart rate to 55–60 beats per minute (bpm) (6). Despite the weight of evidence, several observational studies suggest that this target is not systematically achieved in clinical practice. Moreover, it appears that this may be traced to suboptimal prescription of beta-blockers. Indeed, data from the Euro Heart Survey show that only two-thirds of patients with stable angina are prescribed a beta-blocker (7). The actual rate of administration may even be lower, since a recent study based on the UK General Practice Research Database found that a quarter of patients taking a beta-blocker in primary care appear to discontinue it within one year, rising to half of patients by 3 years (8). The reasons for this failure to align with international guidelines include contraindications or tolerability issues, which may limit beta-blocker use and up-titration in clinical practice.

Beta-blockers act by competitive inhibition of the effects of circulating catecholamines on the beta-adrenergic receptors, and are associated with a variety of physiological actions, including reduction in blood pressure and myocardial contractility, as well as heart rate. Current international guidelines recommend beta-blockers as the initial treatment for angina in patients with stable CAD (6,9). Beta-blockers are also widely used in asymptomatic patients with CAD, particularly in those who have suffered a myocardial infarction (MI) or have left ventricular systolic dysfunction or heart failure; in both groups, a reduction in mortality has been documented (10-12). At least part of the beneficial action of beta-blockers is believed to be related to the lowering of elevated heart rate.

With these issues in mind, we set out to perform an analysis of the use of beta-blockers in the CLARIFY (ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) registry. CLARIFY is an ongoing international prospective observational longitudinal registry that included a broad population of over 33 000 patients living in 45 countries, receiving standard management for stable CAD (13,14). It has already been reported that 75% of CLARIFY patients were receiving a beta-blocker (13). In the analysis described herein, we used the CLARIFY database to explore the use of individual beta-blockers and their dosages in patients with stable CAD, as well as the distribution of beta-blocker use according to patient profile (e.g., age, sex, and concomitant diseases) and geographical location to determine how current practice reflects the recent guideline recommendations in terms of heart rate control in CAD (6).

Methods

Study design and patients

The 2898 CLARIFY physicians each recruited between 10 and 15 consecutive patients with stable CAD (i.e. documented MI, coronary artery bypass grafting [CABG], or percutaneous coronary intervention [PCI] >3 months previously, or angiographic demonstration of >50% coronary stenosis, or chest pain with evidence of myocardial ischaemia [stress electrocardiogram]). Patients with recent (<3 months) hospitalization for cardiovascular reasons (including revascularization), planned revascularization, or any serious condition expected to affect follow-up were excluded. Further details of the inclusion and exclusion criteria, as well as the study design, have been published elsewhere (13,14).

CLARIFY is ongoing in 45 countries in Europe, the Americas, Africa, Middle East, and Asia/Pacific (13). One target was to cover an epidemiologically representative population in each of the countries (i.e. 25 patients per million inhabitants [range 12.5 to 50]). Participating physicians were selected on the basis of geographic distribution. CLARIFY is carried out in accordance with the principles laid out in the Declaration of Helsinki and its revisions. Local ethical approval was obtained in all

countries prior to recruitment. All patients gave written informed consent. The study is registered (ISRCTN43070564). The first patient was included on November 26, 2009 and recruitment was completed on June 30, 2010 (13).

Data were collected at baseline on demographics, risk factors and lifestyle, medical history, physical condition and vital signs, current symptoms, and current treatments using standardized electronic case report forms. Heart rate was measured by electrocardiography, or by palpation when electrocardiographic data was not available. We analyzed the CLARIFY population according to the use of different beta-blockers. We also analyzed beta-blocker use according to patient profile, including: age (<65 years, 65-74 years, or ≥75 years); gender; heart rate (≤60 bpm, 61-69 bpm, or ≥70 bpm); presence of angina; Canadian Cardiovascular Society (CCS) class of angina; presence of heart failure defined according to the New York Heart Association (NYHA) classification; diabetes; asthma/chronic obstructive pulmonary disease (COPD); hypertension; peripheral artery disease; and a history of previous MI. We also explored the use of different beta-blockers according to geographic region.

Data collection and statistical methods

Data are presented using descriptive statistics with numbers (%) of patients for categorical variables, and mean and standard deviation for continuous variables. Comparisons between the groups were made using Pearson's χ^2 test for categorical variables. All data were collected and analyzed by the independent academic Robertson Centre for Biostatistics at the University of Glasgow, UK. The SAS (version 9.2) statistical program was used and all tests were two-sided with a significance level of 5%.

Role of funding source

The study was designed and conducted by the investigators, supported by research grants from Servier, France. The sponsor had no role in study design, data collection and analysis, decision to publish, or writing of the manuscript, but did assist with the set up and management of the study in each country.

Results

Information on beta-blocker use was available for 33 243 (99.9%) patients. Of these, 24 984 (75%) were receiving a beta-blocker. Patients receiving a beta-blocker had a mean heart rate of 68±11 bpm. There were 7315 patients with angina at baseline, with a mean heart rate of 69±12 bpm. Of these, 1820 (25%) had heart rate ≤60 bpm. Heart rate was 68±11 bpm in 19 844 patients with previous MI and 70±12 bpm in 4943 patients with NYHA class II/III heart failure at baseline.

As regards the individual beta-blockers, most patients were receiving bisoprolol (34%), metoprolol tartrate (15%) or succinate (13%), atenolol (15%), carvedilol (12%), or nebivolol (6%) (**Table 1**). On the whole, mean beta-blocker dosages were within the therapeutic dosage range for angina or chronic heart failure (15-17). Mean dosages of bisoprolol, metoprolol tartrate, metoprolol succinate, atenolol and carvedilol were 49%, 76%, 35%, 53%, and 45% of the maximum recommended dose. Among patients treated with beta-blockers, 2047 (8%) had intolerance or contraindications to these agents, mainly fatigue (716 patients, 2.9% of total [or 35% of the patients with intolerance or contraindications]), bradycardia (590 patients, 2.4% [or 29%]), erectile dysfunction (398 patients, 1.6% [or 19%]), hypotension (369 patients, 1.5% [or 18%]), dizziness (255 patients, 1.0% [or 12%]), or exacerbation of asthma or COPD (199 patients, 0.8% [or 10%]).

The rates of beta-blocker use according to age, gender, and heart rate are presented in **Table 2.** Younger patients (<65 years) were significantly more likely to receive a beta-blocker than older patients (≥75 years) (78% versus 69%, P<0.0001). There was no difference in beta-blocker use according to gender. Subjects with low heart rate (≤60 bpm) were more likely to be on a beta-blocker than patients with elevated heart rate (≥70 bpm) (80% versus 70%, P<0.0001). As regards beta-blocker dosages in patients with differing levels of heart rate, the mean dosage of atenolol was 52.8±27.8 mg/day in patients with heart rate between 61 and 69 bpm, and 54.3±27.3 mg/day in those with heart rate ≥70 bpm. The corresponding dosages for

other beta-blockers were: bisoprolol 5.0±3.0 and 5.1±3.0 mg/day, metoprolol tartrate 74.0±49.8 and 74.0±51.7 mg/day, and carvedilol 22.7±15.9 and 22.8±16.4 mg/day.

The rate of beta-blocker use according to medical history is presented in **Table 3**. There were significantly higher rates of beta-blocker use in patients with angina (79% versus 74% with no angina), and greater levels in patients with higher CCS class (75% in CCS class I, 80% in class II, and 81% in class III/IV). Of the angina patients with heart rate ≤60 bpm, 1507 (83%) were taking a beta-blocker. Patients with previous MI were more likely to receive beta-blocker (79% versus 70% in those without history of MI). In patients with MI in the same calendar year or the calendar year preceding recruitment (n=4844), the rate of BB use was 82%. Higher rates were also found in patients with heart failure (74% with no heart failure versus 83% in NYHA class II/III), diabetes (77% versus 74% with no diabetes), and hypertension (77% versus 70% with no hypertension) (all P<0.0001). Lower rates of beta-blocker use were observed in patients with PAD (71% versus 76% without PAD) (P<0.0001). Patients with asthma/COPD were considerably less likely to be receiving a beta-blocker (51% versus 77% without asthma/COPD) (P<0.0001).

As regards comorbidities, 43% of patients with NYHA class II/III heart failure were taking bisoprolol, 14% carvedilol, 12% metoprolol tartrate, 14% metoprolol succinate, 8% nebivolol, and 5% atenolol. The mean dosages of beta-blocker in the patients with NYHA class II/III heart failure were: bisoprolol 5.5±3.1 mg/day, carvedilol 23.5±15.7 mg/day, metoprolol tartrate 72.8±51.1 mg/day, metoprolol succinate 69.8±42.6 mg/kg, nebivolol 4.7±1.7 mg/day, and atenolol 54.7±28.3 mg/day. Similar distribution was observed for the individual beta-blockers in patients with diabetes (bisoprolol, 31%; metoprolol tartrate 16% and succinate 11%; atenolol, 16%; carvedilol, 15%; nebivolol, 5%) and PAD (bisoprolol, 36%; metoprolol tartrate 11% and succinate 11%; atenolol, 12%; carvedilol, 15%; nebivolol, 8%). There was no clear pattern in the distribution of the use of individual beta-blockers in other patient profiles (data not shown).

There was a substantial variation in beta-blocker use according to geographical region. Rates of beta-blocker use were highest in Russia and the Ukraine (87%), the Middle East (87%), and Europe (excluding UK) (77%), and lowest in Canada, South Africa, Australia, and UK (67%). The other regions had rates around 70% (Asia, 71%; India, 70%; and Central/South America, 70%). There were considerable differences in the use of various agents between the regions, with bisoprolol dominating in Europe, Russia, Ukraine, and the Middle East, and metoprolol dominating in India, and Central and South America (**Figure 1**).

Discussion

The mean heart rate in the CLARIFY population was 68±11 bpm. Within this population, mean heart rates in patients with angina, previous MI, and heart failure were 69±12, 68±11, and 70±12 bpm, respectively. Three-quarters (75%) of patients with stable CAD in the CLARIFY registry were receiving treatment with a beta-blocker. Patients with angina, heart failure and recent MI were more likely to be receiving beta-blocker: 79% of angina patients, 83% of heart failure patients, and 82% of patients with recent MI. The most commonly used beta-blockers were bisoprolol (34%) and metoprolol tartrate (15%) or succinate (13%). The Euro Heart Survey, which collected data in 2002 (18), reported that about two thirds (67%) of patients with stable angina in Europe were on a beta-blocker (19). Higher rates of beta-blocker use in CLARIFY, which collected data in 2009 to 2010, imply that there has been some improvement in the management of these patients in recent years.

The use of beta-blockers has also been explored in the REACH (Reduction of Atherothrombosis for Continued Health) registry, which included nearly 45 000 stable outpatients with and without CAD in 2004 (20). Two thirds (67%) of REACH patients with prior MI were receiving a beta-blocker at baseline, versus 57% of patients with CAD but no prior MI (20). Like the CLARIFY patients, the REACH beta-blocker patients were significantly younger and more likely to have hypertension or heart failure (all $P<0.001$); also like CLARIFY, there was no significant difference in beta-blocker use according to gender. REACH also assessed cardioprotective benefits

of beta-blockers in stable CAD. Since the time of the landmark beta-blocker trials in heart failure and post-MI (10-12,21), these agents have been used to prevent MI or death, and their cardioprotective effects have been broadly extrapolated to all patients with stable CAD, including those without MI. It is not known, however, if these extrapolations are justified. Moreover, the long-term efficacy of beta-blockers in patients treated with contemporary medical therapies is unclear, even in patients with prior MI. The REACH investigators demonstrated that, in a contemporary stable CAD population, beta-blocker use is not associated with a lower event rate of cardiovascular events at 44-month follow-up, even among patients with a history of MI (20).

Our results regarding the use of individual agents confirm that majority of physicians are following evidence-based guidelines on the management of heart failure (17), since 83% of patients with NYHA class II/III heart failure are prescribed beta-blockers known to be effective in heart failure, such as bisoprolol (43%), carvedilol (14%) or metoprolol (14% succinate and 12% tartrate). As regards other comorbidities, we also observed that patients with comorbid PAD and diabetes are well treated. This is an important point since beta-blockers are not contraindicated in PAD and diabetes.

While beta-blockers are clearly not being withheld in patients who require them, there is an indication that physicians tend to prescribe considerably lower doses than those recommended (15-17). This finding is in line with the reports from several observational studies (7,8,22). For example, mean beta-blocker dosages in CLARIFY are similar to those reported from the Euro Heart Survey (7). Generally, while beta-blockers are the most frequent drug class prescribed to patients with stable CAD, they are used at low doses (7). In the Euro Heart Survey, this was linked to a concern over the risk for adverse effects or caution related to comorbidities such as respiratory diseases (23). The same may be true in CLARIFY, insofar as 19% of the patients on beta-blockers have symptoms indicative of intolerance or contraindications to the treatment. The submaximal dosing may be partly due to the absence of recommended dosages in patients with stable CAD without heart failure. In patients with heart failure, the dosages of beta-blockers were also lower than

recommended dosages for their condition, generally at 50% of target dosages, for bisoprolol (6 mg/day instead of the target of 10 mg/day), metoprolol (73 mg/day for tartrate and 70 mg/day for succinate, versus target dose of 200 mg/day), and carvedilol (24 mg/day versus target dose of 50 mg/day).

Patients with low heart rate were significantly more likely to receive a beta-blocker. However, 70% of patients with heart rate ≥70 bpm were on a beta-blocker. While this suggests that beta-blockers were prescribed to the majority of patients with elevated heart rate, it may also indicate that the heart rate–lowering effects of beta-blockers are not always sufficient to reduce heart rate below 70 bpm. The CLARIFY data indicate that global control of heart rate is poor in daily clinical practice (13). Among 7315 patients with angina symptoms, only 1820 (25%) had heart rate ≤60 bpm. This may reflect the lack of knowledge of the optimal resting heart rate among physicians. Guidelines in stable CAD and acute MI recommend heart rates of 55–60 bpm for prevention of myocardial ischemia and prognostic benefits (6). Indeed, it is now well established that patients with heart rate ≥70 bpm have a higher risk of MI and other major outcomes compared with patients with heart rate <70 bpm (2,24,25). Moreover, there is evidence that clinical benefits are tightly associated with magnitude of heart rate reduction (26-28). In this context, the use of more than one heart rate–reducing agent to achieve lower heart rate may be beneficial in patients with stable CAD and elevated heart rate (13).

Geographical differences in beta-blocker use are consistent with other reports in angina and in heart failure (19,29,30). The Euro Heart Survey reported substantial geographical differences within Europe, with 52% of angina patients in Western Europe receiving beta-blocker versus 77% patients in Central Europe (19). Some of the variations in the use of different beta-blockers may be due to cultural habits or availability of certain agents, rather than a clinical decision per se.

The limitations associated with investigations within the CLARIFY registry have been extensively detailed elsewhere (13). Most importantly, the CLARIFY population was not randomly selected and not consecutive, but within each center the data were

collected consecutively. The centers were not selected randomly, but their choice was based on the ability to enroll patients into the registry.

Conclusions

Patients with stable CAD are likely to receive a beta-blocker (75% of patients), particularly when they have angina, heart failure or recent MI), with the most common agents being bisoprolol and metoprolol. Despite this, heart rate is insufficiently controlled in a high proportion of patients, which may have a negative effect on their health status. Recent ACCF/AHA guidelines suggest that the heart rate, rather than the beta-blocker dose, should guide the use of heart rate–reducing agents in clinical practice (6). Clearly, there is still much room for improvement in heart rate control in patients with stable CAD.

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Conflicts of Interest

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GlaxoSmithKline, Medtronic, Merck Sharpe and Dohme, Pfizer, Roche, sanofi-aventis, Servier, and The Medicines Company; and has equity ownership in Aterovax.

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Table 1. Use of beta-blockers in the CLARIFY population (33 243 patients).

[a]Percentages of patients receiving any beta-blocker (patients could be taking more than one beta-blocker at the baseline visit). According to recommendations in stable angina[b] (15,16) and/or chronic heart failure[c] (17).[d]75% of the total CLARIFY populations.

	Patients, n (%)[a]	**Dosage (mg/day), mean±SD**	**Recommended range[b] (mg/day)**
Any beta-blocker	24 984[d]		
Atenolol	3775 (15%)	52.59±27.01	25–100[b]
Bisoprolol	8506 (34%)	4.92±2.95	2.5–10[b]/10[c]
Carvedilol	2905 (12%)	22.68±15.9	50[c]
Metoprolol tartrate	3862 (15%)	75.65±51.96	50–100[b]
Metoprolol succinate	3127 (13%)	70.86±44.55	200[c]
Nebivolol	1408 (6%)	4.68±1.83	2.5–5[b]/10[C]
At least one other beta-blocker	1390 (6%)		

Table 2. Beta-blocker use in patients according to age, gender, and heart rate.

*P value for between-group difference.

	Patients with data available	Any beta-blocker
Age		
• Age <65 years	17 214	13 473 (78%)
• Age 65-74 years	10 812	7937 (73%)
• Age ≥75 years	5197	3563 (69%)
P-value*		P<0.0001
Gender		
• Males	25 751	19 366 (75%)
• Females	7481	5610 (75%)
P-value*		P=0.71
Heart rate		
• ≤60 bpm	9828	7854 (80%)
• 61-69 bpm	9616	7489 (78%)
• ≥70 bpm	13 795	9637 (70%)
P-value*		P<0.0001

Table 3. Beta-blocker use in patients according to medical history.

*P value for between-group difference. CCS=Canadian Cardiovascular Society. NYHA=New York Heart Association. COPD=chronic obstructive pulmonary disease. MI=myocardial infarction. PAD=peripheral arterial disease.

	Patients with data available	Any beta-blocker
Angina		
• Angina	7315	5748 (79%)
• No angina	25 922	19 230 (74%)
P-value*		P<0.0001
Angina CCS class		
• Class I	2091	1572 (75%)
• Class II	3888	3097 (80%)
• Class III/IV	1332	1075 (81%)
P-value*		P<0.0001
Heart failure		
• No heart failure	28 289	20 863 (74%)
• NYHA class II	4135	3446 (83%)
• NYHA class III	808	665 (82%)
P-value**		P<0.0001
Diabetes		
• Diabetes	9691	7487 (77%)
• No diabetes	23 545	17 491 (74%)
P-value*		P<0.0001
Asthma/COPD		
• Asthma/COPD	2452	1252 (51%)
• No asthma/COPD	30 785	23 730 (77%)
P-value*		P<0.0001
Myocardial infarction		
• Previous MI	19 844	15 645 (79%)
• No previous MI	13 393	9335 (70%)
P-value*		P<0.0001
MI in the last two calendar years		
• Previous MI	4844	3965 (82%)
• No previous MI	28399	21 019 (74%)
P-value*		P<0.0001
Hypertension		
• Hypertension	23 583	18 260 (77%)
• No Hypertension	9653	6718 (70%)
P-value*		P<0.0001
PAD		
• PAD	3253	2322 (71%)
• No PAD	29 982	22 655 (76%)
P-value*		P<0.0001

Figure 1. Distribution of beta-blocker use by geographical region.

SA=South Africa.