We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

19

Ivabradine Versus Beta-Blockers in Patients with Conduction Abnormalities or Left Ventricular Dysfunction Undergoing Coronary Artery Bypass Grafting

Luminita Iliuta[1,2] and Roxana Enache[2]
[1]*Department of Cardiac Surgery, "Prof. Dr. C. C. Iliescu" Emergency Institute of Cardiovascular Diseases, Bucharest*
[2]*"Carol Davila" University of Medicine and Pharmacy, Bucharest*
Romania

1. Introduction

Postoperative rhythm disorders are a serious complication of coronary surgery and they are associated with increased morbidity and mortality. Atrial fibrillation is the most common complication after cardiac surgery, with an incidence of 30% after coronary artery bypass grafting (Camm et al.,2010). There are few data about the etiology of atrial fibrillation in this setting, factors such as intraoperative atrial ischemia, pericarditis, and excessive adrenergic stimulation, were incriminated in its occurrence in vulnerable patients (Lucio et al., 2004). The peak incidence of postoperative atrial fibrillation is between postoperative days 2 and 4 (Camm et al.,2010). Although frequently these arrhythmias are benign and transient, patients developing postoperative atrial fibrillation are more likely to have perioperative myocardial infarction, stroke, congestive heart failure, respiratory failure, prolonged hospitalization and intensive coronary unit (ICU) stay and therefore increased economic burden of their care (Lucio et al., 2004; Iliuta et al., 2009; Burgess et al., 2006).

Many clinical trials and multiple meta-analyses evaluated the efficacy of pharmacological and non-pharmacological interventions in prevention of postoperative atrial fibrillation. The meta-analyses and systematic reviews showed that interventions to prevent and/or treat postoperative atrial fibrillation with beta-blockers, sotalol, or amiodarone and, less convincingly, atrial pacing, are favoured with respect to outcome (atrial fibrillation occurence, stroke, and length of hospitalisation) (Burgess et al., 2006; Crzstal et al., 2004). Currently, preoperative or early postoperative administration of beta-blockers is considered a first line choice to prevent atrial fibrillation after coronary artery bypass grafting except in patients with contraindications to beta-blocker therapy (Camm et al.,2010; Eagle et al., 2004). In patients with conduction abnormalities, severe left ventricular dysfunction, active bronchospasm or marked resting bradycardia the use of beta-blockers is difficult and controversial.

The hyperpolarization-activated pacemaker current (If) channel inhibitor ivabradine, which induces heart rate reduction by selective sinus node inhibition, showed improvement of clinical outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction (Fox et al., 2008) or chronic heart failure (Swedberg et al., 2010). Data regarding

the benefits of ivabradine used postoperatively in patients with conduction abnormalities or left ventricular dysfunction undergoing coronary surgery are scarce.
The main objectives of our study were to compare the efficacy and safety of heart rate lowering agent ivabradine versus beta-blocker metoprolol used perioperatively in patients undergoing coronary artery bypass grafting and having conduction abnormalities (first degree atrioventricular block or bundle branch block) or left ventricular dysfunction and also to determine whether prophylactic therapy with ivabradine can reduce hospital stay and economic costs after cardiac surgery by lowering the risk associated with an increased heart rate.

2. Methods

This trial was an open-label, randomized, clinical trial which enrolled 315 patients undergoing coronary artery bypass grafting with arteries (internal mammary, radial, gastroepiploic) or inverted saphenous veins in a single center (Cardiac Surgery Department of "Prof. Dr. C. C. Iliescu" Emergency Institute of Cardiovascular Diseases, Bucharest, Romania) between January 1st, 2006 and December 31st, 2007. Surgical management and treatment of the patients were based on a common standard protocol.

2.1 Eligibility criteria

Patients included in the clinical trial were patients undergoing elective coronary artery bypass grafting who had conduction abnormalities, left ventricular systolic dysfunction or both.

2.2 Exclusion criteria

Patients non-eligible for the study were patients exhibiting one or more of the following conditions:

1. second and third degree atrioventricular block
2. bradycardia (heart rate less than 50 beats per minute) or conditions associated with increased risk for bradycardia (vagal predominance, sick sinus syndrome)
3. NYHA class IV heart failure
4. cardiogenic shock
5. severe chronic obstructive pulmonary disease or pulmonary impairment
6. known hypersensitivity to beta-blockers or ivabradine
7. active participation in another clinical trial
8. failure to comply with the hospital protocol or absence to follow-up.

Study drop out criteria included the occurrence of adverse events: severe bradycardia, skin reactions, gastrointestinal symptoms, cold extremities. The study protocol was approved by the institute Management and Ethics Committee. All patients included in the trial gave written informed consent for participation in this study.

2.3 Study groups

After inclusion in the study, two days before surgery, patients were randomized in three groups:

1. Group A: 104 patients to receive metoprolol 100 mg once daily;
2. Group B: 106 patients to receive metoprolol 50 mg once daily and ivabradine 5 mg twice daily;
3. Group C: 105 patients to receive ivabradine 5 mg twice daily.

The treatment phase comprised 2 days preoperatively and at least 10 days postoperatively and the patients were followed-up for 30 days after surgery (Fig. 1).

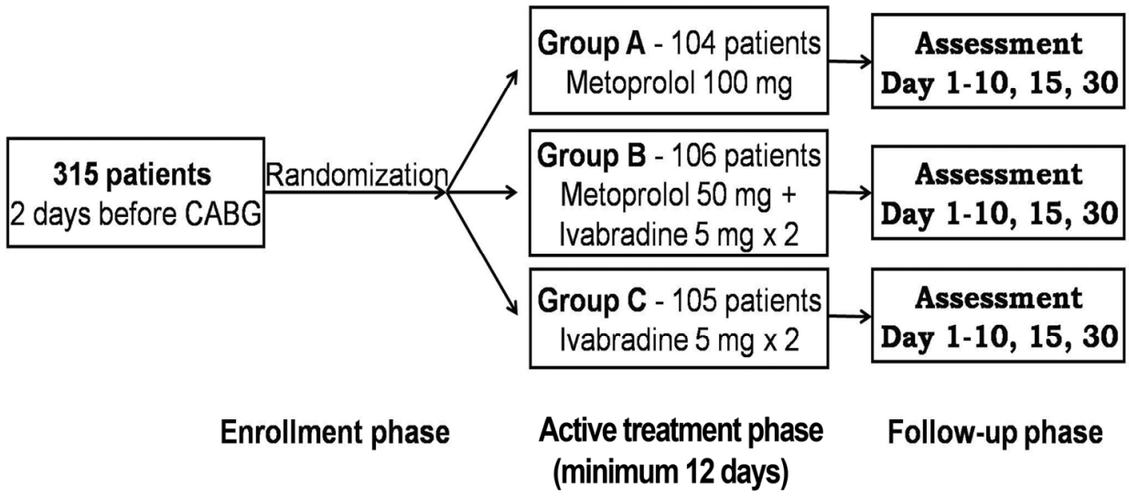


Fig. 1. Study phases and distribution of study population

2.4 Clinical and laboratory assessments

Patients were evaluated at baseline (ie. 2 days before surgery), daily from Day 1 until Day 10 postoperatively, on Day 15, and at the end of the treatment on Day 30 postoperatively. Patients with short in-hospital evolution were evaluated ambulatory.

Clinical parameters included NHYA class, ventricular rhythm, patient compliance, and quality of life.

Laboratory parameters assessed were: usual blood tests (white and red blood cell count, platelet count, hemoglobin, hematocrit, alanine aminotransferase and aspartate aminotransferase, lactate dehydrogenase, blood chemistry), electrocardiogram (ECG) (with the evaluation of rhythm and rate), 24-h ECG Holter monitoring and echocardiographic measurements of the left ventricular dimensions, left ventricular systolic and diastolic performance, left atrium dimensions and compliance (data not shown in the present report). Cardiac rhythm was continuously monitored in the intensive care unit. During further hospital stay, subsequent ECG tests and a 24-h ECG Holter monitoring was carried out prior to discharge.

Follow-up visits were in Day 15 and in Day 30 postoperatively and included a physical examination and a 15-minutes interview, a resting ECG, an echocardiogram and a 24-h ECG Holter monitoring. Early episodes of heart failure were diagnosed based on clinical signs and symptoms and by transthoracic and transesophageal echocardiography. The presence of bradycardia or second or third degree atrioventricular block was assessed using clinical examination, resting ECG and 24-h ECG Holter monitoring.

2.5 Study endpoints

The efficacy endpoints were 30-days mortality, in-hospital occurrence of atrial fibrillation/arrhythmias, in-hospital occurrence of third degree atrioventricular block and need for pacing, in-hospital worsening heart failure and duration of hospitalization and immobilization. Safety endpoints were occurrence of bradycardia, gastrointestinal

complaints, sleep disturbances, and cold extremities. A composite efficacy and safety endpoint including 30-days mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening was also defined.

2.6 Statistical analyses

No sample size assumptions have been made for this trial. Continuous variable are presented as mean ± standard deviation (SD). Categorical variables are displayed as percentages. To analyze the differences between the treatment groups, the Student *t* test was used for the continuous variables and the chi-square test for the categorical variables For each endpoint, a two-sided 95% confidence interval (CI) was calculated and an overall χ^2-test comparing the two treatment groups was used. Also, we performed simple and multivariate, linear and logistic regression analysis and we calculated relative risks and correlation coefficients. For the primary endpoints Kaplan–Meier curves were constructed and log-rank tests were used. All statistical analyses were performed using SYSTAT and SPSS software. A p value <0.05 defined the statistical significance.

3. Results

In the entire study population (315 patients), mean age was 62 ± 8 years, and 65.7% of patients were males. Baseline demographics and clinical characteristics of the three treatment groups are displayed in Table 1. There were no differences in age and gender of patients, presence of left ventricular dysfunction or conduction abnormalities between study groups, systolic blood pressure or mean baseline heart rate. Also, there were no differences between groups in mean number of grafts/patient and grafts type, risk score for atrial arrhythmias and mean duration of treatment.

The percentages of patients with previous episodes of atrial fibrillation were similar in the three groups (18.3% in group A, 19.8% in group B, and 19.1% in group C). There were similar proportions of patients with left ventricular dysfunction and conduction abnormalities (first degree atrioventricular block, complete left bundle branch block, bifascicular and trifascicular block) in the three treatment groups.

The primary efficacy and safety, single and composite endpoints in the treatment groups are shown in Table 2. In-hospital postoperative atrial fibrillation or tachyarrhythmias occurred less frequently with combined therapy (metoprolol and ivabradine) than with metoprolol or ivabradine alone used in the postoperative management of patients with coronary artery bypass grafting (7.6% events in group B versus 11.5% events in group A and 17.1% events in group C, $p < 0.001$). The associated relative risk showed a higher protective value for the occurence of postoperative atrial fibrillation in patients with coronary artery bypass grafting treated with combined therapy compared with metoprolol monotherapy (-2.9 vs. -1.8) (Fig. 2).

In group C the frequency of early postoperative third degree atrioventricular block or need for pacing was lower (2.9%) than in group A (13.5%) and in group B (9.4%) ($p < 0.0001$). The frequency of heart failure worsening was lower in patients treated with ivabradine only (1.9%) or ivabradine combined with metoprolol (6.6%) than in patients receiving only metoprolol (11.5%) ($p < 0.001$) (Table 2). The associated relative risks for early postoperative complete atrioventricular block or need for permanent pacing and for postoperative heart failure worsening were lower in ivabradine-treated groups (Fig. 2).

Characteristic	Group A N = 104	Group B N = 106	Group C N = 105
Age (years)	63 (12)	63 (12)	63 (13)
% female	32.7%	35.9%	34.3%
Weight (kg)	75 (15)	76 (13)	77(14)
Height (cm)	172 (9)	170 (11)	171 (10)
Heart rate/24h	78 (15)	76 (16)	77 (14)
Left ventricular dysfunction	43.3%	43.4%	41.9%
Conduction abnormalities	46.2%	47.2%	46.7%
Systolic blood pressure (mmHg)	152 (22)	150 (28)	153 (23)
Previous episodes of atrial arrhythmias	18.3%	19.8%	19.1%
Hypertension	62.5%	66.0%	64.8%
Diabetes mellitus	28.9%	33.1%	30.5%
Re-intervention (previous coronary artery bypass grafting)	10.6%	12.3%	11.4%

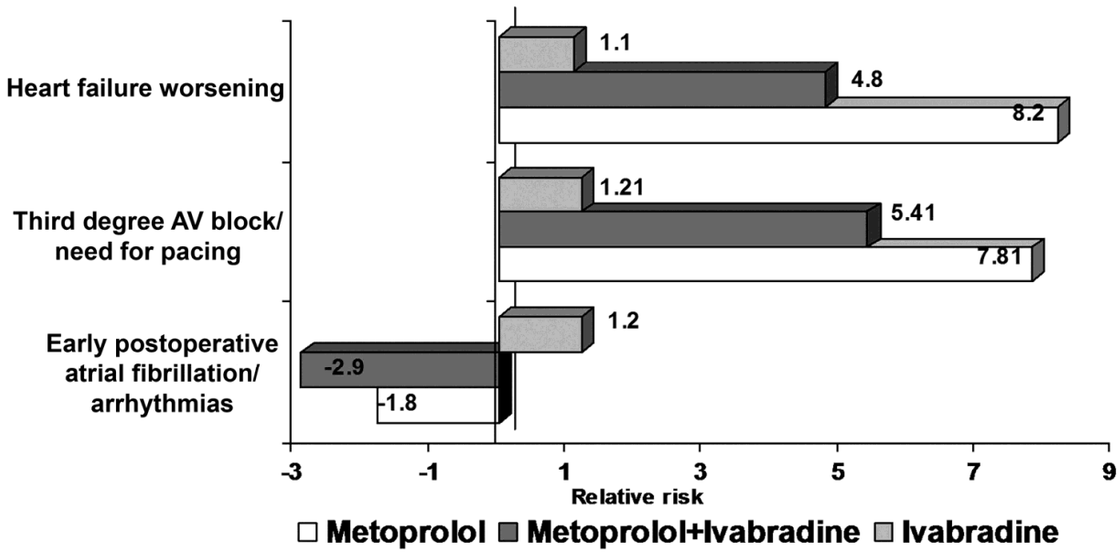
Note. Parameters are expressed as mean values (standard deviation) or percentages. All p values for comparisons between groups were non-significant.

Table 1. Baseline demographics and clinical characteristics of study population by treatment group

Endpoint	Group A N = 104	Group B N = 106	Group C N = 105
30-day mortality, in-hospital atrial fibrillation/arrhythmias	16 (15.4%)	11 (10.4%)	22 (21.0%)
30-day mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening	42 (40.4%)	28 (26.4%)	27 (25.7%)
Death at 30 days	4 (3.8%)	3 (2.8%)	4 (3.8%)
In-hospital atrial fibrillation/arrhythmias	12 (11.5%)	8 (7.6%)	18 (17.1%)
In-hospital 3 degree atrioventricular block/need for pacing	14 (13.5%)	10 (9.4%)	3 (2.9%)
In-hospital heart failure worsening	12 (11.5%)	7 (6.6%)	2 (1.9%)
Hospitalization duration >15 days	12 (11.5%)	10 (9.4%)	9 (8.6%)
Immobilization for >3 days	10 (9.6%)	7 (6.6%)	7 (6.7%)
Sleep disturbances/ gastrointestinal symptoms/ skin reactions	3 (2.9%)	3 (2.8%)	3 (2.9%)

Table 2. Composite and single efficacy and safety endpoints by treatment group

The rates of 30-day mortality were lower in the combined therapy group (2.8%) versus metoprolol or ivabradine monotherapy groups (3.8% in each monotherapy group).



Note. AV, atrioventricular.

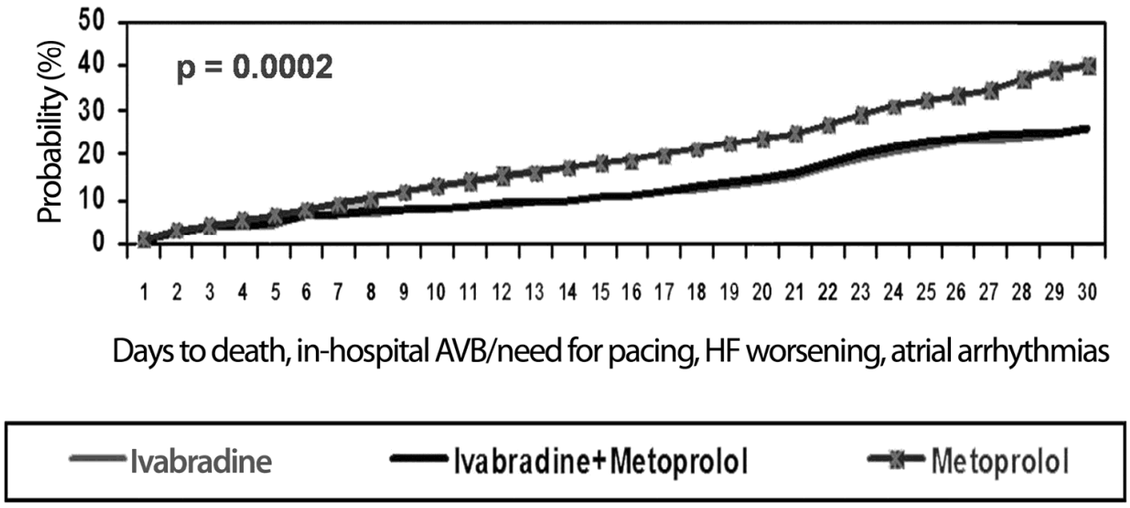
Fig. 2. The relative risks of ivabradine and combined therapy with ivabradine and metoprolol versus metoprolol monotherapy for early postoperative atrial fibrillation, complete atrioventricular block/need for pacing and postoperative heart failure worsening.

The overall quality of life was better in ivabradine groups. Ivabradine-treated patients had shortened hospital stay (the mean duration of hospital stay in the group A was 10.2 ± 6.3 days, compared to 8.5 ± 6.8 days in group B and 8.2 ± 6.4 days in group C), and reduced immobilization duration in the immediate postoperative period (2.0 ± 3 days in group A, 1.1 ± 3 days in group B and 1.1 ± 3 days in group C) (Table 2).

The cumulative incidence of non-cardiac side effects (sleep disturbances, gastrointestinal symptoms, and skin reactions) was similar in ivabradine (2.9%), metoprolol (2.9%) or combined ivabradine or metoprolol therapy (2.8%) groups (Table 2).

For the composite efficacy endpoint of 30-day mortality and in-hospital atrial fibrillation/arrhythmias the rates were 10.4% in the combined therapy group, 15.4% in the metoprolol group and 21.0% in the ivabradine monotherapy group. For the composite efficacy and safety endpoint of 30-day mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening, the rates were 25.7% in the ivabradine group, 26.4% in the ivabradine plus metoprolol group and 40.4% in the metoprolol group respectively ($p = 0.0002$) (Table 2), thus showing ivabradine therapy was superior to metoprolol therapy in terms of these composite endopoints. Kaplan Meier curves generated for primary endpoints also showed the superior efficacy and safety in ivabradine groups, either ivabradine monotherapy or combined

ivabradine and metoprolol therapy (Fig. 3). Log-rank tests were highly significant from Days 4-5 of treatment period to Day 30.



Note. AVB, atrioventricular block, HF, heart failure.

Fig. 3. Kaplan-Meier curves for the composite endpoint of 30-days mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening in the three treatment groups: ivabradine alone versus combined ivabradine plus metoprolol and metoprolol alone

The associated relative risks for the composite efficacy and safety endpoint of 30-day mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening in ivabradine-treated groups (with or without metoprolol) versus metoprolol-treated group in a subgroups analysis according to age, preoperative conduction abnormalities, NYHA class, previous episodes of atrial fibrillation and grafts number and type are shown in Table 3 and illustrated in Fig. 4. Ivabradine therapy (alone or associated to metoprolol) remained superior to metoprolol therapy in terms of the composite efficacy and safety endpoint of of 30-day mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening.

4. Discussion

The present study is, to the best of our knowledge, the first study which evaluated the use of ivabradine for prevention of postoperative atrial fibrillation or other tachyarrhythmias in patients undergoing coronary artery bypass surgery and assessed the efficacy and safety of ivabradine therapy in this setting. Atrial fibrillation is the most common complication which occurs after cardiac surgery, with frequencies ranging from 30% after coronary artery bypass grafting, 40% after valve surgery, and 50% after combined coronary artery bypass grafting/valve surgery (Camm et al., 2010). Development of atrial fibrillation immediately after coronary artery bypass grafting results in longer intensive care unit and hospital stays (Villareal et al., 2004; Tamis & Steinberg, 2000), and a significantly higher (two- to three-fold)

Composite endpoint of 30-days mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening	Relative risk metoprolol group N = 104	Relative risk ivabradine groups (with or without metoprolol) N = 211
Age		
≤70 years	1.5	1.5
>70 years	7.8	4.9
Previous episodes of atrial fibrillation	7.9	5.3
Preoperative conduction abnormalities	8.2	6.3
NYHA class		
NYHA I-II	1.5	1.2
NYHA III-IV	8.7	5.7
Number of grafts		
≥3 grafts	3.9	2.5
2 grafts	1.3	1.2
1 graft	1.2	1.1
Graft type		
Exclusively arterial	6.2	3.8
Exclusively venous	6.7	3.8
Combined venous and arterial	6.3	3.3

Table 3. Relative risks for the composite efficacy and safety endpoint of 30-days mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening in metoprolol versus ivabradine-treated patients

risk of postoperative stroke (Villareal et al., 2004; Reed et al., 1988). Post-operative atrial fibrillation has also been shown to independently predict post-operative delirium and neurocognitive decline (Burgess et al., 2006). Patients at risk for postoperative atrial fibrillation have been identified and include those with chronic obstructive pulmonary disease, proximal right coronary artery disease, prolonged cross-clamp time, atrial ischemia, advanced age, and withdrawal of beta-blockers (Eagle et al., 2004). Withdrawal of beta-blockers before surgery is a significant risk factor for the development of postoperative atrial fibrillation and should be avoided (Camm et al., 2010).

Because of the increased morbidity and mortality risk and of longer hospitalisations (up to five days [Eagle et al., 2004]) associated with the development of atrial fibrillation during the immediate postoperative period and because of the economic burden of these outcomes, prevention of postoperative atrial fibrillation becomes increasingly important. Various meta-analyses and systematic reviews assessed and identified pharmacologic and non-pharmacologic intervention to best prevent and treat postoperative atrial fibrillation.

At present, beta-blockers are the mainstay of therapy for prevention of postoperative atrial fibrillation in cardiac surgery. Both the ACC/AHA 2004 Guideline update for coronary artery bypass graft surgery for and the most recent ESC Guidelines for the management of atrial fibrillation recommend beta-blocker therapy as a class I indication in the prophylactic management of postoperative atrial fibrillation in patients without contraindications to beta-blocker therapy (Camm et al., 2010; Eagle et al., 2004). Studies showed that withdrawal of

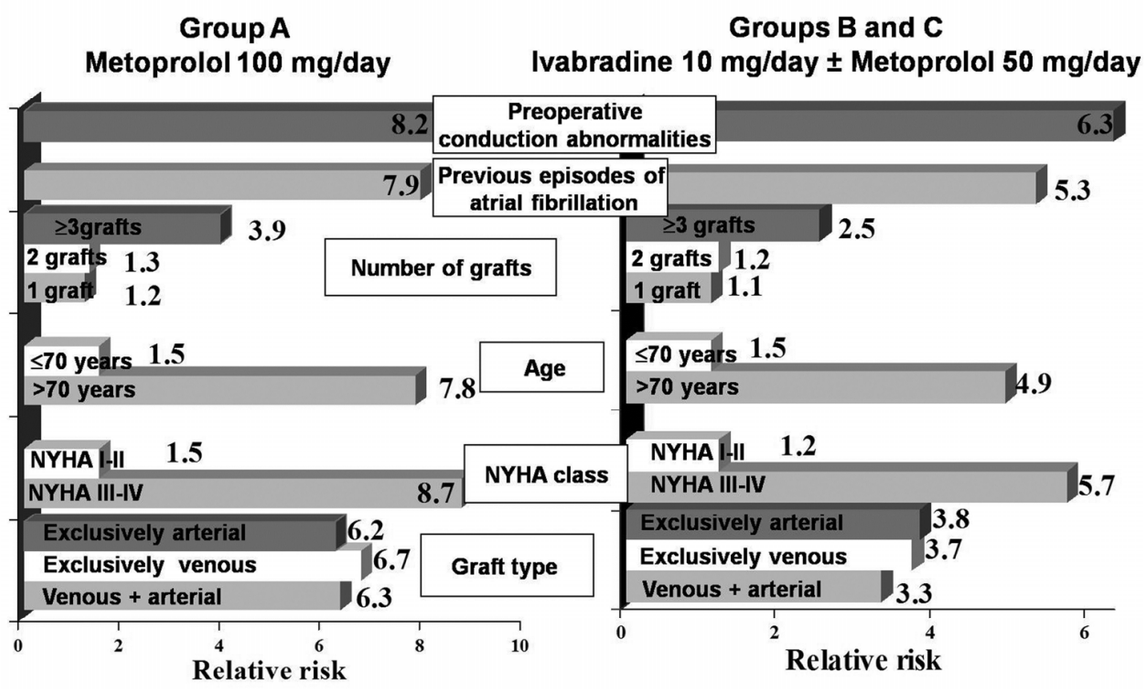


Fig. 4. Relative risks for the composite efficacy and safety endpoint of 30-days mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening in metoprolol versus ivabradine-treated patients in a subgroup analysis according to age, preoperative conduction abnormalities, NYHA class, previous episodes of atrial fibrillation and grafts number and type.

beta-blockers in the perioperative period doubles the incidence of postoperative atrial fibrillation after coronary artery bypass grafting (Eagle et al., 2004). Virtually every study of beta-blockers administered for the purpose of reducing postoperative atrial fibrillation has shown benefit in this regard, even if data regarding improvement of hospital stay or reduction of stroke incidence are still controversial (Iliuta et al., 2009). Most beta-blockers trials have examined the initiation of prophylaxis in the postoperative period. But it seems to be an even greater benefit if beta-blocker therapy is initiated before surgery. That is why the ESC guidelines for the management of atrial fibrillation recommend that treatment should be started at least 1 week before surgery with a $beta_1$-blocker without intrinsic sympathomimetic activity (Camm et al., 2010). The beta-blockers used in studies assessing atrial fibrillation prevention in cardiac surgery were propranolol (Matangyi et al., 1985), atenolol (Lamb et al., 1988), metoprolol (Lucio et al., 2004; Crystal et al., 2004; Kamei et al., 2006; Celik et al., 2009), acebutolol (Daudon et al., 1986), timolol (White et al., 1984), carvedilol (Kamei et al., 2006; Celik et al., 2009), betaxolol (Iliuta et al., 2009), either compared to control or to another beta-blocker.

Another antiarrhythmic agent used for the prevention of atrial fibrillation in cardiac surgery patients is sotalol which was shown to reduce the incidence of postoperative atrial fibrillation (Burgess et al., 2006; Crystal et al., 2004) compared to placebo or to other beta-blocker such as atenolol (Sanjuan et al., 2004), metoprolol (Parikka et al., 1998) or propranolol (Suttorp et al., 1990) but it had no impact on length of hospital stay, risk of strokes, or mortality (Crystal et al., 2004). However, the use of sotalol in postoperative atrial fibrillation is limited because of its significant side effects such as bradycardia and torsade de pointes, especially in patients with electrolyte disturbances. For these reasons, sotalol therapy for atrial fibrillation prevention in cardiac surgery patients is a class IIb indication in the ESC Guidelines for the management of atrial fibrillation (Camm et al., 2010).

Amiodarone and its beneficial effect in postoperative atrial fibrillation prevention was the subject of various studies and meta-analyses. Amiodarone decreased the incidence of postoperative atrial fibrillation (Burgess et al., 2006; Bagshaw et al., 2006) and significantly shortened the duration of hospital stay, and reduced the incidence of stroke and postoperative ventricular tachyarrhythmia (Burgess et al., 2006; Bagshaw et al., 2006), but not postoperative mortality (Bagshaw et al., 2006). The beneficial effects of amiodarone were observed irrespective of patients age, type of cardiac surgery (coronary artery bypass grafting only or valve surgery with or without coronary artery bypass grafting), and preoperative beta-blocker therapy. At present, amiodarone has a class IIa indication for atrial fibrillation prevention in patients undergoing cardiac surgery as recommended in the in the ESC Guidelines for the management of atrial fibrillation (Camm et al., 2010).

Other pharmacologic agents used in clinical study for the prevention of postoperative atrial fibrillation were digoxin, which was not found to be effective for atrial fibrillation prevention (Kowey et al., 1992) or calcium channel blockers, of which non-dihydropyridines significantly reduced supraventricular tachyarrhythmias in a subgroup analysis of a meta-analysis (Wijeysundera et al., 2003). Hypomagnesaemia is an independent risk factor for postoperative atrial fibrillation. A meta-analysis of randomized trials showed that prophylactic i.v. magnesium reduced the probability of postoperative atrial fibrillation (Miller et al., 2005).

From the non-pharmacologic interventions investigated for atrial fibrillation prevention in the postoperative setting, prophylactic atrial pacing reduced the incidence of post-operative atrial fibrillation regardless of the atrial pacing site or pacing algorithm used, (Burgess et al., 2006; Crystal et al., 2004) but results are controversial.

Despite this relative large range of prophylactic interventions for postoperative atrial fibrillation, there are subgroups of patients with conditions that limit the use of beta-blockers or other antiarrhythmic drugs. Among such conditions are cardiac conduction abnormalities or severe left ventricular dysfunction, active bronchospasm. In these patients ivabradine, a selective sinus node inhibitor, could be a viable alternative. Ivabradine is a specific inhibitor of the If current in the sinoatrial node. Consequently, it is a pure heart-rate-lowering agent in patients with sinus rhythm, without affecting blood pressure, myocardial contractility, intracardiac conduction, or ventricular repolarisation.

In BEAUTIFUL study, performed in patients with coronary artery disease and left ventricular systolic dysfunction (left ventricular ejection fraction of less than 40%), even if ivabradine failed to change the primary composite endpoint of cardiovascular death, admission to hospital for acute myocardial infarction, or admission to hospital for new-onset or worsening heart failure in any of the subgroups analysed, in a subgroup of patients with baseline heart rate of 70 bpm or higher it reduced the incidence of endpoints related to

coronary artery disease (admission to hospital for fatal and non-fatal acute myocardial infarction) (Fox et al., 2008). Therefore, ivabradine can be used safely to patients with coronary artery disease and impaired left-ventricular systolic function, in conjunction with beta-blockers. Furthermore, a combination of ivabradine with β blockade also improved coronary artery disease outcomes in patients with heart rates of 70 bpm or more (Fox et al., 2008). These results suggest that further lowering of heart rate has beneficial effects on coronary disease outcomes.

In SHIFT study, performed in patients with stable symptomatic chronic heart failure and a left ventricular ejection fraction of 35% or lower, with a resting heart rate of 70 bpm or higher, ivabradine substantially and significantly reduced major risks associated with heart failure when added to optimal standard treatment: cardiovascular death or hospital admission for worsening heart failure (Swedberg et al., 2010).

The results of these two studies supporting the importance of heart rate reduction with ivabradine for improvement of clinical outcomes in heart failure or coronary artery disease with systolic left ventricular dysfunction were the rationale for using ivabradine alone or in combination with metoprolol for prevention of postoperative atrial fibrillation and reduction of subsequent morbidity, mortality and associated economic costs in patients undergoing coronary artery bypass grafting.

In our study, heart rate reduction and prevention of postoperative atrial fibrillation or tachyarrhythmias in the combined therapy group (ivabradine and metoprolol) was proven to be more effective than with metoprolol or ivabradine alone during the immediate postoperative management of patients undergoing coronary artery bypass grafting. Ivabradine-treated patients' quality of life was improved due to shortened hospital stay, reduced immobilization duration in the immediate postoperative period, less atrial or ventricular arrhythmias, less worsening heart failure.

Because postoperative atrial fibrillation is associated with increased morbidity and mortality and longer, more expensive hospital stays, we defined a composite efficacy and safety endpoint of 30-days mortality, in-hospital atrial fibrillation/arrhythmias, in-hospital atrioventricular block/need for pacing, or in-hospital heart failure worsening. Ivabradine and combined therapy (ivabradine and metoprolol) were superior to metoprolol in respect to the composite efficacy and safety endpoints for prevention of atrial fibrillation after coronary artery bypass grafting.

4.1 Study limitations

One limitation of our study is the absence of an washout period. About 85% of patients had preoperative beta-blocker therapy and it was not stopped before the randomization. The practice in our department was to routinely continue preoperative beta-blocker therapy without any pause and changing the active principle according to the study group. Another limitation is the fact that about 30% of the patients with previous episodes of atrial fibrillation received prior to the inclusion in the study an antiarrhythmic agent such as amiodarone or sotalol. These limitations would induce a possible underestimation of some results.

5. Conclusion

In patients treated with ivabradine the quality of life was improved due to shorter hospital stay, less atrial or ventricular arrhythmias, less need for permanent pacing, less worsening

heart failure, shortened immobilization during the immediate postoperative period with subsequent improvement in the psychological status, as well as due to lack of significant side effects.

Considering the ivabradine efficacy and safety profile, the heart rate reduction in the early postoperative period after coronary surgery in patients with conduction abnormalities or left ventricular dysfunction with ivabradine therapy emerged as the best treatment in this trial.

Ivabradine should be regarded as an attractive alternative pharmacological strategy for rhythm and heart rate control in the early postoperative period in patients undergoing coronary artery bypass grafting with relative or absolute contraindications to beta-blocker therapy.

6. References

Bagshaw SM, Galbraith PD, Mitchell LB, et al (2006). Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. *The Annals of Thoracic Surgery*, Vol.82, No.5, (November 2006), pp. 1927–1937, ISSN 0003-4975

Burgess DC, Kilborn MJ, Keech AC (2006). Interventions for prevention of postoperative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. *European Heart Journal*, Vol.27, No.23, (December 2006), pp. 2846–2857, ISSN 0195-668x

Camm AJ, Kirchhof P, Lip GYH, et al (2010). Guidelines for the management of atrial fibrillation. *European Heart Journal*, Vol.31, No.19, (October 2010), pp. 2369–2429, ISSN 0195-668x

Celik T, Iyisoy A, Jata B, et al (2009). Betablockers for the prevention of atrial fibrillation after coronary artery bypass surgery: carvedilol versus metoprolol. *International Journal of Cardiology*, Vol.135, No.3, (July 2009), pp. 393-396, ISSN 0167-5273

Crystal E, Garfinkle MS, Connolly SS, et al (2004). Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database of Systematic Reviews*, No.4, (October 2004), Art. No.CD003611

Crystal E, Thorpe KE, Connolly SJ, et al (2004). Metoprolol prophylaxis against postoperative atrial fibrillation increases length of hospital stay in patients not on preoperative beta blockers: the beta blocker length of stay (BLOS) trial. *Heart*, Vol.90, No.8, (August 2004), pp. 941–942, ISSN 1355-6037

Daudon P, Corcos T, Gandjbakhch I, et al (1986). Prevention of atrial fibrillation or flutter by acebutolol after coronary bypass grafting. *American Journal of Cardiology*, Vol.58, No.10, (November 1986), pp. 933–966, ISSN 0002-9149

Eagle KA, Guyton RA, Davidoff R, et al (2004). ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation*, Vol.110, No.14, (October 2004), pp. e340-437, ISSN 0009-7322

Fox K, Ford I, Steg PG, et al; BEAUTIFUL Investigators (2008). Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*, Vol.372, No.9641, (September 2008), pp. 807-16, ISSN 0140-6736

Iliuta L, Christodorescu R, Filipescu D, et al (2009). Prevention of perioperative atrial fibrillation with betablockers in coronary surgery: betaxolol versus metoprolol.

Interactive Cardiovascular and Thoracic Surgery, Vol.9, No.1, (July 2009), pp. 89-93, ISSN 1569-9293

Kamei M, Morita S, Hayashi Y, et al (2006). Carvedilol versus metoprolol for the prevention of atrial fibrillation after off-pump coronary bypass surgery: rationale and design of the carvedilol or metoprolol post-revascularization atrial fibrillation controlled trial (COMPACT). Cardiovascular Drugs and Therapy, Vol.20, No.3 (June 2006), pp. 219–227, ISSN 0920-3206

Kowey PR, Taylor JE, Rials SJ, Marinchak RA (1992). Meta-analysis of the effectiveness of prophylactic drug therapy in preventing supraventricular arrhythmia early after coronary artery bypass grafting. *American Journal of Cardiology*, Vol.69, No.9 (April 1992), pp. 963–965, ISSN 0002-9149

Lamb RK, Prabhakar G, Thorpe JA, et al (1988). The use of atenolol in the prevention of supraventricular arrhythmias following coronary artery surgery. *European Heart Journal*, Vol.9, No.1, (January 1988), pp. 32–36, ISSN 0195-668x

Lucio Ede A, Flores A, Blacher C, et al. Effectiveness of metoprolol in preventing atrial fibrillation and flutter in the postoperative period of coronary artery bypass graft surgery. *Arquivos Brasileiros de Cardiologia*, Vol.82, No.1, (January 2004), pp. 42–46; 37–41, ISSN 0066-782X

Matangi MF, Neutze JM, Graham KJ, et al (1985). Arrhythmia prophylaxis after aorta-coronary bypass: the effect of minidose propanolol. *The Journal of Thoracic and Cardiovascular Surgery*, Vol.89, No.3, (March 1985), pp. 439-43, ISSN 0022-5223

Miller S, Crystal E, Garfinkle M, et al (2005). Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. *Heart*, Vol.91, No.5, (May 2005), pp. 618–623, ISSN 1355-6037

Parikka H, Toivonen L, Heikkila L, et al (1998). Comparison of sotalol and metoprolol in the prevention of atrial fibrillation after coronary artery bypass surgery. *Journal of Cardiovascular Pharmacology*, Vol.31, No.1, (January 1998), pp. 67–73, ISSN 0160-2446

Reed G III, Singer DE, Picard EH, DeSanctis RW (1988). Stroke following coronary-artery bypass surgery. A case-control estimate of the risk from carotid bruits. *New England Journal of Medicine*, Vol.319, No.19 (November 1988), pp. 1246–1250, ISSN 0028-4793

Sanjuan R, Blasco M, Carbonell N, et al (2004). Preoperative use of sotalol versus atenolol for atrial fibrillation after cardiac surgery. *The Annals of Thoracic Surgery*, Vol.77, No. 3 (March 2004), pp. 838–843, ISSN 0003-4975

Suttorp MJ, Kingma JH, Tjon Joe Gin RM, et al (1990). Efficacy and safety of low- and high-dose sotalol versus propranolol in the prevention of supraventricular tachyarrhythmias early after coronary artery bypass operations. *The Journal of Thoracic and Cardiovascular Surgery*, Vol.100, No.6, (December 1990), pp. 921–926, ISSN 0022-5223

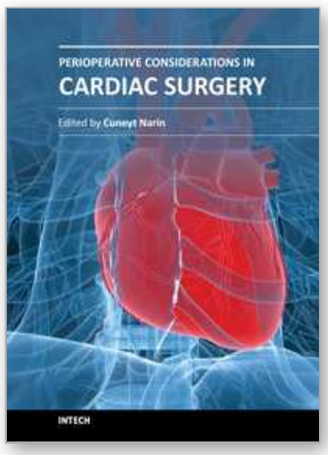
Swedberg K, Komajda M, Böhm M, et al; SHIFT Investigators (2010). Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*, Vol.376, No.9744, (September 2010), pp. 875-85, ISSN 0140-6736

Tamis JE, Steinberg JS (2000). Atrial fibrillation independently prolongs hospital stay after coronary artery bypass surgery. *Clinical Cardiology*, Vol.23, No.3, (March 2000), pp. 155–159, ISSN 1932-8737

Villareal RP, Hariharan R, Liu B, et al (2004). Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *Journal of the American College of Cardiology*, Vol.43, No.5, (March 2004), pp. 742–748, ISSN 0735-1097

White HD, Antman EM, Glynn MA, et al (1984). Efficacy and safety of timolol for prevention of supraventricular tachyarrhythmias after coronary artery bypass surgery. *Circulation*, Vol.70, No.3, (September 1984), pp. 479–484, ISSN 0009-7322

Wijeysundera DN, Beattie WS, Rao V, Karski J (2003). Calcium antagonists reduce cardiovascular complications after cardiac surgery: a meta-analysis. *Journal of the American College of Cardiology*, Vol.41, No.9, (May 2003), pp. 1496–1505, ISSN 0735-1097



Perioperative Considerations in Cardiac Surgery

Edited by Prof. Cuneyt Narin

ISBN 978-953-51-0147-5
Hard cover, 378 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen