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Review of international clinical trials in cardiology for 2014

Factors affecting the increase of follicle-stimulating hormone in women with cardiovascular pathology

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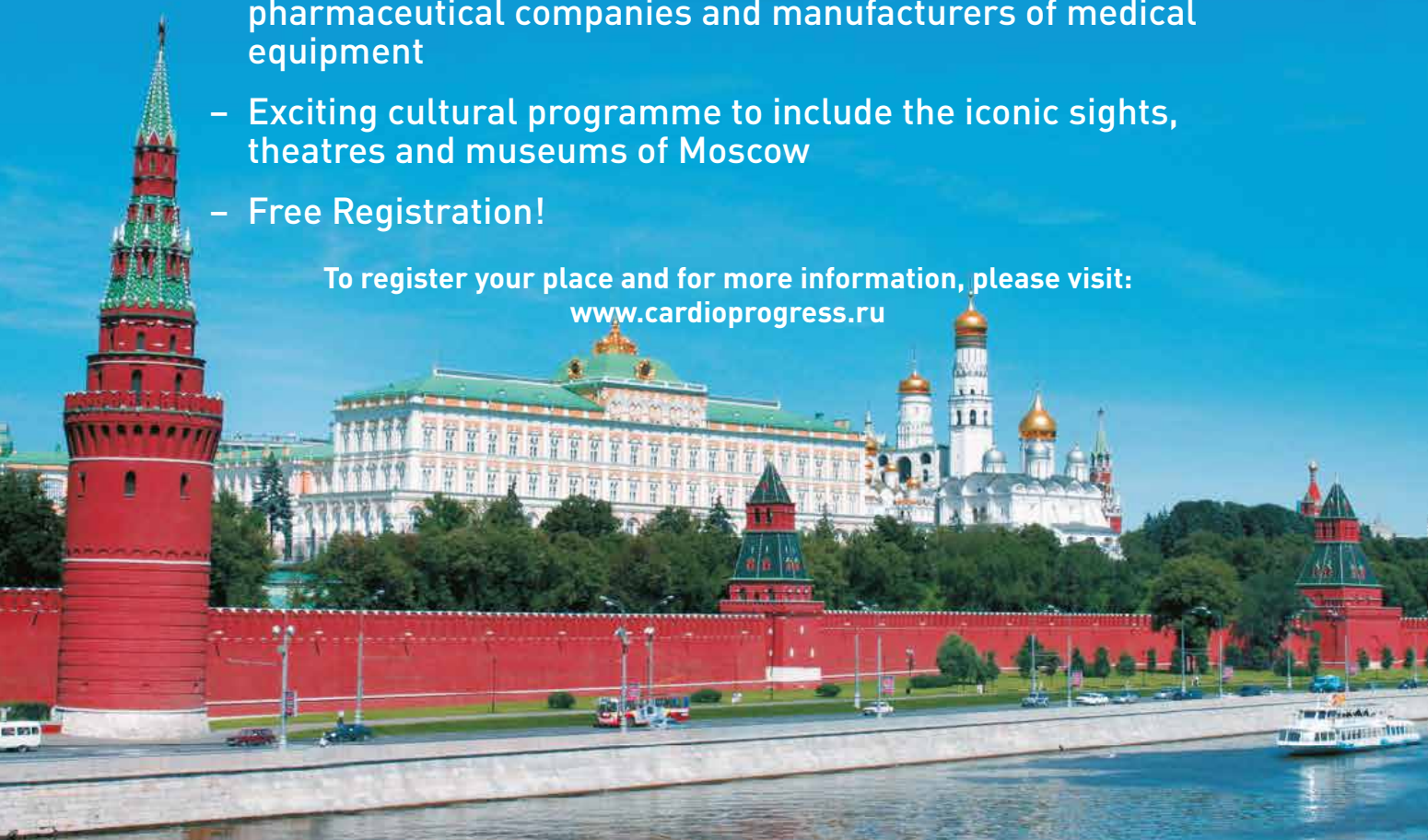

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Contact details:
Cardioprogress Foundation and Editorial Office:
Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia
Editorial Office tel.: (+7) 965 236 1600
Official website: www.cardioprogress.ru

Editorial correspondence should be sent to:
Mehman Mamedov, Deputy Editor,
editor.ihvdj@gmail.com
Articles for publication should be sent to:
Anna Arteyeva, Associate Editor,
submissions.ihvdj@gmail.com

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Contents

Editor's Welcome

Dear Colleagues,

This issue, like the previous ones, is dedicated to various problems of cardiovascular pathology, and also reviews international clinical studies presented at the European Society of Cardiology (ESC) Congress 2014.

In the review article about the side effects of tyrosine kinase and mammalian target of rapamycin inhibitors, which are used to treat cancer patients, their cardiotoxic effect was shown and, in particular, the influence on development of hypertension. Approaches are proposed to reduce their adverse impact.

Three articles presented problems of therapies for specific clinical conditions:

- electromagnetic disturbances in the treatment of arrhythmias by radiofrequency ablation;
- development of a method for predicting the onset of reproductive ageing and the progress of menopause complications by determining the spectrum of sex hormones;
- progression of atrial fibrillation from paroxysmal to its permanent forms, and consideration of available treatment options, their efficacy and safety.

Another review article summarized the results of 28 international clinical studies presented in the Hot Line sessions at the ESC Congress 2014.

I hope that the content of this issue will be interesting and useful for all doctors involved in cardiovascular pathology. I would like to invite everyone to cooperate with our journal. We look forward to your original articles, literature reviews, discussions, opinions on the problem, and recommendations for treatment and prevention.

Yours sincerely,
Rafael G. Oganov
President, Cardioprogress Foundation
Editor-in-Chief

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LEADING ARTICLE

Antiarrhythmic therapy in patients with paroxysmal and persistent atrial fibrillation: prediction and prevention of progression to permanent form of arrhythmia

Kanorskiy S.G.*

State Budget Educational Institution of Higher Professional Education «Kuban State Medical University» of the Ministry of Healthcare of the Russian Federation, 350 063, Russia, Krasnodar, 4 Sedin Street

Author:

Sergey G. Kanorskiy, MD, Professor, Head of the Department of Therapy № 2 of Faculty of Advanced Training and Professional Retraining of Specialists of the State Budget Educational Institution of Higher Professional Education «Kuban State Medical University» of the Ministry of Healthcare of the Russian Federation, Krasnodar, Russia

Summary

A realistic objective for treatment of patients with paroxysmal and persistent atrial fibrillation (AF) should be to prevent its progression to a permanent form of arrhythmia, which is associated with an increased risk of complications and worsening prognosis. This review presents easily identifiable predictors of AF progression, reviews available treatment options, and their efficacy and safety. Early and active measures to restore and maintain sinus rhythm by pharmacological and non-drug methods will prevent the development of arrhythmia substrate; inhibit the progression from paroxysmal to permanent AF, with potentially beneficial effects on prognosis.

Keywords

Atrial fibrillation, progression, treatment

* Corresponding author. Tel: +7 918 355 82 81. Fax: +7 (861) 268 17 95. E-mail: kanorskysg@mail.ru

Between 1990 and 2010, the prevalence of AF worldwide, and its associated morbidity and mortality, increased about two times despite the best efforts of medical science and health care [1]. According to epidemiological studies conducted in Western Europe, AF is already detected in 2.0–4.7% of cases in the general population [2]. According to forecasts, by 2050 the number of patients with AF may increase more than two times [3]. AF is a major cause of stroke and congestive heart failure (HF). Even in AF patients under the age of 65 years without concomitant diseases, there is a two-fold increase in mortality compared with general population [4].

In six randomized clinical trials (PIAF, AFFIRM, RACE, STAF, HOT CAFÉ, AF CHF), treatment strategies in AF patients to restore and maintain sinus rhythm did not reduce mortality compared with the tactics of shortening the ventricular rate while maintaining AF. This result is associated with a lack of efficacy and safety of modern anti-arrhythmic drugs, and with the limitations of design of research studies [5]. In those studies, elderly patients with late-stage development of an AF substrate in atria and considerable stability arrhythmia were included. Meanwhile, even in those studies a decrease in symptoms and improvement in quality of life has been convincingly demonstrated while maintaining sinus rhythm, as well as a significant reduction in total mortality by 47% (P<0.0001) in the actual maintenance of normal sinus rhythm during observation period [6].

In general, the results of AF treatment are far from desired, which is often attributed to an inadequate understanding of the mechanisms of its development. At the same time, cellular and molecular mechanisms of AF initiation have been well studied [7]. It has been established that aging, hypertension, valve disease, HF, myocardial infarction, obesity, smoking, diabetes, thyroid dysfunction and intense physical endurance training contribute to structural remodeling of the atria [8]. With regard to clinical practice, special attention is drawn to the concept of AF progression from paroxysmal to a permanent clinical form [9].

Paroxysmal AF may take up to 7 days, but differs by spontaneous termination, usually within the first 48 hours. In paroxysmal AF lasting more than 48 hours, the probability of spontaneous termination of arrhythmia is low, but the risk of systemic thromboembolism significantly increases, which requires consideration of initiating antithrombotic therapy. Persistent AF, unlike paroxysmal, does not stop by itself, continues for more than 7 days, and medication or electrical cardioversion may be useful in resolving the problem. Prolonged persistent AF is diagnosed when AF continues for a year or more, and the strategy of sinus rhythm restoration and conservation using anti-arrhythmic drugs and/or ablation in the left atrium are chosen. Permanent AF is diagnosed in cases when a patient and a doctor consider possible to preserve arrhythmia, or when previous attempts of cardioversion or cardiac surgery treatments have been unsuccessful [10,11].

In recent years, antithrombotic therapy in patients with AF has become the most popular, which actually changes the prognosis for patients. It is emphasized that the risk of stroke depends not on the form of AF (paroxysmal, persistent or permanent), but on other clinical factors, summarized by scales, $CHADS_2$ and more modern CHA_2DS_2-VASc, designed to assess stroke risk [10,11]. Indeed, according to the ACTIVE W study, the incidence of stroke in patients with paroxysmal (n=1,202, the average score $CHADS_2$ 1.79±1.03), persistent and permanent AF (n=5,495, the average score $CHADS_2$ 2.04±1.12, P <0.00001) was not significantly different (P=0.496), even after adjusting for baseline clinical differences (P=0.755) [12]. One might think that in paroxysmal AF a shorter period of blood stagnation in the atria during fibrillation takes place, but the rapid restoration of mechanical atrial systole contributes to dislocation of fresh blood clots into the arterial system. In persistent/permanent AF, long/continuous stagnation of blood in the atria creates a constant environment for thrombus formation in the atria, but long-term/permanent absence of mechanical atrial systole allows blood clots to organize, to grow together with the wall of the atrium and even dissolve by the fibrinolytic system in the body.

However, in a large modern study, ARISTOTLE, the frequency of stroke or systemic embolism was significantly higher in patients with persistent or permanent AF (n=15,412) than in patients with paroxysmal AF (n=2,786) (1.52% vs. 0.98%, P=0.003, adjusted for baseline clinical differences P=0.015). There was also a tendency towards higher mortality in patients with persistent or permanent AF (3.90% vs. 2.81%, P= 0.0002, adjusted P=0.066) [13].

K. Imai *et al*. [14] recently developed and tested a scale assessing the risk of severe HF in New York Heart Association (NYHA) functional class III or IV patients with non-valvular AF – ARC2H. According to this scale, a patient gains 1 point if he/she is 72 years and older, has heart rate of 80 beats per minute or more, hypertension, and he/she gains 2 points if there is previously established HF.

The annual risk of severe HF ranged from 0.8% to 35% in patients with 0 and 5.4 points according to ARC2H, respectively. In the largest study, AFFIRM, which compared the tactics of restoring and maintaining sinus rhythm with the tactics of shortening of ventricular rate while maintaining AF, the long duration of AF was directly related to the high prevalence of symptoms of chronic HF [15].

According to S. Taillandier et al. [16], among 1,906 patients with a combination of AF and chronic HF, 55% of patients had persistent or paroxysmal and 45% – permanent form of arrhythmia. During an about 1.9 years of follow-up, the risk of hospitalization for decompensation of HF was significantly higher in patients with permanent AF, especially in a subgroup of individuals with preserved left ventricular ejection fraction.

The presented data confirm the known position [17] – slowing the progression of AF to its more prolonged forms may be considered as one of the goals of its therapy that can mitigate a risk of thromboembolism, HF and mortality. Modern ideas about the factors of such AF progression necessarily include structural and electrical remodeling of the atria. Sustained AF can cause an inflammatory reaction that leads to activation of myofibroblasts and the release of cytokines, such as transforming growth factor-ß and platelet-derived growth factor, and also profibrotic proteins. Activation of signaling cascades involving the latter is essential for the development of fibrosis. It leads to dysfunction of ion channels, apoptosis of cardiomyocytes and growth of extracellular matrix, which contributes to both electric and structural remodeling – the basis for preservation of AF [18,19].

Studies of modern pharmacological types of treatment of underlying disease (upstream therapies) to prevent electric (blockers of slow calcium channels) and structural remodeling, fibrosis (renin-angiotensin system blockers, statins, omega-3 fatty acids), revealed contradictory, mostly negative results [20,21]. Despite this, one of the objectives of treating AF patients should be regression of left ventricular hypertrophy. Multivariate data analysis of the AFFIRM project has shown that thickening of the left ventricular wall, especially the interventricular septum, is an independent predictor for overall mortality (1.46 relative risk (RR), 95% confidence interval (CI), from 1.14 to 1.86, *P*=0.003) and stroke (1.89 RR, 95% CI, from 1.17 to 3.08, *P*=0.01). Concentric left ventricular hypertrophy was associated with the highest overall mortality (1.53 RR, 95% CI, from 1.11 to 2.12, *P*=0.009) [22]. It is known that the presence of left ventricular hypertrophy increases the risk of death because of ventricular tachyarrhythmia, including instigated antiarrhythmic therapy.

Moreover, left ventricular hypertrophy predisposes to the resumption of AF during a therapy to maintain sinus rhythm. In a cohort of 1,088 participants of the AFFIRM study, the median time of AF recurrence in patients with concentric left ventricular hypertrophy was 13.3 months (95% CI, from 8.2 to 24.5) versus 28.3 months (95% CI, from 20.2 to 48.6) in patients without hypertrophy. Concentric type of hypertrophy was an independent predictor of AF recurrence (1.49 RR, 95% CI, from 1.10 to 2.01, *P*=0.01) [23].

R. Chung *et al*. [24] selected 537 AF patients with left ventricular hypertrophy where the wall thickness ≥1.4 cm (mean age 67.5±11.7 years, left ventricular ejection fraction (LVEF) 48.3±13.3%), some not receiving antiarrhythmic drugs and some receiving amiodarone or other antiarrhythmic agents to maintain sinus rhythm. Amiodarone therapy was associated with lower survival (*P*=0.001), even after age adjustment, LVEF and the presence of coronary artery disease (CAD) (*P*=0.023). These data do not support expert opinion that treatment of persistent AF in patients with left ventricular hypertrophy should be conducted with amiodarone due to the fact that, compared to it, other antiarrhythmic drugs increase mortality [25].

According the Euro Heart Survey registry [26] and J-RHYTHM II study [27], within one year 10–15% of patients have progression from paroxysmal to persistent AF. It is shown that old age, organic heart disease, hypertension, AF lasting more than 3 months, tactics of shortening ventricular rate contribute to progression to more sustainable forms of AF, but restoration and maintenance of sinus rhythm, left atrial dilatation and obesity do not [28]. Also, the HATCH score was suggested, according to which a patient gets 2 points for the presence of HF and history of transient ischemic attack / stroke, and 1 point for the age over 75 years, hypertension, chronic obstructive pulmonary disease [17]. If the total score is from 5 to 7 the risk of progression from paroxysmal to persistent AF on the background of a drug therapy can reach 35–50%, and at 0 points – about 6%.

It is important to note that psychological status of AF patients deteriorates as arrhythmia progresses. In a study conducted by A.F. von Eisenhart Rothe *et al*. [29], after eliminating the influence of gender, age and other relevant factors, major depressive disorder occurred 44% more often (*P*=0.007) at persistent AF compared to paroxysmal.

Antiarrhythmic drugs, despite their well-known shortcomings, remain the only widely available means for the effective suppression of AF, i.e. implementation of tactics of maintaining sinus rhythm. Are they able to slow the progression of this arrhythmia to its permanent form? In AF patients with maintaining sinus rhythm, the left atrium decreases in size and left ventricular systolic function improves. Both of these indicators are important factors associated with progression of AF [30]. However, in a study conducted by S.B.de Vos *et al.* [31], only class IC antiarrhythmic medications significantly (P=0.0013) inhibited the progression of AF during a year of observation.

The most dangerous, though rare, side effect of class I drugs is a ventricular tachyarrhythmia. Its harbinger is an expansion of the QRS complex on the electrocardiogram (ECG). In the AFFIRM study, to maintain sinus rhythm it was allowed to use drugs of class IA (disopyramide, procainamide, quinidine) and class IC (moricizine, propafenone, flecainide). The QRS duration ⩾120 ms was associated with a significant (1.61 RR, 95% CI, from 1.29 to 2.03, P<0.001) increase in the risk of death (all-cause, cardiovascular and arrhythmic) and hospitalization (1.14 RR, 95% CI, from 1.07 to 1.34, P=0.043). Increased mortality (P=0.03) was also observed among patients with QRS duration 90–119 ms and concomitant HF [32].

These recently published data require consideration when choosing between available in Russian class IC antiarrhythmic drugs allapinin, propafenone and etatsizin. When used in normal dosages allapinin the least expands the QRS complex, which ensures the highest safety of therapy, but does not at least inferior to propafenone and etatsizin efficiency. According to our data, in comparable groups of patients with highly symptomatic persistent AF (Table 1), allapinin in dose of 67±12 mg/day caused widening of the QRS complex by 14% in average, propafenone – 385±44 mg/day – 19%, and etatsizin – 126±20 mg/day – 23%, respectively.

To prevent such side-effect of class IC antiarrhythmic drugs as atrial flutter with a high frequency of impulses to the ventricles, to achieve a therapy of high anti-relapse activity for AF even at lower doses of drugs it is appropriate to take them in combination with sotalol or amiodarone [33]. According to the latest data of the PREFER registry [34], in 461 centers of 7 European countries frequently AF patients, in order to maintain sinus rhythm, are assigned amiodarone (24.1% of cases), flecainide or propafenone (13.5%), sotalol (5.5%), and dronedarone (only 4.0%, respectively). Similar statistics from 9 European countries was presented by the authors of the EORP-AF registry [35]. Before starting treatment with amiodarone and every 6–12 months of therapy, it is required to monitor the lungs, liver and thyroid. The ORBIT-AF registry in the US [36] showed that among 10,061 AF patients, the majority of them (often elderly people with hypertension, HF, previous stroke, and minimally symptomatic arrhythmias) received therapy which slows down the ventricular rate. Of course, this treatment strategy does not provide reverse remodeling of the heart and enhances morphological changes in the atria that perpetuate the arrhythmia [37].

Currently, the EAST study, in order to prevent stroke and other adverse events by early therapy of preserving sinus rhythm, includes patients with newly emerging AF and a CHA2DS2-VASc score of 2 or more [38]. It is assumed that preservation of sinus rhythm from the early detection of AF will keep the structure and function of the atria more effectively than the standard treatment (transition to the restoring and maintaining sinus rhythm in case of continued symptoms with effective reduction of ventricular contractions on the background of AF). The EAST project suggests using not only antiarrhythmic drug therapy of AF, but also catheter ablation in the left atrium.

In 2012, two authoritative expert groups expanded indications for radiofrequency catheter ablation to maintain sinus rhythm in patients with AF [25,39].

Table 1. **Baseline characteristics of patients with persistent AF**

Parameter	Allapinin (n=28)	propafenone (n=24)	Etatsizin (n=25)
Age, years, (M±m)	59.5±5.3	57.7±4.8	56.8±4.9
Men/Women	14/14	11/13	13/12
Hypertension,%	78.6%	83.3%	76.0%
Idiopathic AF, %	10.7%	4.6%	12.0%
CAD,%	10.7%	12.5%	12.0%
Functional class of chronic HF, (M±m)	1.50±0.33	1.43±0.26	1.58±0.29
Anteroposterior diameter of the left atrium, mm (M±m)	43.6±2.1	44.2±2.3	43.8±2.0
LVEF, % (M±m)	60.5±4.2	58.6±3.8	62.1±4.5

Recently, the first results of the multicenter, prospective, randomized SARA study of 146 patients with persistent AF were published, it established the superiority of catheter ablation in the maintenance of sinus rhythm compared with antiarrhythmic drug therapy. From 3 to 12 months after initiation of the therapy, there were no records of episodes of AF or atrial flutter lasting more than 24 hours in 70.4% of patients who underwent ablation, and in 43.7% of patients treated with class IC or III antiarrhythmic drugs (P=0.002) [40].

Regression of dilatation and remodeling of the left atrium was observed in AF patients after catheter isolation of pulmonary veins [41]. As a result of sinus rhythm restoration and maintenance, initially decreased LVEF significantly increases, exercise tolerance and quality of life improves compared with the tactics of shortening of ventricular rate while maintaining AF [42,43].

Despite these positive data directly indicating preferred tactics of sinus rhythm control, the left atrial catheter ablation in terms of its implementation requires further research [44]. It is still carefully studied and evaluated the frequency of such immediate complications of this invasive procedure as pericardial effusion, cardiac tamponade, pulmonary vein stenosis, ulcers or esophageal perforation with the atrio-esophageal fistula formation, stroke/transient ischemic attack, phrenic nerve injury, arteriovenous fistula in a puncture on the hip [45].

No one denied the presumption of a possible deterioration of atrial function in years after ablation. H. Cochet *et al*. [46] studied the structure and function of the left atrium in 26 patients with persistent AF 80±15 months after radiofrequency catheter ablation. According to magnetic resonance imaging (MRI), contractility and compliance of the left atrium noticeably deteriorated after 5 years of successful ablation of persistent AF in direct relation to scar size.

Radiofrequency catheter ablation appears to be the most appropriate in paroxysmal AF. Observation of 889 patients with paroxysmal or persistent/long-lasting persistent AF for an average of 64 months after catheter ablation in the left atrium (pulmonary vein isolation and linear effects) showed an early advantage of such procedure. AF progression to its permanent form was significantly more frequently observed in patients with persistent (10%) or long-lasting persistent AF (14.6%) than in patients with paroxysmal AF (2.7%, P<0.001) [47].

The ongoing big CABANA and EAST projects will help in the future answer the remaining questions, including the long-term efficacy of catheter ablation and the impact of the underlying disease on treatment outcomes.

During open heart surgery, some surgical effects can be performed on the atria to eliminate AF. According to the results of 7 comparative studies of surgical ablation on the epicardial surface and radiofrequency ablation on the endocardial surface of the left atrium, the first procedure usually eliminates AF during a year (74% versus 43% of patients; 3.91 RR, 95% CI, from 2.38 to 6.42, P<0.00001). However, the surgical ablation often required pacemaker implantation, and the number of neurological complications and cardiac tamponade appeared to be comparable to those in the group of catheter ablation [48].

A tolerant attitude toward asymptomatic AF is erroneous. K.Senoo *et al*. [49] observed 1,176 patients with paroxysmal AF in average for 1,213±905 days, noting the progress of arrhythmia toward its permanent form with a frequency of 6% per year. In 468 asymptomatic, at the first examination, patients, even at low levels of risk, a more frequent progression of AF was noted compared to patients who had arrhythmia symptoms. This paradoxical result, according to the authors, is due to less intensive drug treatment and rare use of radiofrequency ablation to maintain sinus rhythm.

Management of the known risk factors may also be useful. According to a 16-year observation of 34,720 female participants in the Women's Health Study project who did not initially have AF and cardiovascular disease, obesity and elevated levels of hemoglobin A1c contribute to the occurrence of persistent and permanent AF. It is expected that reduction of overweight and glycemic control can reduce the proportion of people with persistent AF [50].

Conclusion

Large clinical investigations have not yet shown prognostic benefits of rhythm control compared with ventricular rate control during persistent AF, but they included patients in the late stages of the disease. It is likely that only intervention at an early stage of AF progression will be more effective. Early and active measures to detect AF, restoration and maintenance of sinus rhythm by pharmacological and non-drug methods will prevent the development of arrhythmia substrate, inhibit the progression from paroxysmal to persistent AF with potentially beneficial effects on prognosis. Therefore, for relatively young patients and/or for patients with severe symptoms of AF, restoration and maintenance of sinus rhythm is preferred.

Conflict of interest: None declared

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Tyrosine kinase inhibitors and mammalian target of rapamycin inhibitors related to cardiac toxicity

Asawaeer M.*, Riaz I.bin, Carli S., Singh P.

Authors:

Majid Asawaeer, MD, Clinical Assistant Professor, Division of Medical Education, Midwestern University, 300 El Camino Real, Sierra Vista, AZ 85635, USA
Irbaz bin Riaz, MD, Internal Medicine Resident, Internal Medicine Department, University of Arizona, USA
Samuel Carli, MD, Internal Medicine Resident, Internal Medicine Department, University of Arizona, USA
Parminder Singh, MD, Assistant Professor, Department of Medicine, University of Arizona Cancer Center, University of Arizona, USA

Abstract

Background

Tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors (mTORIs) are emerging as one of the most commonly used targeted chemotherapeutic agents in cancer treatment. As with any other medication, adverse effects are not uncommon, especially cardiac adverse effects. Given the improved survival with the use of these medications, it is anticipated that primary care providers are going to manage them and deal with the adverse effects they developed from using these medications more frequently.

Aim

We reviewed comprehensively the cardiovascular adverse effects of the oral TKIs and mTORIs. In addition, we offered the current recommendations regarding management of these cardiovascular adverse effects to help the primary care providers manage these side effects.

Methods and Materials

A formal literature review of PubMed and ClinicalTrials.gov using the following terms: "sunitinib, sorafenib, pazopanib, temsirolimus, and everolimus" was used, with only phase 2 and 3 clinical trials in English language and published up to April 5, 2013 were consider in this review article.

* Corresponding author. Tel. (office): +1-520-251-8593. Fax: +1-520-417-3174. Email: masawaeer@gmail.com

Results

We found that hypertension is the most commonly reported adverse effect with the use of TKIs. Pazopanib was associated with the highest incidence of hypertension. 32% of the patients who received pazopanib developed grade 1/2 hypertension and 6% developed grade 3/4 hypertension. The use of oral mTORIs was associated more with endocrinological derangements including hypertriglyceridaemia and hyperglycaemia, especially with everolimus usage.

Conclusion

It is not uncommon to see cardiac adverse effects with the usage of oral TKIs and mTORIs.

Keywords

Oral TKIs, mTORIs, adverse effects, cardiac

Introduction

It is estimated now that two thirds of patients diagnosed with cancer today will experience at least 5-year survival [1]. This rise in cancer survivors has created new challenges to the primary care providers and internists as they deal more often with patients who are on oral chemotherapy including oral TKIs and mTORIs. In this review article, we will discuss the cardiac toxicity of three oral small molecule TKIs, which are sunitinib, sorafenib, and pazopanib as well as the mTORIs, temsirolimus and everolimus. In addition, we will tailor this review to help the primary care providers and internists manage these side effects.

In the era of targeted cancer chemotherapy, TKIs and mTORIs have been one of the most commonly used targeted chemotherapies. These novel medications play a key role in the transmission of growth, differentiation, and migration and apoptotic signals. However, the use of these agents is not without limitations, including the development of resistance, the financial cost and adverse effects associated with the use of these drugs.

Methods and Materials

A formal literature review of PubMed and ClinicalTrials.gov using the following terms: "sunitinib, sorafenib, pazopanib, temsirolimus, and everolimus" was done. And only phase 2 and 3 clinical trials in English language completed and published up to April 5, 2013 were considered in this review article.

The TKIs (pazopanib, sorafenib, sunitinib)

There are two classes of tyrosine kinases, receptor tyrosine kinases (extracellular) and cellular tyrosine kinases (intra-cytoplasm or intra-nuclear). Fifty-six receptor tyrosine kinases are expressed, which can be subdivided into 19 families (AATYK, ALK, AXL, DDR, EGFR, EPH, FGFR, INSR, MET, MUSK, PDGFR, PTK7, RET, ROR, ROS, RYK, TIE, TRK and VEGFR family). In addition, 32 cellular tyrosine kinases are expressed, which can be subdivided into 11 families (ABL, ACK, CSK, focal adhesion kinase (FAK), FES, FRK, JAK, SRC-A, SRC-B, TEC and SYK family) [2]. See table 1.

Sunitinib works as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRß), vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3), stem cell factor receptor (KIT), FMS-like tyrosine kinase-3 (FLT3), colony stimulating factor 1 receptor (CSF1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib is currently approved for the treatment of gastrointestinal stromal tumour (GIST) after disease progression on or intolerance to imatinib mesylate, advanced renal cell carcinoma (RCC), and progressive well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease [3].

Table 1. **A list of the oral TKI with their taget receptors and the currently approved targeted tumors**

TKI	Tyrosine kinase target	Neoplasm (s) targeted
Sunitinib	PDGFRα, PDGFRß, VEGFR1, VEGFR2, VEGFR3, KIT, FLT3, CSF1R, and RET	GIST RCC pNET
Sorafenib	KIT, FLT3, RET, VEGFR-1, VEGFR-2, VEGFR-3, PDGFRβ CRAF, BRAF, and mutant BRAF	of unresectable hepatocellular carcinoma, and advanced RCC
Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFRα and -β, FGFR -1 and -3, KIT, ITK, Lck, and c-Fms	RCC soft tissue sarcoma

Sorafenib works as an inhibitor of KIT, FLT3, RET, VEGFR-1, VEGFR-2, VEGFR-3, PDGFRß, CRAF, BRAF, and mutant BRAF. Sorafenib is currently approved for the treatment of unresectable hepatocellular carcinoma and advanced RCC, and other trials for thyroid and brain tumours are underway [4].

Pazopanib works as an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFRα and PDGFRß, fibroblast growth factor receptor (FGFR) -1 and -3, KIT, interleukin-2-inducible T-cell kinase (ITK), lymphocyte-specific protein tyrosine kinase (Lck), and transmembrane protein receptor tyrosine kinase (c-Fms). Pazopanib is currently approved for the treatment of patients with advanced RCC, and advanced soft tissue sarcoma who have received prior chemotherapy [5].

The mTORIs (everolimus, temsirolimus)

The mTORIs, including temsirolimus and everolimus, have seen a rapid rise in use for targeted chemotherapy [6]. Mammalian target of rapamycin (mTOR) is one of several kinases that are receptors involved in complex molecular pathways including those of cellular metabolism, growth, and proliferation. Initially discovered as an antibiotic, rapamycin was found to have immunosuppressing effects, shown to inhibit cellular proliferation and cell cycle progression. Continued research and development has led to development of additional mTORIs, which affect the same pathways, particularly with T-cell proliferation and with regard to cancer therapy, showing benefit with increased apoptosis of tumour cell lines and with diminishing tumour vascular angiogenesis [7].

Both temsirolimus and everolimus work in the same manner, all based off the initial immunosuppressive qualities noted of rapamycin, a novel antibiotic isolated from bacteria harvested from the island of Rapa Nui. Rapamycin was found to arrest cell growth and additional studies showed extensive immunosuppressive qualities, which led to creation of analogues that target the mTOR pathway, one that is instrumental in cell proliferation and growth [7]. It has been found that this mTOR pathway is often dysregulated in human diseases, such as diabetes, obesity, depression, and certain cancers. These mTOR inhibitors bind to kinases and portions of this pathway, limiting angiogenesis (helpful in particularly vascular tumours) as well as inhibiting cellular proliferation.

Everolimus has been approved for the treatment of advanced kidney cancer after failure with approved TKIs; subependymal giant cell astrocytomas associated with tuberous sclerosis not amenable to surgery; pancreatic neuroendrocine tumors not amenable to surgery; breast cancer in receptor positive, HER2-negative patients in conjunction with exemestane; and in prevention of organ rejection in both renal and liver transplant. Temsirolimus has been approved for use in advance RCC.

Cardiac toxicity

Cardiotoxicity is not uncommon side effect of targeted cancer chemotherapy. Commonly seen cardiac toxicities include: left ventricular (LV) dysfunction, hypertension, QTc prolongation, myocardial ischaemia, arrhythmia and peripheral oedema.

The NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) was the adverse effects grading system in almost all the trials we reviewed. CTCAE classify the severity of adverse events (AEs) in 5 grades. In general, grade 1 encompasses mild AEs, grade 2 – moderate, grade 3 – severe, grade 4 – life-threatening or disabling, grade 5 – death related to AEs, respectively. Table 2 shows the definition of each cardiac AE observed with the use of the oral TKIs and mTORIs [8].

Sunitinib

LV ejection fraction (LVEF) / CHF

In the study for the use of sunitinib in patients with GIST [9], 11% of patients on sunitinib developed decline in LVEF; 59% of these patients required intervention with dose reduction and addition to anti-failure treatment; compared to 3% on placebo. In the same study, 2 (out of 209) patients on sunitinib and 2 patients on placebo died of sudden cardiac arrest. In a recent study by Demetri *et al.* [10], one patient experienced CHF (grade 2) who was managed clinically with anti-failure treatment.

In the study for the use of sunitinib in patients with RCC, 27% of patients on sunitinib developed decline in their LVEF (grade 1 and 2). Two patients (<1%) developed grade 3 CHF while on sunitinib [11]. Two phase 2 clinical trials, each reported grade 3 CHF in one patient out of total 38 patients [12] and 53 patients [13].

We can conclude from the above studies that the incidence of symptomatic decline in the EF, i.e. CHF, with the use of sunitinib is low. We recommend obtaining a baseline evaluation of EF if patients have any history of cardiac dysfunction. If patients develop any symptoms they can be managed with beta-blockers, diuretics, and ACE inhibitors. Metoprolol is safer as compared with carvedilol which may require monitoring of therapy as sunitinib may increase level of carvedilol. Lisinopril, enalapril and also losartan are all safe with sunitinib.

Table 2. **The NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) classification of the cardiac AE observed with the use of oral TKIs and mTORIs**

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Prolonged QTc interval	QTc >0.45–0.47 second	QTc >0.47–0.50 second or ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second with life-threatening signs or symptoms (e.g., arrhythmia, congestive heart failure (CHF), hypotension, shock syncope) or torsade de pointes	Death
Atrial fibrillation (AF)	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously within normal limits (WNL); intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death
LV systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60–50%; shortening fraction (SF) <30–24%	Asymptomatic, resting EF <50–40%; SF <24–15%	Symptomatic CHF responsive to intervention; EF <40–20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
Limb oedema	5–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting oedema	>10–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with activities of daily living	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death

Follow-up echocardiogram in 3–6 months based on symptom progression is recommended.

QT interval

Sunitinib related QT prolongation is a dose dependent and may lead to torsade de pointes. Upon reviewing all the phase 2 and 3 studies of sunitinib use, one study had one patient who developed electrocardiogram (ECG) QT prolongation without any clinical sequel [14]. The other one, 4 patients developed grade 1 prolonged QT; 2 patients developed grade 2; 2 patients developed grade 3. None of them developed torsade de pointes [15].

Incidence of clinically significant QT prolongation is very low (0.1%) with sunitinib use. It is recommended to have a baseline ECG prior to initiation. Patients with baseline QTc prolongation should be monitored closely. In patients with no prior abnormality we do not monitor QTc in our practice.

Hypertension

In a large randomized study of patients with RCC, who received sunitinib, 34% experienced hypertension. 13% of total patients developed grade 3 or more hypertension [11].

In the study for the use of sunitinib in GIST, grade 3 hypertension was reported in 4% of patients on sunitinib compared to none on placebo [9].

In the study for the use of sunitinib in pNET, 27% of patients experienced hypertension. Grade 3 hypertension was reported in 10% of total patients on sunitinib. Dose reduction or treatment delay controlled blood pressure (BP) in 80% of patients with hypertension in the RCC study and 86% of patients with hypertension in the pNET study [16].

The reported incidence of hypertension as an adverse effect to the use of Sunitinib was variable among the phase 2 and 3 clinical trials that we reviewed with the incidence of grade 1/2 ranging from (3–71)%. The incidence of grade 3 ranging from (0–17)% and no reported cases of grade 4 or 5. Please refer to figure 1. These patients who developed hypertension while on sunitinib were treated with standard antihypertensive therapy and strict surveillance with weekly visits and early intervention of hypertension [10,11,13,15, 17–29].

Significant number of patients developed hypertension while on sunitinib. Hypertension was treated with standard antihypertensive therapy and strict surveillance with weekly visits and early intervention

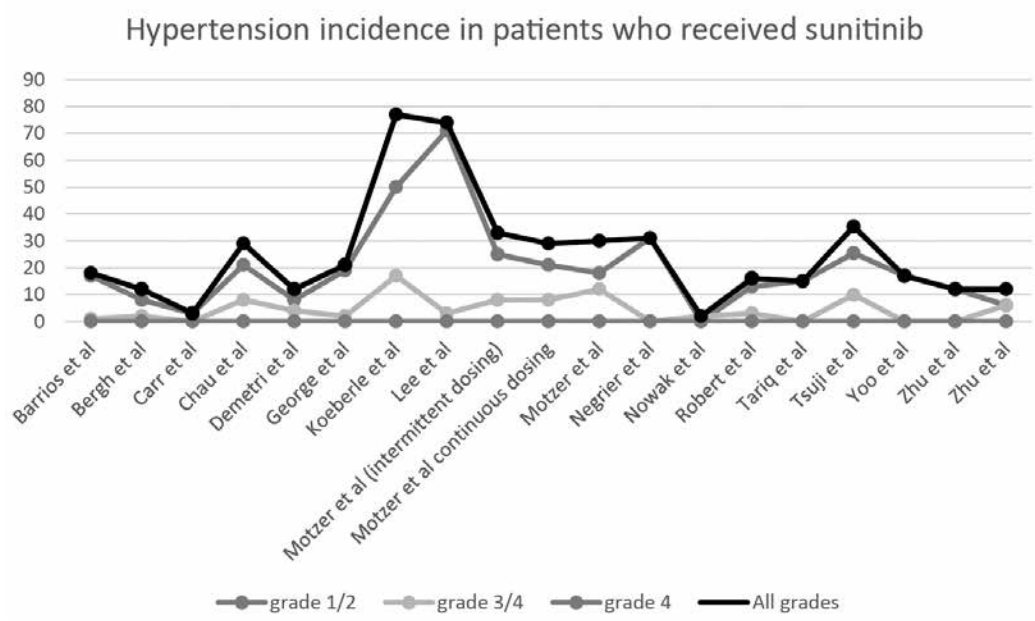

Figure 1. A line-graph diagram showing the incidence of hypertension in paitents who received sunitinib as reported in the phase 2 and 3 clinical trials that we reviewed

of hypertension. None of the patients on sunitinib developed grade 4 or 5 hypertension.

We recommend use of metoprolol, amlodipine, lisinopril, losartan or hydrochlorthiazide based on physician choice. Therapy can be titrated as required. Dose reduction for hypertension is usually not required unless adequate antihypertensive are not able to control BP adequately.

Other reported cardiac AEs

No reported AF or hyperlipidaemia were reported with sunitinib use [12–15,17–22,24–36]. Peripheral oedema grade 1 and 2 was ranging between 13–55% in phase 2 and 3 studies [17,20,22].

In summary, the total number of patients from all the trials we reviewed and reported AEs were 2,795. These who developed hypertension grade 1/2 were 377 patients (13%) and these who developed hypertension grade 3/4 were 129 patients (5%). And none developed grade 5. In regard to the development of reduction in EF, 84 patients (3%) developed grade 1/2, and 14 patients (0.5%) developed grade 3/4, and none developed grade 5. 13 patients (0.5%) developed grade 1/2 clinical CHF, 2 developed grade 3/4, and one patient (~0%) developed grade 5 (Table 3).

Table 3. **A table showing the pooled data from all the sunitinib trials we reviewed. A total of 2,795 patients developed AEs. It is evident that hypertension grade 1/2 is the most common observed cardiac AE from the use of sunitinib**

	Grade 1/2		Grade 3/4		Grade 5	
	n	%	n	%	n	%
Hypertension	377	13	129	5	0	0
Reduction in EF	84	3	14	0.5	0	0
Clinical CHF	13	0.5	2	~0	1	~0

Pazopanib

LVEF/CHF

In the study for the use of pazopanib in soft tissue sarcoma (STS) [37], LV dysfunction occurred in 11% of patients on pazopanib. One percent of patients on pazopanib in the STS trial had CHF. 88% of patients with LV dysfunction treated with pazopanib in the STS trial had concurrent hypertension which may contribute to the worsening LV function in patients at risk.

Though overall incidence of symptomatic LV dysfunction is low we recommend to carefully monitoring patients on pazopanib for clinical signs or symptoms of CHF in addition to obtaining a baseline and periodic evaluation of LVEF in patients at risk of cardiac dysfunction including previous anthracycline exposure, and patients with history of coronary artery disease or CHF.

Beta-blockers (metoprolol, carvedilol), ACE inhibitors (lisinopril, enalapril), angiotensin II receptor blocker (ARB) (losartan), diuretics (hydrochlorothiazide (HCTZ)) and calcium channel blockers (Norvasc) are generally safe to use in these patients and do not interact with pazopanib adversely.

QT interval

In the studies for the use of pazopanib in RCC [38–42], QT prolongation was identified on routine ECG moni-

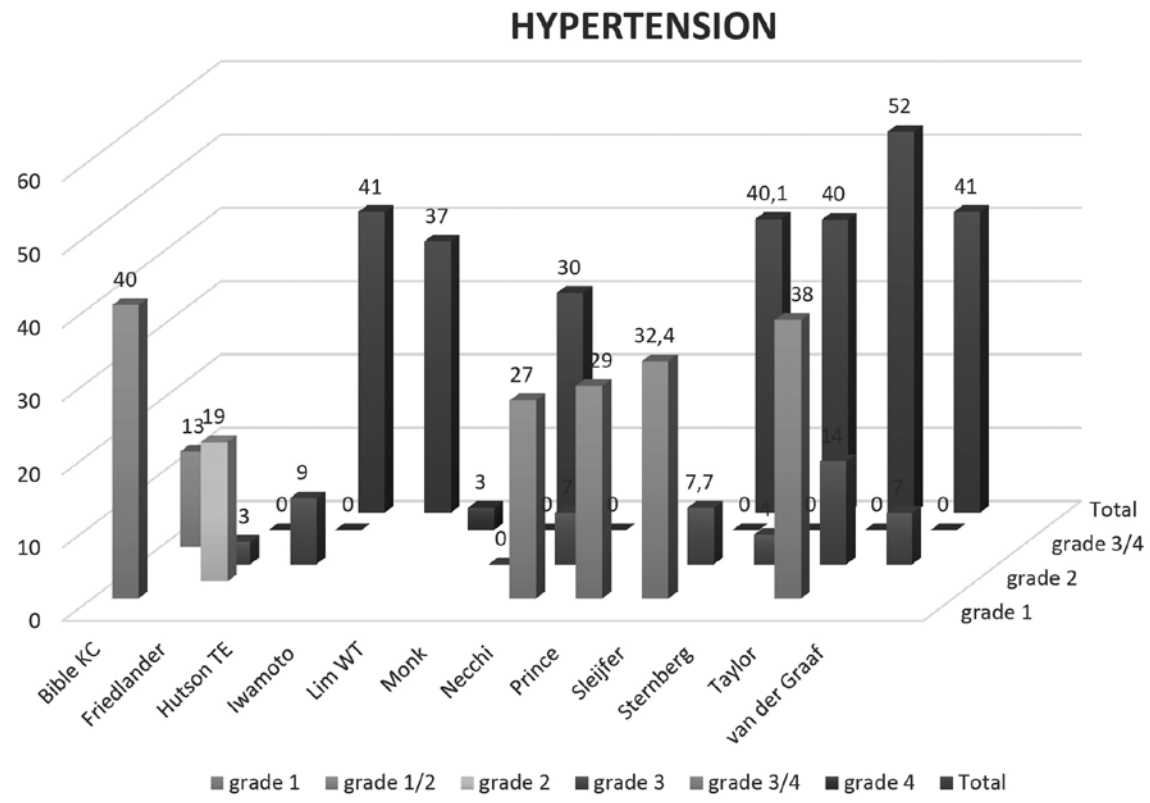

Figure 2. A 3D-column graph showing the incidence of hypertension in paitents who received pazopanib as reported in the phase 2 and 3 clinical trials that we reviewed

toring in 2% of patients. Torsades de pointes occurred in less than 1% of patients who received pazopanib.

In the randomized RCC and STS trials [37–46], 1% (3/290) of patients and 0.2% (1/240) of patients respectively, who received pazopanib had post-baseline values between 500 to 549 msec. Post-baseline QT data were only collected in the STS trial if ECG abnormalities were reported as an adverse reaction. None of the 268 patients who received placebo on the two trials had post-baseline QTc values more than 500 msec.

None of the clinical trials we reviewed reported prolonged QT internal. This may be attributed to the fact that these studies didn't report AEs with incidence less than 10% unless they were grade 4 or 5.

Until we get more post marketing studies for pazopanib, we recommend periodic monitoring with on-treatment ECGs and electrolytes (magnesium, potassium).

Hypertension

In the study for the use of pazopanib in RCC [42], hypertension occurs early in the course of treatment (40% of cases occurred by day 9 and 90% of cases occurred in the first 18 weeks). Approximately 40% of patients who received pazopanib experienced hypertension. Grade 3 hypertension was reported in 4% to 7% of patients receiving pazopanib. Approximately 1% of patients required permanent discontinuation of pazopanib because of uncontrolled hypertension.

The incidence of hypertension in the phase 2 and 3 studies we reviewed was similar to the incidence of hypertension in a company-sponsored study [42] as shown in figure 2.

Hypertension is a significant AE to the use of pazopanib. Therefore we recommend to treat patients with standard antihypertensive therapy. Drugs, considered safe with pazopanib, are lisinopril, HCTZ, amlodipine and metoprolol. Patients should be monitored closely early during start of treatment and then with BP check at every visit. The side effect is generally considered to be reversible and BP may return to normal after cessation of therapy.

Other reported cardiac AEs

AF was reported in 6.7% in one trial [44]. Peripheral oedema was reported in 10% [39] in one study and in another 3% [47]. Chest pain was attributed to pazopanib usage. It was reported one patient with grade 1 chest pain and one patient with grade 3 chest pain [44]. 3% (1 patient) developed hyperlipidaemia in one trail [47], and 7 patients developed grade 1 hyperlipidaemia in another study [44].

In summary, the total number of patients who received pazopanib from all the trials we reviewed and reported AEs were 1,244. 400 patients (32%) developed hypertension grade 1/2 and 71 patients (6%) developed grade 3/4. None developed grade 5 hypertension.

Sorafenib

Hypertension

As seen in similar medications above, sorafenib most reported AE was hypertension. For example in one long-term study of patients from the TARGET trial, 95% of patients experienced some type of AEs and 25% experienced new-onset hypertension [48] (Table 4).

Table 4. **A table showing the pooled data from all the sorafenib trials we reviewed. A total of 2,625 patients developed AEs in the trials which reported hypertension and a total of 198 patients developed AEs in the trials which reported arrhythmias**

	Grade 1/2		Grade 3/4		Grade 5	
	n	%	n	%	n	%
Hypertension	364	13.8	103	4	0	0
Arrhythmias	11	5.5	0	0	0	0

In addition, as TKIs are often added to other chemotherapy regimens, one study showed a doubling of hypertension (12% vs. 6%) when this TKI was added to cisplatin and paclitaxel regimen in non-small cell lung cancer (NSCLC) [49].

Our recommendations are in line with treating hypertension with the use of the other TKIs. We recommend the use of metoprolol, amlodipine, lisinopril, losartan or hydrochlorthiazide based on physician choice and close monitoring with visits every 6–8 weeks until stable is prudent.

Arrhythmias

Another commonly reported AE of this medication was arrhythmias, typical seen as AF with an average incidence of 5.5% grade 1 or 2 (Table 4). A clinician will need to assess a multitude of factors, including hypertension and LV function (along the lines of Cha2DSVasc2) to determine if a patient will need anticoagulation.

Oedema

In the trials we researched with regard to sorafnib, there were relatively low rates of oedema as a reported AE. In only one trial, 3% of patients developed significant oedema edema which was thought to be secondary to medication use [50].

mTORIs

Cardiovascular side effects found in patients treated with mTORIs differed from those in the TKI population – anaemia, mucositis and rashes were commonly reported AEs and often endocrinological derangements were typical. Serum lipid profiles often worsened and hyperglycaemia was consistently an issue for many. In one study, dyslipidaemia was reported in nearly three-fourths of all patients [51].

Dyslipidaemia

Dyslipidaemia whether elevated in cholesterol or in triglycerides was the most reported event and the percentage affected was marked (Tables 5 and 6). While non-pharmacological interventions such as weight loss in obese patients, aerobic exercise, avoidance of concentrated sugars and medications that raise serum triglyceride levels and strict glycaemic control in diabetics should be suggested as first-line therapy, these metabolic derangements are more likely to be drug-induced and often a pharmacological approach may be needed. While there is evidence that cardiovascular risk is diminished by the use of statins regardless of the elevated lipid type, with moderate to severe elevations in triglycerides (>500 mg/dL [5.7 mmol/L]), our recommendations would be to start a therapy with a fibrate or, possibly, use of fish oil, however fibrates seem to have improved microvascular outcomes in recent trials. Once patient's triglycerides have been brought down to more acceptable levels, a statin can be considered as dual therapy for the overall dyslipidaemia present and as a reduction of cardiovascular risk. Nicotinic acid is not recommended, given the risk of worsening glycaemic control, one of the very side effects of these medications.

Hyperglycaemia

In clinical use of mTORIs, patients are likely to have an increase in serum glucose, which may in turn result in the need to increase the dose or initiate insulin or an oral hypoglycaemic agent. Many of the reviewed studies showed a significant increase in elevated serum glucose (Tables 5 and 6). Clinicians should be aware of this and the myriad complications this may cause. Treatment with mTORIs may be prolonged and thus elevated blood glucose may require closer vigilance. Changes in dietary habits would be recommended and an increase in oral hypoglycaemic dosages or initiation of insulin may be necessary.

Conclusion

With the continued improvements in targeted cancer therapies and recently with much decreasing costs of

Table 5. **A table showing the pooled data from all the temsirolimus reviewed trials**

Temsirolimus	Grade 3/4		All	
	n (total number of patients who developed AEs)	%	n (total number of patients who developed AEs)	%
Hypercholesterolaemia	6 (498)	1.2	85 (498)	17
Hypertriglyceridaemia	20 (608)	3.2	125 (608)	20.5
Hyperglycaemia	32 (608)	5.2	111 (608)	18.2

Table 6. **A table showing the pooled data from all the everolimus reviewed trials**

Everolimus	Grade 3/4		All	
	n (total number of patients who developed AEs)	%	n (total number of patients who developed AEs)	%
Hypercholesterolaemia	0	0	633 (1943)	32.5
Hypertriglyceridaemia	2 (985)		480 (985)	49
Hyperglycaemia	66 (1174)	5	303 (1174)	26

certain therapies, the cost drops from $5,000/month to about $175/month [52]. A primary care provider will begin to see more patients using these medications and with improved survival only to have the more insidious 'daily' effects causing problems. Overall, hypertension was the most commonly reported adverse effect and clinicians will need to encourage closer monitoring and implement aggressive antihypertensive regimens for their patients (Table 7). With closer monitoring, the other effects such as bleeding risk, anaemia and thrombosis may be picked up on sooner and mitigated too much benefit for these patients.

Conflict of interest: None declared

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Table 7. **Table showing a monitoring and intervention plan summary for ae primary care provider to guide him/her when dealing with TKIs cardiac AEs**

Clinical follow-up	Sunitinib	Sorafenib	Pazopanib
CHF/Low LVEF	• baseline evaluation of EF if risk factor • monitor for clinical signs and symptoms of CHF	• baseline evaluation of EF if risk factor • monitor for clinical signs and symptoms of CHF	• baseline evaluation of EF if history or risk factors • monitor for clinical signs and symptoms of CHF
QT prolongation	• baseline evaluation monitoring with ECG and electrolytes based on symptoms	• not significantly reported	• baseline evaluation and periodic monitoring with ECG and electrolytes based on symptoms
Hypertension	• treated as needed with standard antihypertensive therapy • dose reduction or delay treatment as clinically warranted • strict surveillance with weekly visits • discontinue in hypertensive crisis or if hypertension is severe and persistent despite antihypertensive therapy and dose reduction	• treated as needed with standard antihypertensive therapy • dose reduction or delay treatment as clinically warranted • strict surveillance with weekly visits • discontinue in hypertensive crisis or if hypertension is severe and persistent despite antihypertensive therapy and dose reduction	• treated as needed with standard antihypertensive therapy • dose reduction or delay treatment as clinically warranted • strict surveillance with weekly visits • discontinue in hypertensive crisis or if hypertension is severe and persistent despite antihypertensive therapy and dose reduction

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Review of international clinical trials in cardiology reported in 2014

Oganov R.G., Kanorskiy S.G., Mamedov M.N.*

State Budget Educational Institution of Higher Professional Education "Kuban State Medical University" of the Ministry of Healthcare of the Russian Federation, 350063, Russia, Krasnodar, 4 Sedin Street

Authors:

Rafael G. Oganov, MD, Professor, Academician of Russian Academy of Medical Sciences, Head of the Department for Prevention of Comorbid Conditions, National Research Centre for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia

Sergey G. Kanorskiy, MD, Professor, Head of the Department of Therapy №2 of Faculty of Advanced Training and Professional Retraining of Specialists of the State Budget Educational Institution of Higher Professional Education "Kuban State Medical University" of the Ministry of Healthcare of the Russian Federation, Krasnodar, Russia

Mehman N. Mamedov, MD, Professor, Head of the Laboratory for Interdisciplinary Approaches on the Prevention of Chronic Non-communicable Diseases, National Research Centre for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia

Summary

In this review article we summarized the results of 28 large international clinical studies presented in the framework of five scientific Hot Line sessions at the European Society of Cardiology Congress 2014. The analyzed studies cover a wide range of issues on diagnosis, treatment and prevention of cardiovascular disease (CVD).

Keywords

Cardiovascular disease, clinical studies

* Corresponding author. Tel. +7 926 228 33 09. Fax. +7 499 5536 903. Email: mmamedov@mail.ru.

Every year at the scientific Hot Line sessions of the European Society of Cardiology Congress, results of large completed clinical studies are traditionally presented. The last European Congress which was held between 30 August and 03 September 2014 in Barcelona (Spain) was no exception. To conduct a review analysis, the results of 28 international clinical trials within five scientific Hot Line sessions were used. In general, the presented studies cover a wide range of issues on diagnosis, treatment and prevention of CVD.

Clinical studies presented at the scientific Hot Line I session – Cardiovascular disease: novel therapies

Angiotensin-converting enzyme (ACE) inhibitors have been the primary means of treatment of chronic heart failure (CHF) patients with reduced left ventricular ejection fraction (LVEF) for almost 3 decades, and enalapril was proved to reduce the risk of death in these patients. Neprilysin is a neutral endopeptidase, degrading endogenous vasoactive substances: natriuretic peptides, bradykinin and adrenomedullin. Neprilysin inhibition increases the levels of these substances, which prevents excessive neurohormonal activation, responsible for vasoconstriction, sodium retention and maladaptive remodeling. In the PARADIGM-HF (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients with Chronic Heart Failure) study [1], patients with any classes of CHF, usually New York Heart Association (NYHA) functional class II/III, and LVEF ⩽40%, which were, in the background of the recommended therapy, randomized for an additional intake of an experimental drug LCZ696 (a combination of valsartan and sacubitril (neprilysin inhibitor)) – 200 mg 2 times a day (n=4.187) or enalapril – 10 mg 2 times a day (n=4.212). The study was stopped prematurely at 27 month mean follow-up of patients due to the apparent benefits of LCZ696. The primary endpoint (cardiovascular death or hospitalization because of CHF) was recorded 20% (P<0.0000002) less often, death from cardiovascular cause – 20% (P=0.00004), hospitalization due to CHF – 21% (P<0.001), and death from any cause – 16% (P<0.001) less often, respectively, in the group of LCZ696 therapy. Treatment with LCZ696, compared to enalapril, has been often accompanied by hypotension and mild angiooedema, less often – by renal failure, hyperkalaemia, and cough. Superiority of LCZ696 over enalapril in reducing the risk of death and hospitalization due to CHF suggests that a new drug can replace ACE inhibitors and angiotensin II receptor blockers in the treatment of CHF.

It is assumed that under the conditions of sympathetic hyperactivity typical for CHF, an increase of vagal influences on the heart is able to align the neurohumoral imbalance and slow down the progression of the disease. In the first randomized NECTAR-HF (NEural Cardiac TherApy foR Heart Failure) trial [2], assessing this idea, 96 patients with symptomatic CHF were involved. The patients underwent electrical stimulation of the right vagus nerve in the neck (the mean pulse amplitude of 1.24 mA first and 1.42 mA after 3 months, frequency of 20 Hz) or were performed a simulation of stimulation. After 6 months the decrease in left ventricular (LV) end-systolic diameter (the primary endpoint) was 0.04±0.25 cm in the therapy group and 0.08±0.32 cm in the control group (P=0.60). Other echocardiographic parameters, maximal oxygen consumption during exercise, and the level of N-terminal brain natriuretic peptide precursor also did not differ in groups of real and imaginary vagus nerve stimulation. There was a statistically significant improvement in quality of life according to the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (P=0.049) and the physical component according to the 36-item Short Form (SF-36) Health Survey (P=0.016) and NYHA Functional Classification (FC) (P=0.032) in the therapy group. Surprisingly often (7.4% of cases), infectious complications occurred. As a result, it was failed to demonstrate a significant effect of right-sided vagus nerve stimulation on heart remodeling and exercise tolerance in patients with symptomatic CHF.

Iron deficiency occurs in about half of patients with CHF, which leads to deterioration of their functional status, quality of life and increased mortality. The CONFIRM-HF (Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure) study [3] included 304 patients with symptomatic CHF and LVEF⩽45%, increased levels of natriuretic peptide and iron deficiency (ferritin <100 ng/mL or 100–300 ng/mL, if transferrin saturation <20%). After randomization, in addition to the recommended treatment of CHF in half of the cases, intravenous ferric carboxymaltose was re-applied, and the other half received placebo, monitoring the results of the treatment during 52 weeks. Ferric carboxymaltose significantly (33±11 metres; P=0.002) prolonged the distance of 6-minute walk after 24 weeks (primary endpoint) compared with placebo, improved NYHA FC of CHF, quality of life, reduced symptoms, and lowered the risk of CHF hospitalization by 61% (P=0.009). The frequency of adverse events in the groups did not differ significantly.

Intravenous administration of iron supplement is not yet recommended for the treatment of CHF, but very useful when identifying iron deficiency.

During cardiac resynchronization therapy (CRT) with LV stimulation by bipolar electrode, it is often not possible to achieve simultaneous contraction of the ventricles. The MORE-CRT (More Options available with a quadripolar LV lead pRovidE in-clinic solutions to CRT challenges) [4] study compared the quadrupole electrical stimulation of LV by Quarter™ (n=720) with traditional bipolar (n=348). Survival without intra- and postoperative complications within 6 months (primary endpoint) was observed in 85.97% and 76.86% of cases using the quadrupole and bipolar electrodes, respectively (P=0.0001) – relative risk reduction by 40.8%. Intraoperative complications occurred in 5.98% vs. 13.73% of cases (P<0.0001) in groups of the quadrupole and bipolar electrical stimulation of LV, respectively.

After heart surgery, pericardial effusion is found in 50-85% of patients, and 1–2% develop pericardial tamponade. In the randomized POPE-2 (Post-Operative Pericardial Effusion-2) [5] trial in patients underwent coronary artery bypass surgery, heart valve or aortic surgeries, 1 mg/day of colchicine (n=98) or placebo (n=99) were used for 14 days, estimating the frequency of pericardial effusion (primary endpoint) for 30 days. Colchicine, comparable to the placebo, influenced the severity of the pleural effusion according to echocardiography (P=0.23), frequency of pericardial tamponade (P=0.80), and the need to drain its cavity, in other words, did not provide with the desired therapeutic effect.

Postpericardiotomy syndrome and postoperative atrial fibrillation (AF) worsen morbidity and increase the costs of treating patients who underwent coronary artery bypass surgery or surgery on the heart valves. Such patients with sinus rhythm in the COPPS-2 (COlchicine for Prevention of the Post-pericardiotomy Syndrome and Post-operative Atrial Fibrillation) trial [6] were appointed after randomization colchicine (n=180) 0.5 mg 2 times a day or 0.5 mg once a day if body weight <70 kg 48–72 hours prior to surgery and for 1 month thereafter or placebo (n=180). Postpericardiotomy syndrom (primary endpoint) was detected in 19.4% of patients treated with colchicine and in 29.4% – placebo. However, the incidence of postoperative AF and significant pericardial effusion in two groups were not significantly different. Observed side effects of colchicine from the gastrointestinal tract limit its potential advantages when used in cardiac surgery.

Clinical studies presented at the scientific Hot Line II session – Coronary artery disease and lipids

Lipoprotein-associated phospholipase A2 is an enzyme that is secreted by leukocytes and binds to circulating lipoproteins and macrophages of atherosclerotic plaques. It is considered as a marker of inflammation of the arteries, predictor of plague destabilization and vascular complications. The SOLID-TIMI 52 (Stabilization Of pLaques usIng Darapladib-Thrombolysis In Myocardial Infarction 52) study [7] of a direct inhibitor of this enzyme, darapladib, included patients hospitalized for acute coronary syndrome in the last 30 days. After randomization, in addition to recommended therapy patients were assigned darapladib (n=6,504) or placebo (n=6,522). After an average of 2.5 years of treatment, darapladib did not reduce, compared with placebo, total number of deaths from coronary artery disease (CAD), myocardial infarction (MI), and emergency coronary revascularization for myocardial ischaemia (primary endpoint) (P=0.93), cardiovascular death, MI, or stroke (P=0.78), and total mortality (P=0.40).

Increased heart rate (HR) is a recognized marker of the risk of cardiovascular complications. It was previously shown that ivabradine improves outcomes in patients with stable CAD, LV dysfunction and sinus rate ≥70 beats per minute (bpm). The SIGNIFY (Study assessInG the morbidity–mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery disease) study [8] included patients with stable CAD without CHF and with sinus rhythm ≥70 bpm, in most cases with FC ≥II activity-limiting angina. After randomization, ivabradine was added to the recommended therapy at a dose of 10 mg 2 times a day (n=9,550) (the target heart rate from 55 to 60 bpm) or placebo (n=9,552). After 3 months an average sinus rhythm was 60.7±9.0 bpm in a group of ivabradine vs. 70.6±10.1 bpm in the placebo group. At an average of 27.8-month follow-up, death from cardiovascular causes or non-fatal MI (primary endpoint) was detected in 6.8% and 6.4% of cases (P=0.20) in the ivabradine and placebo groups, respectively, with no significant differences in the incidence of death from cardiovascular causes and non-fatal MI. Ivabradine intake was associated with an increase in the frequency of the primary endpoint in patients with activity-limiting angina, but not in patients without such angina. Bradycardia was observed in 18.0% and 2.3% of patients (P<0.001) in the ivabradine and placebo groups, respectively. It is likely that in patients with stable CAD and normal LVEF, increased heart rate is

a marker of risk, but not modifiable determinant of outcomes.

Proprotein convertase subtilisin/kexin type 9 is a molecule that plays a key role in the destruction of low-density lipoprotein (LDL) receptors, which leads to a decrease in the capture and catabolism of circulating LDL, and an increase in their plasma levels. Alirocumab is a fully human monoclonal antibody of above molecule, effectively correcting hypercholesterolaemia. The ODYSSEY COMBO II (Efficacy and Safety of Alirocumab Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients with Hypercholesterolemia) study [9] included patients with history of CVD and LDL ≥1.8 mmol/L or with risk factors and LDL ≥2.6 mmol/L despite treatment with the maximum tolerated daily dose of statin. After randomization, there was further application of alirocumab 75 mg (18.4% of cases – 150 mg) subcutaneously every 2 weeks (n=479) or ezetimibe 10 mg/day (n=241). After 24 weeks, a reduction in LDL was noted by 50.6% and 20.7% (*P*=0.0001), with the achievement of its levels <1.8 mmol/L in 77% and 45% of cases in groups of alirocumab and ezetimibe, respectively. The frequency of alirocumab or ezetimibe discontinuation due to the side-effects (most often, vertigo and myalgia) was 7.5% and 5.4%, respectively.

The ODYSSEY FH I (Efficacy and Safety of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy) [10] and FH II (Study of Alirocumab in Patients With Heterozygous Familial Hypercholesterolemia Who Are Not Adequately Controlled With Their Lipid-Modifying Therapy) [11] studies included patients with two genetic variants of heterozygous familial hypercholesterolaemia and insufficient effect of the maximum tolerated daily dose of statin or other therapy. After randomization, alirocumab 75 mg subcutaneously every 2 weeks increasing its dose to 150 mg if after 8 weeks LDL remained ≥1.8 mmol/L or placebo were added to the treatment. After 24 weeks at the first genetic variant of hypercholesterolaemia, alirocumab (n=323) reduced LDL by 48.8%, placebo (n=163) – by 9.1% (*P* < 0.0001), while at the second variant of hypercholesterolaemia, alirocumab (n=167) reduced LDL by 48.7%, placebo (n=82) – by 2.8% (*P*<0.0001). As a result, the target LDL levels were achieved in >70% of patients and >80% of patients with two investigated variants of heterozygous familial hypercholesterolaemia with the cancellation frequency of alirocumaba because of side effects (injection site reactions, nasopharyngitis, headache) in 3.1% and 3.7% of cases, respectively.

The ODYSSEY Long Term (Long-term Safety and Tolerability of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia) study [12] included patients with CAD, high risk of cardiovascular complications or heterozygous familial hypercholesterolaemia (17.7% of cases) and LDL levels ≥1.81 mmol/L in the background of receiving the maximum tolerated dose of statins and/or other lipid-lowering therapy. After 24 weeks of alirocumab application (n=1,553) in dose of 150 mg subcutaneously every 2 weeks or placebo (n=788), LDL levels decreased by 61.0% and 0.8%, respectively (*P* < 0.0001), reaching on average 1.25 mmol/L vs. 3.08 mmol/L. There was retrospectively found a decrease in total incidence of coronary death, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization by 54% (*P*=0.0089). The incidence of discontinuation in alirocumab and placebo groups was 6.2% and 5.5%, respectively.

Statins can increase the risk of diabetes, but their influence on the course of existing diabetes has not been sufficiently studied. In the LISTEN (LIpid lowering with highly potent Statins in hyperlipidemia with Type 2 diabetes patiENts) study [13], Japanese patients with type 2 diabetes and hypercholesterolaemia were given after randomization rosuvastatin 5 mg/day (n=514) or atorvastatin 10 mg/day (n=504) during one year. After 3 months, LDL levels decreased in groups of rosuvastatin and atorvastatin by 39.4% and 36.4% (*P*=0.0106), and after a year – by 34.8% and 32.8%, respectively. Blood glucose levels after 3 and 6 months increased more under effect of atorvastatin (*P*=0.0104), but in a year, they changed equally, on average by 0.11% and 0.12%, in groups of rosuvastatin and atorvastatin, respectively. At the same time, 1.46 times greater (*P*=0.05) number of patients treated with atorvastatin, received enhanced diabetes therapy to correct the observed hyperglycaemia. Therefore, rosuvastatin is the best treatment choice for patients with type 2 diabetes compared with atorvastatin.

Clinical studies presented at the scientific Hot Line III session – Heart failure: devices and interventions

Improvement of a stent design, affecting the thickness of their wall, surface of the polymer and a drug release, resulted in the improvement of clinical outcomes by using drug-eluting stents. In the BIOSCIENCE (Ultrathin strut biodegradable poly-

mer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation) study [14], patients with stable CAD or acute coronary syndromes had compared the efficacy and safety of a new ultrafine cobalt chromium stent releasing sirolimus from a biodegradable polymer, and thin stent releasing everolimus from a durable polymer. In 1,063 patients treated with sirolimus-eluting and 1,056 with everolimus-eluting stents, cumulative incidence of complications (cardiac death, MI in the area of the target artery, revascularization – primary endpoint) during 12 months was 6.5% and 6.6% (P=0.0004 for noninferiority), the frequency of stent thrombosis was 0.9% and 0.4% of cases (P=0.16), respectively. A decrease of primary endpoint events was reported in patients with biodegradable stents in the subgroup of patients with ST segment elevation MI (STEMI) (3.3% vs. 8.7%; P=0.024), which requires further study.

Vegetative regulating therapy by stimulating the vagus nerve on the right (n=29) or left (n=31) of the neck area was evaluated in the ANTHEM-HF (Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure) study [15] in patients with NYHA FC II / III CHF and LVEF ⩽40%, receiving optimal pharmacotherapy. Electrical stimulation was performed by current pulses of 2.0±0.6 mA with a natural frequency (10 Hz) and was well tolerated regardless of the stimulation side, and it rarely caused mild dysphonia, cough or pain in the oropharynx. After 6 months of vegetative regulating therapy, LVEF increased on average by 4.5%, LV end-systolic volume decreased by 4.1 mL, NYHA FC was improved in 77% of patients, and the six minute walking distance was lengthened by 56 and 77 m at the left and right electrical stimulation respectively.

In patients with atrioventricular block and rare heart rhythm, right ventricular electrical stimulation is applied, which might impact negatively on the structure and function of the heart. In the BIOPACE (Biventricular pacing for atrIo-ventricular BlOck to Prevent cArdiaC dEsynchronization) study [16], such patients (mean age 73.5 years) were randomized to perform right ventricular (n=908) or biventricular pacing (n=902). After an average of 5.6 years of follow-up, the time before death or hospitalization for CHF (primary endpoint) tended to decrease in biventricular pacing group (-13%; P=0.08). There was no significant reduction in the total incidence of these events in patients with LVEF ⩽50% (-8%; P=0.47) and >50% (-12%; P=0.21). Dysfunction of an expensive biventricular pacing was noted in 14.8% of cases in the absence of such problems in a right ventricular pacing.

Resynchronization therapy is recommended for patients with CHF and wide QRS complex, but the optimal area of electrical stimulation of the right ventricle is specified. The SEPTAL-CRT (Comparison of Right Ventricular Septal and Right Ventricular Apical Pacing in Patients Receiving a CRT-D Device) study [17] included patients with LVEF ⩽35% and QRS >120 ms, who were performed after randomization electrical stimulation of the right ventricle in the apex (n=92) or ventricular septal (n=90). After 6 months there were no significant differences in a reduction of LV end-systolic volume –29.3±44 and 25.3±39 mL (P=0.79), increase in LVEF, frequency of hospitalization for heart failure, total mortality – 3.0 and 3.8% (P=0.77), frequency of complications from electrical stimulation between groups of apical and septal stimulation, respectively.

Patients with persistent AF in order to maintain stable sinus rhythm are recommended not only pulmonary vein isolation but also additional ways of ablation. The STAR AF 2 (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Part 2) study [18] after randomization performed only isolation of the pulmonary veins (n=64), isolation of the pulmonary veins and additional ablation based on the results of electrophysiological 3D-mapping (n=263), isolation of the pulmonary veins and linear ablation in the left atrium (n=259). The mean duration of catheter ablation procedure was 167, 229 and 223 mins (P<0.001) in each of the three groups. After 18 months, free from AF with duration >30 s (primary endpoint) were 59%, 48% and 44% (P=0.15) of patients, including 48%, 37% and 33% (P=0.11) of patients, respectively, without antiarrhythmic drug therapy. In patients with persistent AF, adding ablation for eliminating complex electrograms or linear ablation to pulmonary vein isolation lengthens the procedure, but does not provide the best prevention of arrhythmia recurrence. The EuroEco (European Health Economic Trial on Home Monitoring in ICD Patients) study [19] compared the cost of managing 303 patients with implantable cardioverter-defibrillators, randomized for home telemonitoring technology or traditional visits to a medical facility. Despite the higher cost of the home telemonitoring, in its application, patients required fewer doctor's visits – 3.79±1.67 vs. 5.53±2.32 (P<0.001), with a slight increase in unscheduled visits – 0.95±1.50 vs. 0.62±1.25 (P<0.005), more out of office – 1.95±3.29 vs. 1.01±2.64 (P<0.001) and Internet sessions – 11.02±15.28 vs. 0.06±0.31 (P<0.001), more

discussions in a clinic – 1.84±4.20 vs. 1.28±2.92 (P<0.03), but fewer hospitalizations – 0.67±1.18 vs. 0.85±1.43 (P=0.23) with their insignificantly shorter duration – 6.31±15.5 vs. 8.26±18.6 days. (P=0.27). As a result, the cost of home telemonitoring and traditional monitoring of patients with implantable cardioverter-defibrillators did not differ significantly.

Clinical studies presented at the scientific Hot Line IV session – Myocardial infarction

In accordance with the current recommendations, primary percutaneous coronary intervention (PCI) in patients with STEMI is limited by infarct-related artery. In the CvLPRIT (Results of the Complete versus Lesion only PRimary-PCI Trial) study [20], after randomization such patients were performed revascularization of the infarct-related only (n=146) or all arteries with hemodynamically significant stenoses (n=150). After 12 months the cumulative incidence of death from any cause, recurrent MI, heart failure and revascularization due to myocardial ischaemia (primary endpoint) was significantly lower in the group of complete revascularization – 10.0% vs. 21.2% (P=0.009). There was also observed a tendency towards a decrease of overall mortality – 1.3% vs. 4.1% (P=0.14), frequency of recurrent MI – 1.3% vs. 2.7% (P=0.39), heart failure – 2.7% vs. 6.2% (P=0.14), re-PCI – 4.7% vs. 8.2% (P=0.20) without increasing the risk of stroke, bleeding or contrast-induced nephropathy during complete revascularization.

The ATLANTIC (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) study [21] compared the effects of earlier ticagrelor intake in the pre-hospital (in ambulance) and stationary (in a catheterization laboratory) stages of treatment of patients with STEMI. After MI diagnosis with the duration of symptoms >30 mins but <6 hours and the estimated time before PCI <120 mins, in addition to standard therapy after randomization, patients in the 'pre-hospital' group (n=909) started treatment with a loading dose of 180 mg ticagrelor and then a matching placebo when in the hospital. Patients in the 'in-hospital' group (n=953) received placebo in the ambulance, and then 180 mg of ticagrelor in the hospital on average by 31 mins later. All patients subsequently received ticagrelor 90 mg 2 times a day. There was no distinction between 'pre-hospital' and 'in-hospital' groups in the absence of ST segment depression by ≥70%–86.8% vs. 87.6% (P=0.63), blood flow in the infarct-related artery with thrombolysis in myocardial infarction (TIMI) grade 3 – 82.6% vs. 83.1% (P=0.82), amount of cardiovascular complications in the first 30 days – 4.5% vs. 4.4% (P=0.91). However, incidence of definite stent thrombosis was lower in the 'pre-hospital' group of ticagrelor treatment after 24 hours – 0% vs. 0.8% (P=0.008) and 30 days – 0.2% vs. 1.2% (P=0.02). The incidence of bleeding and serious side effects in compared groups did not differ significantly.

Treatment selection for non-ST elevation myocardial infarction (NSTEMI) in the randomized FAMOUS-NSTEMI (Fractional Flow Reserve Versus Angiographically Guided Management to Optimise Outcomes in Unstable Coronary Syndromes) trial [22] was carried out by taking into account the results of fractional flow reserve (FFR) measurement (n=176) or initially without FFR only according to coronary angiography (n=174). FFR ≤0.80 was an indication for PCI or coronary bypass surgery. The proportion of patients who initially had drug therapy was higher in the group where results of determining FFR were taken into account – 22.7% vs. 13.2% (P=0.022). Accounting for FFR resulted in a change of tactics (drug treatment, PCI or coronary artery bypass surgery) in 21.6% of patients. After 12 months revascularization rate remained lower in the group of treatment under the control of FFR – 79.0% vs. 86.8% (P=0.054). There were no statistically significant differences in indicators of health and quality of life between compared groups.

The randomized NOMI (Nitric Oxide for inhalation to reduce reperfusion injury in acute st-elevation Myocardial Infarction) study [23] included patients with STEMI without manifestations of heart failure in the first 2–12 hours after the onset of symptoms. In order to reduce damage to the myocardium before PCI and 4 hours after the reperfusion, inhalation of nitric oxide and oxygen via a face mask was performed (n=125) or was not (n=125). According to magnetic resonance imaging (MRI), 48–72 hours after the procedure, the mean infarct size was 18% vs. 19.4% of LV mass (P=0.44) in patients receiving and not receiving nitric oxide, respectively. Its positive effect on the volume of necrosis was significantly higher in patients who had not received an infusion of nitroglycerin (n=132) compared with those who received it (n=93). After 4 months in the group of patients used inhaled nitric oxide, better recovery of LV function was observed (P=0.048), there was noted a trend to a reduction of the total frequency of death, recurrent myocardial ischaemia, stroke, and rehospitalization (P=0.10).

In the MITOCARE (Effect of Intravenous TRO40303 as an Adjunct to Primary PCI For Acute STEMI) study

[24], an agent TRO40303 was evaluated in respect of reducing reperfusion injury in STEMI patients underwent revascularization. Within 6 hours of the onset of the pain syndrome, patients received intravenous TRO40303 6 mg/kg (n=83) or placebo (n=80) before the primary PCI. In both groups, no significant differences in the dynamics of creatine kinase and troponin I were observed. Also the size of the infarct was comparable according to the results of MRI – 17% vs. 15% of LV mass, LVEF in the first day – 46% vs. 48%, and after 30 days – 51.5% vs. 52.2% in the groups of TRO40303 and placebo, respectively.

Clinical studies presented at the scientific Hot Line V session – Coronary artery disease and atrial fibrillation

According to the results of small randomized studies, perioperative statin therapy reduced the likelihood of developing AF after cardiac surgery, and also prevented damage of myocardium and kidneys. In the STICS (Statin Therapy In Cardiac Surgery) study [25], 8 days before and 5 days after elective heart surgery, rosuvastatin 20 mg/day (n=960) or placebo (n=962) were used. The incidence of AF was 21% vs. 20% (*P*=0.72) in the groups of rosuvastatin and placebo, respectively. In both groups, there were no significant differences in plasma levels of troponin I (*P*=0.72), reflecting perioperative myocardial injury, duration of hospitalization, cardiac and cerebrovascular complications during hospitalization, LV function by echocardiography, and plasma creatinine levels.

In the X-VeRT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with nonvalvular aTrial fibrillation scheduled for cardioversion) study [26], rivaroxaban (20 mg once a day or 15 mg for creatinine clearance of 30-49 mL/min) (n=1,002) and adjustable dose warfarin (n=502) were compared in patients with AF lasting >48 hours, undergoing cardioversion. Subject to prior anticoagulation or exclusion of thrombosis in the atria according to transesophageal echocardiography, early (after 1-5 days after randomization) and in other cases delayed (after 3–8 weeks) cardioversion was performed. The overall incidence of stroke, transient ischemic attack, peripheral embolism, MI and cardiovascular death (primary efficacy endpoint) was 0.51% and 1.02% in the groups of rivaroxaban and warfarin (relative risk (RR) 0.50, 95% confidence interval (CI) 0.15–1.73). Major bleeding was recorded at a frequency of 0.6% and 0.8% when taking rivaroxaban and warfarin, respectively (RR 0.76, 95% CI 0.21–2.67). Therefore rivaroxaban is an effective, safe and convenient alternative to warfarin during cardioversion of AF.

In the first months after catheter ablation of AF, recurrences of arrhythmias are often observed, but long-term effects of a short-term antiarrhythmic drug therapy are not well studied. In the AMIO-CAT trial (Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study) [27] after pulmonary vein isolation, supplemented by linear ablation, amiodarone (800 mg/day for 2 weeks; 400 mg/day during 3rd and 4th week; 200 mg/day from 5th to 8th week, n=108) or placebo (n=104) were applied in patients with paroxysmal or persistent AF. Registered episodes of AF lasting >30 seconds during 4-6 months after ablation were observed in 39% and 48% of patients in the placebo and amiodarone groups, respectively (*P*=0.18). In the first 3 months after ablation, patients, receiving amiodarone, had significantly lower recurrence rate of AF – 34% vs. 53% (*P*=0.006), arrhythmias which required hospitalization (*P*=0.006), and cardioversion (*P*=0.0004). Despite the side effects of amiodarone, due to antiarrhythmic action, it ultimately did not reduce patients' quality of life (according to the SF-36 questionnaire).

The effect of a long-term, high-intensity statin therapy on coronary atherosclerosis in STEMI patients remained unknown. In the IBIS 4 (Integrated Biomarkers and Imaging Study-4) study [28], the effect of rosuvastatin at a dose of 40 mg/day on plaque size and phenotype in two non-infarct related epicardial arteries, according to intravascular, including radiofrequency, ultrasound, was evaluated in 103 STEMI patients. After 13 months LDL levels decreased from 3.29 to 1.89 mmol/L (*P*<0.001), high-density lipoprotein (HDL) levels increased from 1.10 to 1.20 mmol/L (*P*<0.001), and the amount of plaque was reduced by 0.9% (*P*=0.007). The proportion of patients with plaque regression in at least one artery was 74%. There were no significant changes in the amount of necrotic core of plaque (-0.05%; *P*=0.93) and number of radio frequency ultrasonic slices revealed thin covering of plaque (*P*=0.15).

Tuberculous pericarditis is associated with high morbidity and mortality, even on the background of antituberculous treatment. The IMPI (Investigation of the Management of Pericarditis) trial [29], using a 2×2 factorial design, assessed the impact of 6 weeks of adjuvant prednisolone therapy (initial dose of 120 mg/day with a reduction to 5 mg/day) and immunotherapy with Mycobacterium indicus pranii (5 injections for 3 months) in 1,400 patients with tuberculous pericar-

ditis. Two-thirds of the trial participants had the human immunodeficiency virus detected. The incidence of the primary endpoint (death, pericardial tamponade or constrictive pericarditis) was not significantly different in patients treated with prednisolone or placebo – 23.8% vs. 24.5% (*P*=0.66), as well as in those receiving immunotherapy or placebo – 25.0% vs. 24.3% (*P*=0.81). Prednisolone, compared with placebo, significantly reduced the incidence of constrictive pericarditis – 4.4% vs. 7.8% (*P*=0.009). Both prednisolone therapy and immunotherapy, compared with placebo, significantly increased incidence of cancer – 1.8% vs. 0.6% (*P*=0.03) and 1.8% vs. 0.5% (*P*=0.03) respectively, which was explained by the influence of HIV infection.

The next European Society of Cardiology Congress will be held between 29 August and 2 September 2015 in London (UK).

Conflict of interest: None declared

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ORIGINAL ARTICLE

Factors affecting the increase of follicle-stimulating hormone in women with cardiovascular pathology

Isayeva A.S.*, Vysotskaya Ye.V., Strashnenko A.N., Bondar T.N.

National Institute of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine, 2a Postyshev Prospect, Kharkov, 61039, Ukraine, Tel. + 380573739015

Authors:

Anna S. Isayeva, Candidate of Medical Sciences, Head of the Department of Comprehensive Risk Reduction of Chronic Non-Communicable Diseases, the National Institute of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine

Tatyana N. Bondar, Candidate of Biological Sciences, Senior Scientist at the Laboratory of Immunological and Biochemical Research Methods with Immunohistochemistry, the National Institute of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine

Yelena V. Vysotskaya, Candidate of Technical Sciences, Professor at the Biomedical Engineering Department, Kharkov National University of Radioelectronics; Scientist at the National Institute of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine

Anna N. Strashnenko, Candidate of Technical Sciences, Kharkov National University of Radioelectronics; Junior Scientist at the National Institute of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine

Summary

A number of scientific studies have shown that elevated levels of follicle-stimulating hormone (FSH) greater than 25 IU/L act as a marker of women's reproductive age. In this article we show the influence of cardiovascular risk factors on the likelihood of increasing the FSH above 25 IU/L. The study was conducted with 160 women with an average age of 52 years (SD 45–59). All patients had the content of sex hormones determined (FSH, prolactin, estradiol, testosterone, and progesterone) and serum aldosterone by enzyme immunoassay. Among the patients included in this study, hypertension was detected in 105 patients (65.6%); history of myocardial infarction – in 38

* Corresponding author. Tel: +380504006550. Fax: +380577701538. E-mail: anna_isayeva_74@yahoo.co.uk

(23.7%); heart failure – in 101 (63.1%); smoking – in 35 (21.9%). SPSS 21, a computer program for Windows XP, was used for statistical analysis of results. To predict the likelihood of increasing the FSH to more than 25 IU/L under the influence of various parameters, the method of binary logistic regression was used. A number of factors that significantly affect the risk of increasing the FSH levels greater than 25 IU/L were identified, and the mathematical method for predicting an increase in FSH more than 25 IU/L was developed. A statistically significant effect on the potential of increasing the FSH more than 25 IU/L was exerted by patient's age; presence of hypertension and diabetes; cholesterol, estradiol, and prolactin levels, and statin therapy. The model was statistically significant; the value of Nagelkerke's R squared was 0.704. This was appropriate for predicting the onset of reproductive aging and the development of intermediate and late complications of menopause.

Keywords

Menopause, perimenopause, cardiovascular risk, follicle-stimulating hormone

Introduction

Follicle-stimulating hormone (FSH) is one of the earliest markers of women of reproductive age. Increased levels of FSH in the blood appear a few years before menstrual dysfunction and reduction in estradiol [1]. A number of publications show the relationship between FSH level and various factors of cardiovascular risk. It has been demonstrated that in women with retained menstrual function, elevated FSH was associated with the formation of an unfavourable lipid profile. In patients with FSH levels more than 7 IU/L on the 3rd day of the menstrual cycle, levels of total cholesterol and low-density lipoprotein (LDL) cholesterol were significantly higher than in patients with FSH levels less than 7 IU/L. It should be noted that in this study, estradiol levels in groups of patients with varying FSH were not significantly different [2]. A positive correlation between the FSH levels and intima-media thickness (IMT) in patients during perimenopause has been revealed, while there were no established links between IMT and levels of estradiol and testosterone [3]. In the same study, a positive correlation between the FSH levels and the homeostasis model assessment (HOMA) index was revealed, which also was not confirmed for estradiol and testosterone. The relation between the FSH levels and adventitia diameter was found in the sufficiently large SWAN (Study of the Women Health Across the Nation) study which persisted even after normalization of data on the level of estradiol [4]. The study shows an increase in HOMA index with an increase in FSH, although the authors have linked impaired glucose tolerance with the severity of menopause symptoms [5].

Thus, the change of the FSH during natural menopause is associated with a variety of cardiovascular risk factors. It should be kept in mind that natural menopause, an increase in atherogenic cholesterol fractions, and the development of diabetes are the processes associated with aging. Perhaps not only natural menopause is a risk factor for cardiovascular disease, but also the presence of cardiovascular disease contributes to female reproductive aging.

The aim of this study was to examine the factors of cardiovascular risk in women during perimenopause and to distinguish those factors that have the most significant effect on the risk of increasing the FSH levels.

Materials and Methods

We have conducted a cross-sectional study with participation of 160 female patients during their perimenopause. A gynecologist examined all women to rule out genital diseases and to confirm the nature of the natural perimenopause.

The study excluded patients with acute coronary syndrome, the New York Heart Association (NYHA) functional class III-IV heart failure, severe hypertension (blood pressure 180/110 mmHg), violations of a hormone-producing function of the thyroid gland, gastric and duodenal ulcers, diseases limiting life expectancy to 1 year, the duration of menopause more than 5 years, surgical menopause. To verify the coronary heart disease (CHD), the data of stress tests, coronary angiography or a history of Q wave myocardial infarction were used.

All patients had a standard examination, which included a physical examination, general clinical blood and urine tests, ultrasound scan of the heart, and electrocardiography. To assess the lipid metabolism, total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were determined. All biochemical investigations were carried out in the Laboratory of Immunological and Biochemical Research Methods with Immunohistochemistry of the National Institute

of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine.

All patients had their serum FSH determined by using enzyme immunoassay with reagent kit of Gonadotropin EIA-FSH produced by Alcor Bio (Russian Federation). To determine progesterone, Progesterone-EIA was used, prolactin – Prolactin EIA, testosterone – Testosterone EIA. All these reagents were produced by XEMA (Russian Federation). Estradiol was determined using the Estradiol ELISA kit produced by DRG Instruments GmbH (Germany). Contents of aldosterone in blood plasma were determined using the Aldosteron ELISA reagent kit produced by DRG International Inc. (USA).

The semi-automatic immunoassay analyzer Immunochem-2100, 2012 p., №501322057FSE was used for the analysis.

The study protocol was approved by the local Ethics Committee of the National Institute of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine.

Patients, included in the study, were divided into two groups: in group 1, FSH levels were less than 25 IU/L (n=76) and in group 2 – more than 25 IU/L (n=84). This FSH level was chosen in accordance with the classification of the menopausal transition, STRAW +10 (Stages of Reproductive Aging Workshop +10) [1].

The computer program SPSS 21 for Windows XP was used for the statistical analysis of the results. Descriptive statistics, the Mann–Whitney U test, and logistic regression were also used. To test for normality, the Kolmogorov-Smirnov test was conducted. To predict the likelihood of FSH increasing greater than 25 IU/L under the influence of various parameters, there was used binary logistic regression.

In addition to the selection of factorial signs, their reduction was carried out which was aimed at improving the quality of statistical model and contributed to clearer interpretation of the results and possibilities of using it. At the second stage, the created model was tested from the point of its statistical significance and the possibility of practical use of the results of the conducted work was considered.

Results and discussion

Patients in the group 1 were significantly younger than patients in the group 2 (P=0.03). There were no significant differences between the groups on such parameters as a menopause age, levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), left ventricular ejection fraction (EF) and body mass index (BMI) (Table 1).

The clinical characteristics of included in the study patients presented in table 2. In the group 2 (FSH>25 IU/L), there were significantly less patients with type II diabetes. Also in the group 2 significantly greater number of patients experienced hot flashes from 10 to 20 times per day. At the same time, the groups did not differ significantly in the number of patients with less than 10 and more than 20 times of tides per day. In the group 2, also significantly more patients had two abortions. Groups did not differ significantly in the number of patients with 1 abortion as well as 3 or more.

Levels of cholesterol and its fractions were not significantly different in the groups investigated. When comparing hormonal status in groups, estradiol and progesterone levels differed significantly (Table 3).

To identify the predictors that may have a potential impact on the risk of changing the FSH level, the following factors were used: age, the changing nature of menstruation, hypertension, presence of heart failure, functional class of heart failure, the presence of angina, functional class of angina, the presence of diseases of the cardiovascular system (hypertension + CHD + heart failure), smoking, history of cardiac revascularization, type II diabetes, levels of SBP and DBP, HR, BMI, history of myocardial infarction, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, TG), SCORE level, EF, the presence of left ventricular hypertrophy, levels of sex hormones in blood (prolactin, estradiol, testosterone), blood al-

Table 1. **Characteristics of patients according to the level of follicle stimulating hormone in groups**

Parameters	FSH<25 (n=76)	FSH≥25 (n=84)	Mann-Whitney U, (*P*)
Age, years	49 [45.00–52.00]	55.00 [49.00–59.00]	399.5, (0.03)
BMI, kg/m^2	28 [24.00–32.00]	28.00 [26.00–31.65]	617.0, (0.54)
Menopause age, years	49 [45.00–51.00]	50.00 [49.00–53.00]	86.5, (0.19)
SBP, mmHg	125 [110.00–150.00]	130.00 [110.00–140.00]	645.0, (0.76)
DBP, mmHg	80 [71.25–90.00]	80.00 [70.00–90.00]	618.0, (0.54)
HR, beats per minute	74.50 [65.50–83.00]	71.00 [65.00–80.50]	641.0, (0.73)
EF, %	61.50 [55.25–66.00]	63.00 [59.00–66.00]	582.0, (0.32)

Table 2. **Clinical characteristic of patients, depending on the level of follicle stimulating hormone**

Parameters		FSH<25 (n=76)	FSH>25 (n=84)	$\chi 2$, (*P*)
Hypertension		51 (67.1%)	54 (64.3%)	0.14, (0.710)
History of myocardial infarction		17 (22.4%)	21 (25.0%)	0.50, (0.480)
NYHA functional class I heart failure NYHA functional class II heart failure NYHA functional class III heart failure		15 (19.7%) 26 (34.2%) 7 (9.2%)	18 (21.4%) 30 (35.7%) 5 (5.9%)	0.07, (0.790) 0.04, (0.840) 0.61, (0.430)
NYHA functional class II stable angina NYHA functional class III stable angina		17 (22.4%) 4 (5.3%)	17 (20.2%) 5 (5.9%)	0.11, (0.740) 0.04, (0.850)
Cardiovascular disease (CVD)*		51 (67.1%)	60 (71.4%)	0.35, (0.550)
Revascularization		14 (16.3%)	11 (13.1%)	0.86, (0.350)
Menopause		24 (31.6%)	60 (71.4%)	25.41, (0.003)
Smoking		20 (26.3%)	15 (17.9%)	1.67, (0.200)
Diabetes		15 (19.7%)	5 (5.9%)	6.93, (0.009)
Tides, per day	Up to 10 10–20 >20	31 (40.8%) 13 (17.1%) 8 (10.5%)	26 (30.9%) 32 (38.1%) 13 (15.5%)	1.68, (0.190) 8.70, (0.003) 0.86, (0.350)
Births	1 2 3	40 (52.6%) 28 (36.8%) 2 (2.6%)	48 (57.1%) 28 (33.3%) 2 (2.4%)	0.33, (0.570) 0.22, (0.640) 0.24, (0.620)
Abortions	1 2 >3	23 (30.6%) 7 (9.21%) 8 (10.5%)	18 (21.4%) 17 (20.2%) 6 (11.9%)	1.63, (0.200) 7.85, (0.005) 0.24, (0.600)
Myoma		20 (26.3%)	33 (39.3%)	3.03, (0.082)
ACE-inhibitor therapy		47 (61.8%)	48 (57.1%)	0.71, (0.210)
Therapy with beta-adrenergic receptor antagonists		27 (35.5%)	23 (27.4%)	0.21, (0.141)
Statin therapy		54 (71.1%)	51 (60.7%)	0.51, (0.133)
Aspirin therapy		22 (28.9%)	29 (34.5%)	0.40, (0.641)
Therapy with calcium channel antagonists		17 (22.4%)	13 (15.5%)	0.21, (0.551)

* CVD (hypertension + CHD + heart failure)

Table 3. **Parameters of lipid metabolism, sex hormones and aldosterone depending on the level of follicle stimulating hormone**

Parameters	FSH<25 (n=76)	FSH>25 (n=84)	Mann-Whitney U, (*P*)
Total cholesterol, mmol/L	4.96 [4.49–5.69]	5.33 [4.52–5.91]	627.00 2508.00, (0.394)
TG, mmol/L	1.10 [0.90–1.56]	1.36 [1.03–1.75]	2322.00, (0.117)
LDL cholesterol, mmol/L	3.15 [2.35–3.65]	3.16 [2.47–3.60]	2696.00, (0.896)
HDL cholesterol, mmol/L	1.28 [1.12–1.49]	1.23 [1.03–1.52]	2510.00, (0.398)
Prolactin, nmol/L	240.88 [161.10–350.80]	205.08 [161.37–256.58]	2256.00, (0.069)
Testosterone, nmol/L	0.45 [0.32–0.88]	0.48 [0.34–0.63]	2712.00, (0.945)
Progesterone, nmol/L	3.50 [2.46–5.61]	3.45 [2.62–4.11]	2228.00, (0.054)
Estradiol, pg/mL	103.05 [48.67–175.63]	38.87 [31.26–57.37]	1208.00, (0.0001)
Aldosterone, pg/mL	291.87 [241.22–326.60]	292.78 [245.87–356.07]	2518.00, (0.415)

dosterone levels, therapies with ACE-inhibitors, beta-adrenergic receptor antagonists, statins, calcium channel antagonists, and aspirin. All indicators were coded and placed according to 32-dimensional vector, which takes into account the absence, presence, direction and magnitude of each indicator.

When estimating the regression equations, a method of stepwise inclusion of predictor variables was used, which ranks the features according to their contribution to the model. The result was to construct the regression function, which included 7 indicators: X_1 – age; X_2 – presence of hypertension; X_3 – pres-

ence of diabetes; X_4 – statin therapy; X_5 – an increase in cholesterol more than 5.2 mmol/L; X_6 – estradiol level of less than 11 and more than 65 pg/mL; X_7 – prolactin level.

Taking into account the considered indicators, a logistic regression equation was composed, according to which the probability of increasing the FSH levels of more than 25 IU/L was determined

$$\hat{P} = \left[\frac{1}{1 + \exp^{-(0.314 \cdot X_1 - 3.867 \cdot X_2 - 2.986 \cdot X_3 - 1.534 \cdot X_4 + 1.989 \cdot X_5 - 4.847 \cdot X_6 + 2.460 \cdot X_7 - 3.877)}} \right]$$

Where $\hat{P}$ – the likelihood that FSH exceeds 25 IU/L; X_1 – age; X_2 – presence of hypertension; X_3 – presence of diabetes; X_4 – statin therapy; X_5 – increase in cholesterol more than 5.2 mmol/L; X_6 – estradiol level of less than 11 and more than 65 pg/mL; X_7 – prolactin level.

The model itself and its individual coefficients are statistically significant; the value of Nagelkerke's R squared is 0.704. High quality model is confirmed by the calculated value of chi-square (χ^2 =55.051) and almost zero probability (P=0.001) to confirm the null hypothesis.

During the assessment of available publications, we found that there is not much research on the effects of diseases of the cardiovascular system on indicators reflecting female reproductive aging. It was shown, in a small Polish study conducted by Ablewska U. *et al.*, that patients with hypertension have higher FSH levels, although these differences were not statistically significant. The study was conducted with the participation of young patients with myocardial infarction. In this study, FSH levels were slightly lower in the group of patients with myocardial infarction than in the group of healthy women. The observed differences were not statistically significant [6]. In the Hussein Z. and Al-Qaisi J. study, the lower FSH levels were identified in women with type II diabetes [7]. One possible explanation of the lower FSH levels in patients with diabetes is relatively high estrogen levels. An indirect confirmation of the relative hyperestrogenia in patients with diabetes is more frequent development of hyperplastic etsrogen-dependent processes [8,9,10,11,12]. There are almost no articles about the effect of BP on the FSH level. Several authors have demonstrated a link between the level of sex hormones, menopause and an increase in BP [13,14,15]. At the same time in one of the largest studies, SWAN, which was looking into the influence of hormonal changes during menopause on cardiovascular risk, an increase in BP was not seen as a change associated with changes in hormonal status. A rise in BP was classified by authors' as an influence of chronological aging [16].

A special place is occupied by such factor as statin therapy. There is no evidence in publications on the ability of statins to influence the age of menopause. It is known that statins reduce cholesterol which is the precursor of sex steroids. At the same time the metabolism of simvastatin and atorvastatin, as well as estradiol is associated with cytochrome P450, and they all compete for it. Theoretically, estradiol levels may increase in patients receiving statin therapy. At the same time, the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) showed that during therapy with statins and exogenous sex steroids, plasma estradiol levels did not change significantly [17]. It should be noted that most of the patients in this study received pravastatin. In a small pilot study, conducted on animals, it has been shown that statins can reduce the number of hot flashes. The authors attributed this effect to the influence on nitric oxide system and not reaction with hormones [18]. It was not also revealed any significant effect of simvastatin on the levels of estradiol and estrone in patients with breast cancer [19]. Apparently, the effect of statins, which was revealed in our study, on the risk of increasing FSH is not related to the estradiol level. Some confirmation of our findings is evident in the study conducted by Rashidi B. et al. The authors have studied the effect of simvastatin therapy on the efficacy of exogenous human chorionic gonadotropin therapy in patients with polycystic ovaries. It was found that patients in the group treated with simvastatin for 8 weeks had a higher level of maturation of oocytes, higher levels of fertilization and pregnancy [20].

We have also revealed the influence of prolactin levels on the risk of increasing the FSH. It has been established that prolactin is usually reduced in the second year after menopause [22]. The changes of prolactin in this study did not depend on receiving exogenous sex steroids by patients.

Conclusion

Thus, we have identified a number of factors that may influence the risk of increasing the FSH levels greater than 25 IU/L. Of all the evaluated factors, the most statistically significant effect on the probability of increasing the FSH more than 25 IU/L includes age, presence of hypertension and diabetes, levels of cholesterol, estradiol and prolactin, and statin therapy. This method of calculation of the risk of increasing

the FSH can be used to predict the onset of reproductive aging and the development of medium- and long-term complications of menopause.

Conflict of interest: None declared

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CLINICAL CASE

Interference of biventricular ICD with radiofrequency application during ventricular tachycardia ablation in a pacemaker-dependent patient

Güler E.*, Kızılırmak F., Güler G. B., Kılıçaslan F.

Cardiology Department, Medipol University, School of Medicine, Istanbul, Turkey

Authors:

Ekrem Güler, MD, Cardiology Department, School of Medicine, Medipol University, Istanbul, Turkey
Filiz Kızılırmak, MD, Cardiology Department, School of Medicine, Medipol University, Istanbul, Turkey
Gamze Babur Güler, MD, Cardiology Department, School of Medicine, Medipol University, Istanbul, Turkey
Fethi Kılıçaslan, MD, Cardiology Department, School of Medicine, Medipol University, Istanbul, Turkey

Summary

Electromagnetic devices may interfere with cardiovascular implantable electronic devices (CIEDs) in the hospital and outside. Ablation for the cardiac arrhythmia is increasing, and interference is a serious matter for the pacemaker-dependent patients during ablation procedure.

Keywords

Electromagnetic interference, ventricular tachycardia, ablation

Introduction

Usually the interference with implanted cardiovascular implantable electronic devices (CIEDs, pacemaker and implantable cardioverter defibrillators (ICDs)) occurs in the hospital environment. Prolonged inhibition of pacing function may cause serious complications in pacemaker-dependent patients. We report electromagnetic interference of biventricular ICD with radiofrequency (RF) application during ventricular tachycardia (VT) ablation in a pacemaker-dependent patient.

Case report

A 57-year old man presented to our clinic with palpitation. He had a history of coronary artery by-pass op-

* Corresponding author. Tel: +09 0 212 460 77 77 (75 88). Fax: +09 0 212 460 70 59. Mobile: +90 505 445 06 75. E-mail: ekgul@yahoo.com

eration 8 years ago. A biventricular ICD was implanted one year ago in order to treat congestive heart failure symptoms and atrioventricular (AV) block. Electrocardiography (ECG) during palpitation episode revealed monomorphic VT. He had several VT episodes treated by ICD shocks despite being on amiodarone and beta blocker therapy. The patient was admitted to the electrophysiology laboratory for VT ablation. After sedation, RF catheter was advanced to the left ventricle (LV). Basal intracardiac measurements were normal. 3-D LV anatomy was constructed by using CARTO system. VT was induced by programmed ventricular stimulation and had a left bundle branch block (LBBB) pattern with inferior axis. The earliest ventricular activity during VT was adjacent to para-Hisian region at left ventricular outflow tract. VT was ablated successfully. A second VT was induced which had a right bundle branch block (RBBB) pattern and superior axis. Because the VT was not sustained mapping was not possible. Subsequently, another VT with RBBB pattern was induced. Since this VT was very fast and caused hemodynamic collapse, we had to perform cardioversion. Because one of the VTs was non-sustained and the other one was not tolerated hemodynamically, we decided to perform substrate ablation. During RF applications at the close vicinity of the defibrillator lead (Figure 1), transient complete inhibition of pacing was realized (Figure 2). No further RF application was possible because AV block. The pacing mode of the device was switched to V00 and after that we were able to finish our RF ablation. Scar mapping of the LV was constructed. There was a wide scar in the basal part of posterior and inferior LV wall. RF ablation was also performed in the scar area and RF line was created from the scar area to the mitral annulus. Finally there was not any inducible VT.

Discussion

There is an increasing trend in the need of CIEDs for the treatment of heart failure and arrhythmia [1]. In these circumstances, active patients with CIEDs face the risk of electromagnetic interference (EMI) during their daily life.

EMI is a situation that affects an electrical circuit due to either electromagnetic induction or electromagnetic radiation emitted from an external source. There were some attempts in order to reduce EMI; the filtering systems of the devices were improved, the properties that distinguish intracardiac signals were supported and the devices were concealed [2]. Cellular phones, digital media players, headphones, airport security detectors, product surveillance devices and bioelectric impedance analyzers used to measure body fat were reported as outpatient environmental causes of EMI [3,4]. However, in-hospital causes of EMI may be listed as electrosurgery, radiotherapy, cardioversion, left ventricular assist devices, lithotripsy, magnetic resonance imaging (MRI) and RF ablation as it is the case in our report [5]. Oversensing resulting from EMI may cause transient pause in the pacing function, asynchronous pacing, ventricular tracking, enhanced or inhibited pacing and errors in tachyarrhythmia interpretation function of ICDs. Especially when exposed to the static magnetic field of MRI, the pacemaker faucet may move inside the pocket and the electrodes may warm-up causing thermal injury.

RF ablation is commonly used for the treatment of cardiac arrhythmias [6]. During the procedure while signals are transmitted in a unipolar fashion between

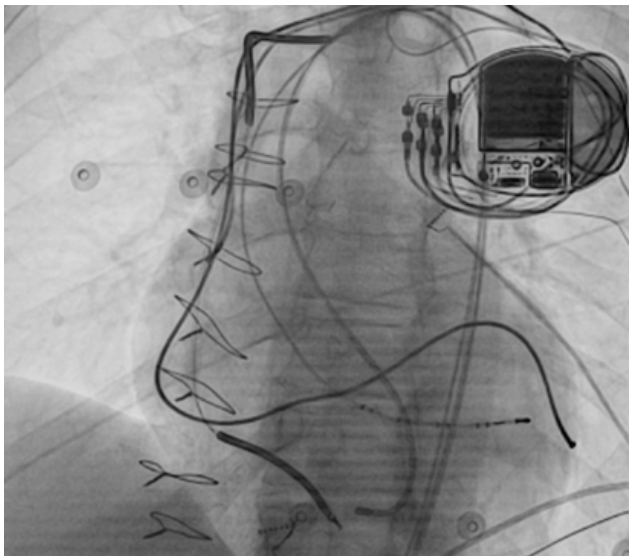

Figure 1. During RF applications at the close vicinity of the defibrillator lead and RF catheter

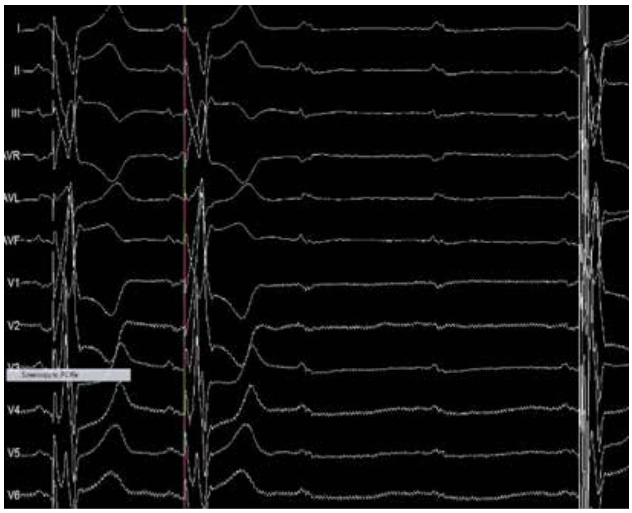

Figure 2. Revealing transient complete inhibition of pacing

the tip of the catheter and the grounding patch, there is a risk of EMI [7]. In our case, after VT was induced and during RF application approximate to the pace lead, EMI occurred and pause was recorded. In ablation procedures using RF in patients with CIEDs, EMI has been reported in various cases and studies [8,10]. During ablation procedures performed using RF, it is crucial to turn off anti-tachycardia treating properties of ICD devices and switch to asynchronous mode in pacemaker dependent patients. Furthermore device settings should be checked after the procedure.

Conclusion

In conclusion, RF application may interfere with cardiac devices and may inhibit pacemaker function in pacemaker dependent patients. Temporary pacing or switching the pacing mode to V00 may be necessary.

Conflict of interest: None declared

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Report on the World Congress of Cardiology, Melbourne, 4–7 May 2014

This year's World Congress of Cardiology took place in Melbourne between 4-7 May 2014. The organizers of the Congress included the *World Heart Federation* (headquartered in Geneva) and the *Cardiac Society of Australia and New Zealand*, together with local assistance.

More than 15,000 delegates from over 60 countries attended the Congress. The scientific programme included educational seminars, symposia, discussions, analyses of clinical cases, joint scientific meetings of national and international societies – members of the *World Heart Federation* – and poster sessions.

At the General Assembly, the leaders announced a global strategy for the Federation, namely, a 25% decrease of cardiovascular mortality and complications by 2025. Also during the Assembly, a new President for the *World Heart Federation* – Salim Yusuf, a well-known Canadian scientist – was elected by general vote and addressed the delegates with a keynote speech.

By tradition, one day of the Congress is declared as a day to highlight the effect of cardiovascular disease and its complications on women. This year, specialized meetings were held and a promotional campaign was conducted. This involved all women-delegates being invited to wear red suits. It was an amazing parade of red national costumes!

At the General Assembly, the *Cardioprogress Foundation* was officially declared a national member *of the World Heart Federation*.

The *Cardioprogress Foundation* was represented at the exhibition of the World Congress of Cardiology for the first time. IV International Forum of Cardiology and Internal Medicine, to be held in Moscow during March 2015, was promoted on the stand. Delegates were pleasantly surprised that there is no registration fee for attending the Forum, nor a fee for foreign scientists presenting their posters at the Forum. The second issue of the International Heart and vascular Disease Journal – one of the official *Cardioprogress Foundation* journals – was also presented. Submissions from authors and distribution of electronic and paper versions are also free. Agreements on cooperation and exchange of information were made with other international and national societies and public organizations.

For the first time at a World Congress of Cardiology meeting, a symposium from a Russian participant, the *Cardioprogress Foundation*, was presented. Professor Mehman Mamedov (Russia) and Zlatko Fras (Slovenia) were the chairmen of the symposium. Two reports were delivered from Russians: by Rafael Oganov, professor, academician, on modern trends of epidemiology in cardiovascular disease (CVD), and by Mehman Mamedov on the prevalence of cardiometabolic disorders in an adult population of Russia and Ukraine. One report was from the USA (Yuling Hong, Trends in community-based CVD prevention in the US) and one – from the United Kingdom (Kornelia Kotseva, Clinical reality of coronary prevention in

Europe: A comparison of EUROASPIRE II, III and IV surveys). The reports aroused great interest and discussion.

It must be emphasized that among the poster speakers' presentations, 18 works were delivered by scientists and doctors from different regions of the Russian Federation.

Within the scientific programme, a symposium on the treatment of dyslipidemia was organized. It is known that at the end of 2013, the American College of Cardiology presented new recommendations for the treatment of dyslipidemia. In the wider scientific community these new recommendations have caused heated discussion, as they are in some way different from the existing international and European recommendations. At the symposium well-known American scientists, Nathan Wong and Robert Eckel, outlined the main provisions of the new recommendations. Mehman Mamedov conducted a comparative analysis of the new US and existing European recommendations, and proposed a consensus for the treatment of dyslipidemia for primary and secondary prevention of coronary artery disease and other CVD associated with atherosclerosis. It is noteworthy that for the first time among reputable US and Australian scientists, there were representations from the Russian scientific school.

The Organizers of the World Congress of Cardiology have pined hopes on closer cooperation with Russian specialized societies and leading scientists.

More information about the World Congress of Cardiology, as well as scientific materials, could be found on the official *World Heart Federation* website: http://www.world-heart-federation.org

The next World Congress of Cardiology will be held in Mexico City (Mexico) in 2016.

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Periodicals

Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-5.

Sources in Russian with transliteration:

Baevskiy RM, Ivanov GG, Chireykin LV, et al. Analiz variabel'nosti serdechnogo ritma pri ispol'zovanii razlichnyh jelektrokardiograficheskih sistem (metodicheskie rekomendacii) [Analysis of heart rate variability using different ECG systems (guidelines)]. Vestnik aritmologii. 2002;24:65-86. Russian.

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Chapters in a book

Swanton RH, Banerjee S. Cardiac Failure. In: Swanton RH, Banerjee S., editors. Swanton's Cardiology: A concise guide to clinical practice. 6th ed. Oxford: Blackwell Publishing; 2008. p. 255-309.

Sources in Russian with transliteration:

Belenkov YuN. Kardiomiopatii [Cardiomyopathies]. In.: Chazov EI, Belenkov YuN., editors. Racional'naja farmakoterapija serdechno-sosudistyh zabolevanij: Rukovodstvo dlja praktikujushhih vrachej [Rationale for drug therapy of cardiovascular diseases: A guide for medical practitioners]. Moscow: Litterra; 2006. p. 431-452. Russian.

Reference to a book chapter should be arranged in the following order: authors of the corresponding chapter; name of the chapter; «In:»; editors (title authors) of the book; name of the book; number of issue, publisher; city of publishing; year of publishing; pages of the corresponding chapter. Punctuation should be considered. There are no quotation marks.

Books

Sources in Russian with transliteration:

Shlyakhto EV, Konradi AO, Tsyrlin VA. Vegetativnaja nervnaja sistema i arterial'naja gipertenzija [The autonomic nervous system and hypertension]. St. Petersburg (Russia): Meditsinskoe izdatel'stvo; 2008. Russian.

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