Efficacy and safety of dabigatran in a "real-life" population at high thromboembolic and hemorrhagic risk: data from MonaldiCare registry

V. RUSSO, V. BIANCHI[1], C. CAVALLARO[1], F. VECCHIONE[1], S. DE VIVO[1],
L. SANTANGELO, B. SARUBBI, P. CALABRÒ, G. NIGRO, A. D'ONOFRIO[1]

Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples, Monaldi
Hospital, Naples, Italy
[1]Department of Cardiology, Monaldi Hospital, AORN Ospedali dei Colli, Naples, Italy

Abstract. – OBJECTIVE: Dabigatran is a novel target specific oral anticoagulant for stroke prevention in non valvular atrial fibrillation. Little is still known about its real-world effectiveness and safety in the italian population. Aim of our study was to evaluate the efficacy and safety of dabigatran in a large single-center cohort of "real-life" italian population with non-valvular AF and to compare the results with those obtained from the RE-LY trial and the Medicare study.

PATIENTS AND METHODS: We studied a prospective cohort of 2108 patients (1119 male; mean age 69.4 ± 9.4 years) who started the oral anticoagulant treatment with dabigatran 110 mg twice-daily (DAB 110; N = 1075; 51%) or 150 mg twice-daily (DAB 150; N = 1033; 49%). Follow-up data were obtained trough outpatients visits each 3-6 months for assessing the clinical status, adherence to treatment, occurrence of side effects and major cardiovascular complications.

RESULTS: In DAB 150 group the mean age was 64.9 ± 8.8 years, 56.8% of patients was male. CHA2DS2Vasc Score was ≥ 3 in 94.3% and HAS-BLED was ≥ 3 in 59.7%. In DAB 110 group (N = 1075) the mean age was 73.9 ± 7.5 years; 49.5% of patients was male. CHA2DS2Vasc Score was ≥ 3 in 73.4% and HAS-BLED was ≥ 3 in 87.4% of DAB 110 patients. One patient taking Dabigatran 110 mg bid had ischemic stroke without significantly neurological sequelae. In both groups, no patient experienced hemorrhagic stroke during the follow-up period. 147 patients (6.9%) of MonaldiCare population reported adverse effects from treatment with dabigatran, of whom 121 patients (5.7%) discontinued therapy. We reported one case of subarachnoid hemorrhage (0.05%) in a patient with high thrombo-embolic and high hemorrhagic risk score who was taking dabigatran 150 mg bid and one case (0.05%) of bladder bleeding in a patient who was taking dabigatran 110 mg bid. No major gastrointestinal bleeding was observed in the MonaldiCare population.

CONCLUSIONS: MonaldiCare registry showed a safety profile of both dosages of dabigatran regarding major of fatal bleeding in a "real life" single center italian population at high thromboembolic and hemorrhagic risk. The majority of MonaldiCare patients tolerated dabigatran treatment without significant side effects. The efficacy of dabigatran was demonstrated by very low prevalence of ictus/TIA, also when patients underwent electrical AF cardioversion independently of the transesophageal examination.

Key Words:
Dabigatran, Safety, Efficacy, Real life, Bleeding, Stroke, Novel oral Anticoagulants.

Introduction

Atrial fibrillation (AF) is one of most common supraventricular arrhythmias, characterized by chaotic and uncoordinated atrial activity which predispose to hypercoagulable state and increased risk of thrombo-embolism[1,2]. Oral anticoagulation with warfarin is an effective treatment for prevention of ischemic stroke and systemic thromboembolism in AF patients[3]. CHA_2DS_2VASc score (calculated by assigning 1 point for each of congestive heart failure, hypertension, diabetes, history of vascular disease, age 65 to 74 years, and female sex; and 2 points for age > 75 years and history of stroke) is a validated score of stroke risk estimation for decide which patients with non-valvular AF are likely to benefit from anticoagulant therapy[4]; according to the European Society of Cardiology guidelines, a CHA_2DS_2VASc Score ≥ 1 suggests anticoagulation therapy[5]. Until 2013 the vitamin K antagonists (VKAs) had been the only oral anticoagu-

lants available for the prevention and treatment of thrombosis, however they were associated with a serious risk of major and fatal bleeding[6,7]. Moreover the need of regular INR checks and significant interaction with diet and drugs are detrimental. The new target-specific oral anticoagulants (TSOACs) are medications that, inhibiting a specific enzyme in the coagulation cascade, offer several advantages over VKAs, including predictable pharmacokinetics, rapid onset of action and comparable efficacy and safety. Dabigatran etixilate (DAB), the first TSOAC available in Italy, is a reversible direct thrombin inhibitor that has rapid and predictable anticoagulant effects. Its pharmacokinetic profile provides fixed twice-daily oral administration and doesn't require routine blood coagulation monitoring. Elimination is predominantly via renal clearance, with no significant hepatic contribution, and differences in pharmacokinetics are attributed primarily to variations in renal function[8]. RE-LY clinical trial showed that in patients with atrial fibrillation dabigatran, given at a dose of 110 mg bid, was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. These "trial life" data were confirmed by the results of Medicare study[10], an observational cohort study conducted by United States Food and Drug Administration. Aim of our study was to evaluate the efficacy and safety of dabigatran in a large single-center cohort of "real-life" italian population with non-valvular AF and to compare the results with those obtained from RE-LY trial and Medicare study.

Patients and Methods

MonaldiCare Registry

MonaldiCare is an observational, open label registry born to evaluate the real-life effectiveness, safety and discontinuation rates of dabigatran in a large cohort of single-center patients with non-valvular AF. We prospectively enrolled, between June 2013 and December 2014 from Department of Cardiology-Monaldi Hospital, 2108 patients (1119 male; age 69.4±9.4 years) who started the oral anticoagulant treatment with dabigatran 110 mg twice-daily (DAB 110; n=

1075; 51%) or 150 mg twice-daily (DAB 150; n= 1033; 49%). Follow-up data were obtained trough outpatients visits each 3-6 months for assessing the clinical status, adherence to treatment, occurrence of side effects and major cardiovascular complications. Laboratory exams included kidney and hepatic function, 12 lead electrocardiogram (ECG) and 24h ECG Holter monitoring were performed.

Statistical Analysis

Categorical data were described by percentages and compared using the chi-square test, and Student's *t*-test was used for continuous data. *p*-value < 0.05 was considered significant. All analyses were performed using SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA).

Results

Study Population

In the DAB 150 group (n: 1033 patients) the mean age was 64.9±8.8 years, 56.8% of patients was male; 92.9% had arterial hypertension; 1.2% had diabetes mellitus; 15.5% had prior myocardial infarction; 30.9% had prior stroke/transient ischemic attack. CHA_2DS_2Vasc Score was ≥ 3 in 94.3% and HAS-BLED was ≥ 3 in 59.7% of DAB 150 patients. 40.2% of patients were taking antiplatelets therapy (aspirin or clopidogrel). 84.5% were previously taking warfarin with a time in therapeutic range lower than 60%.

In the DAB 110 group (n: 1075 patients) the mean age was 73.9 ± 7.5 years; 49.5% of patients was male; 97.4% had arterial hypertension; 16% had diabetes mellitus; 24.7% had heart failure; 26.8% had prior myocardial infarction; 19.6% had prior stroke/transient ischemic attack. CHA_2DS_2Vasc score was ≥ 3 in 73.4% and HAS-BLED was ≥ 3 in 87.4% of DAB 110 patients. 48.9% of patients were taking antiplatelets therapy (aspirin or clopidogrel). 81.8% were previously taking warfarin with a time in therapeutic range lower than 60%.

Ischemic/Hemorrhagic Stroke

One patient who was taking Dabigatran 110 mg bid had ischemic stroke without significantly neurological sequelae. The same patient previously experienced ischemic stroke in therapy with warfarin and refused percutaneous left atrial appendage closure[11,12], so the therapy has

not been interrupted. In both groups, no patient experienced hemorrhagic stroke during the follow-up period.

Adverse Effects and Discontinuation

147 patients (6.9%) of MonaldiCare population reported adverse effects from treatment with dabigatran, of whom 121 patients (5.7%) discontinued therapy for dyspepsia (n: 114, 5.4%), diarrhea (n: 3, 0.14%), bleeding (n: 2, 0.09%), headache (n: 2, 0.09%). 26 patients (18.5% of dyspeptic patients) reported resolution of dyspepsia with concomitant food intake, copious water, proton pump inhibitors or H2-blocking agents. We reported one case of subarachnoid hemorrhage (0.05%) in a patient with high thromboembolic (CHA2DS2VASc score: 5) and high hemorrhagic risk score (HAS-BLED: 4) who was taking dabigatran 150 mg bid and one case (0.05%) of bladder bleeding, due to unknown bladder cancer, in one patient who was taking dabigatran 110 mg bid. No major gastrointestinal bleeding was observed in the MonaldiCare population.

Adherence and Satisfaction

1982 patients (94%) referred no difficulty with adherence to twice daily dosing of dabigatran with no missed doses. Only 216 patients (6%) reported missing occasional doses. The majority of patients (84.5% in DAB 150 group and 81.8% DAB 110 group) had previously been treated with warfarin and everybody preferred taking dabigatran primarily due to the reduced requirement for blood testing and to the absence of food restrictions.

Cardioversion

In MonaldiCare registry, 120 patients (0.6%; n: 19 in DAB 110 group; n: 101 in DAB 150 group) underwent electrical cardioversion performed administering dabigatran for at least 3 weeks prior the procedure. Transoesophageal echocardiography (TEE) was performed in 54 patients (n: 19, 100% of DAB 110 group; n: 31, 30.7% of DAB 150 group) without evidence of atrial cavity or atrial appendage thrombus. The therapy was continued within 30 days after cardioversion or long-term according to the patient's clinical indication. No prevalence of stroke, systemic embolism or major bleeding after cardioversion was observed in our study.

Discussion

Population Characteristics

At present, MonaldiCare is the larger italian observational registry, which has evaluated the efficacy and safety of both doses of dabigatran in a single center "real-life" population. We observed some differences between MonaldiCare patients cohort and those described in the RE-LY trial and in the Medicare study in terms of thromboembolic and hemorrhagic risk, age,

Table I. Clinical characteristics of MonaldiCare population compared to Medicare and RE-LY patients.

Characteristics	Medicare Dabigatran (n = 67207)	MonaldiCare DAB 150 (n = 1033)	MonaldiCare DAB 110 (n = 1075)	RE-LY Dabigatran 150 mg (n = 6076)	RE-LY Dabigatran 110 mg (n = 6015)
Age (± SD)		64.9 ± 8.8	73.9 ± 7.5	71.5 ± 8.8	71.4 ± 8.6
Female sex (%)	51	46.9		36.3	
CHADS2 score (± SD)				2.2 ± 1.2	2.1 ± 1.1
CHADS2 score ≥ 3 (%)	31			35.2	32.7
CHA2DS2-VASc ≥ 3 (%)	41	94.3	73.4	77.7	
HAS-BLED ≥ 3 (%)		59.7	87.4	10.4	
Hypertension (%)	87	95.1		78.8	
Diabetes mellitus (%)	33	15.1		23.2	
Heart failure (%)	18	20.8		32.2	
Antiplatelets (%)	17	44.6		20.4	
Prior stroke/TIA (%)	10	30.9	19.6	20.3	19.9
Prior MI (%)	2	15.5	26.8	17	16.8
Prior VKA (%)		84.5	81.8	50.2	50.1

Table II. Level of significance of clinical characteristics between MonaldiCare population and RE-LY/Medicare patients.

Characteristics	MonaldiCare vs medicare	MonaldiCare vs RE-LY	MonaldiCare 150 vs RE-LY 150	MonaldiCare 110 vs RE-LY 110
Age (± SD)			< 0.001	< 0.1
Female sex (%)	= 0.3	= 0.004		
CHA2DS2-VASc ≥ 3 (%)	< 0.001	< 0.001		
HAS-BLED ≥ 3 (%)	= 0.002	= 0.003		
Hypertension (%)	< 0.04	= 0.004		
Diabetes (%)	= 0.006	< 0.04		
Heart failure (%)	= 0.08	= 0.03		
Antiplatelets (%)	= 0.003	= 0.005		
Prior stroke/TIA (%)	= 0.005		= 0.002	= 0.8
Prior MI (%)	=0.002		= 0.07	= 0.01
Prior VKA (%)			< 0.001	< 0.001

sex, comorbidities, background history. Our findings supports the hypothesis that real-life patients are often different from those of trial-life and that population characteristics usually change from different countries.

Thromboembolic Risk: MonaldiCare population showed an high risk of thromboembolism, as reflected by CHA_2DS_2VASc score ≥ 3 in 94.3% in DAB 150 group and 73.4% in DAB 110 group. It was not possible a direct comparison between MonaldiCare and RE-LY/Medicare, because the thromboembolic risk in their population were stratified according to $CHADS_2$ score. RE-LY population showed a mean $CHADS_2$ score of 2.1 ± 1.1 in dabigatran 110 mg population, and of 2.2 ± 1.2 in dabigatran 150 mg population. 32.7% of RE-LY 110 mg and 35.2% of RE-LY 150 mg population showed $CHADS_2$ score ≥ 3. According to Oldgren et al RE-LY sub-analysis[13], 77.7% of 18.113 AF patients randomized to dabigatran 110 mg, dabigatran 150 mg or warfarin showed $CHADS_2$ score ≥ 3. Medicare population showed $CHADS_2$ score ≥ 3 in 31% of patients.

Hemorrhagic Risk: MonaldiCare population showed an high hemorrhagic risk (HAS-BLED score ≥ 3 in 59.7% of DAB 150 patients and in 87.4% of DAB 110 patients). No data about hemorrhagic risk were given in RE-LY trial. Although according to Eikelboom et al analysis[14], 10.4% of RE-LY population study taking dabigatran 150 and 110 mg bid had HAS-BLED score ≥ 3. Medicare population showed a HAS-BLED score≥ 3 in 41% of patients.

Age: MonaldiCare DAB 150 group showed a medium age significantly lower (64.9 ± 8.9 vs. 71.5 ± 8.8, $p < 0.001$) than RE-LY 150 population, while in MonaldiCare DAB 110 group the medium age did not significantly differ (73.9 ± 7.5 vs. 71.4 ± 8.6; $p < 0.1$) from RE-LY 110 population. Medicare patients taking dabigatran 150 mg bid were more likely to be older than in RE-LY. The 59% of Medicare patients presented an age ≥ 75 years.

Sex: MonaldiCare population was more likely to be female compared to RE-LY population (46.9% vs. 36.3 %; $p = 0.004$), while the gender distribution is similar to the Medicare population (46.9% vs. 51%; $p = 0.3$).

Arterial Hypertension: MonaldiCare population showed an higher percentage of patients with arterial hypertension in both DAB groups compared to RE-LY (95.1% v.s 78.8%; $p = 0.004$) and Medicare (95.1% vs. 87%, $p < 0.04$) population.

Diabetes Mellitus: MonaldiCare population showed lower percentage of patients affected by diabetes mellitus, compared to RE-LY (15.1% vs. 23.2%; $p < 0.04$) and Medicare (15.1% vs. 33%, $p = 0.006$) population.

Prior Myocardial Infarction: In MonaldiCare population the percentage of myocardial infarction history was higher in DAB 110 group compared to RE-LY 110 (26.8% vs. 16.8%; $p = 0.01$) and Medicare (26.8% vs. 2%; $p = 0.002$) population, while the percentage of previous MI was similar in DAB 150 group compared to RE-LY 150 population (15.5% vs. 17%; $p = 0.07$)

Heart Failure: MonaldiCare population showed a lower percentage of heart failure patients, compared to RE-LY (20.8% vs. 32%; $p = 0.03$), but it was similar to Medicare (20.8% vs. 18%, $p = 0.08$) population.

Prior Stroke/TIA: In MonaldiCare population the percentage of stroke history was higher in DAB 150 group compared to RE-LY 150 (30.9% *vs.* 20.3%, *p* = 0.002) and Medicare population (30.9% *vs.* 10%, *p* = 0.005), while in DAB 110 group it was similar to RE-LY 110 population (19.6% *vs.* 19.9%; *p* = 0.8).

Antiplatelets Therapy: In MonaldiCare population the percentage of patients taking continuously antiplatelets therapy during the treatment period was higher than RE-LY (44.6% *vs.* 20.4%; *p* = 0.005) and Medicare (44.6% *vs.* 17%; *p* = 0.003) population.

The study cohort included also small groups of special populations at high risk of developing atrial fibrillation according to our previous evaluations, such as patients with obesity[15], neuromuscular disorders[16-23], beta thalassemia major[24-25], congenital diseases[26-27].

Adverse Effects and Discontinuation

In MonaldiCare registry, we identified an overall discontinuation rate of 5.7% after a median 38 days of treatment with dabigatran. This percentage is lower than 16% one year discontinuation rate demonstrated in the RE-LY trial. No data about the one year discontinuation rate were given in Medicare study; but only one time drug prescription was reported that 52% of dabigatran patients from October 2010 to December 2012 had made. Reported adverse events rate in MonaldiCare population was 6.9%, much lower compared to the RE-LY trial data (78% total adverse effects). Dyspepsia, which was the most common adverse event, occurred in 6.8% of the MonaldiCare population compared to over 11% in the RELY trial. No data about dyspepsia rate was given in Medicare study. However, only 5.7% of MonaldiCare patients discontinued dabigatran therapy for dyspeptic symptoms, unresolved by taking dabigatran therapy with concomitant food intake, copious water, proton pump inhibitors or H_2-blocking agents. The majority of MonaldiCare patients (84.5% of DAB 150 group and 81.8% of DAB 110 group) were previously treated with warfarin and everybody preferred taking dabigatran primarily due to the reduced requirement for blood testing and no foods intake restriction.

Safety

A total bleeding complication rate of 0.1% was identified in MonaldiCare population, much lower than 2.87% and 3.32% major bleeding rate described in the RE-LY group taking respectively dabigatran 110 and 150 mg and than 4.3% annual rate described in the Medicare population. After a critical revision of our results, we hypothesized that the low rate of reported adverse events might be related to the small sample size, compared to the RE-LY and the Medicare population; the accurate clinical anamnesis and physical examination; and the use of dabigatran 110 mg according to a "patient centered tailoring approach".

Cardioversion

In our clinical experience we didn't report stroke and systemic embolism and major bleeding after cardioversion. The use of TEE was higher in patients assigned to DAB 110 group compared with those assigned to DAB 150 group. This difference was attributable to investigator preference for cardioverting with prior TEE on novel oral anticoagulant therapy[28]. Nagarakanti et al[29] reported a posthoc analysis based on the RE-LY trial. A total of 1.983 cardioversions were performed in 1.270 patients during the course of the trial. Stroke and systemic embolism rates at 30 days were 0.8%, 0.3%, and 0.6% (D110 versus warfarin, *p* = 0.71; D150 versus warfarin, *p* = 0.40) and similar in patients with and without transesophageal echocardiography. Major bleeding rates were 1.7%, 0.6%, and 0.6% (D110 versus warfarin, *p* = 0.06; D150 versus warfarin, *p* = 0.99).

Limitations

This is a single-hospital registry but, to our knowledge, it is the largest Italian cohort taking dabigatran. The observation and reporting of adverse effects are usually more accurate and careful in randomized controlled trials than in clinical practice. The median CHA_2DS_2VASc score of 3 seen in our study population is comparable to the RE-LY $CHADS_2$ score finding and clearly identifies the individuals in this cohort as high thromboembolic risk population. We opted for the use of the CHA_2DS_2VASc score in preference to $CHADS_2$ given the improved performance in terms of stroke risk stratification. The comparison of our data with those from RE-LY and Medicare was affected by the limitations due to different types of study design and the different used dabigatran dosages. RE-LY is a randomized controlled trial, Medicare refers to dabigatran new user cohorts of propensity score-matched elderly patients, while MonaldiCare is an observa-

tional trial. RE-LY and Medicare included warfarin as comparator for dabigatran, while in the MonaldiCare registry dabigatran in the real life setting is the only observed anticoagulant treatment. In RE-LY and MonaldiCare dabigatran 110 mg or 150 mg twice daily were used, while in Medicare dabigatran 75 mg or 150 mg twice daily were used. Data collection may have been subject to inter-observer variability. In order to minimize the potential for error, standardized database definitions and interview questions were utilized.

Conclusions

MonaldiCare registry showed a safety profile of both dosages of dabigatran regarding major or fatal bleeding in a "real life" single center italian population at high thromboembolic and hemorrhagic risk. The majority of MonaldiCare patients tolerated dabigatran treatment without significant side effects. Successful adherence to twice daily dosing with dabigatran was high. A percentage higher than 80% in both MonaldiCare groups, who previously experienced treatment with both warfarin and dabigatran, preferred novel oral anticoagulation treatment. The efficacy of dabigatran was demonstrated by very low prevalence of ictus/TIA, also when patients underwent electrical AF cardioversion independently of the transesophageal examination.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) STEWART S, HART CL, HOLE DJ, MCMURRAY JJ. Population prevalence, prevalence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart 2001; 86: 516-521.

2) WATSON T, SHANTSILA E, LIP GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. Lancet 2009; 373: 155-166.

3) AGUILAR MI, HART R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev 2005; (3): CD001927.

4) LIP GY, NIEUWLAAT R, PISTERS R, LANE DA, CRIJNS HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factorbased approach: the euro heart survey on atrial fibrillation. Chest 2010; 137: 263-272

5) GUIDELINES FOR THE MANAGEMENT OF ATRIAL FIBRILLATION. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31: 2369-2429.

6) LANDEFELD CS, BEYTH RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med 1993; 95: 315-328.

7) PROIETTI R, PORTO I, LEVI M, LEO A, RUSSO V, KALFON E, BIONDI-ZOCCAI G, ROUX JF, BIRNIE DH, ESSEBAG V. Risk of pocket hematoma in patients on chronic anticoagulation with warfarin undergoing electrophysiological device implantation: a comparison of different peri-operative management strategies. Eur Rev Med Pharmacol Sci 2015; 19: 1461-1479.

8) STANGIER J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet 2008; 47: 285-295.

9) CONNOLLY SJ, EZEKOWITZ MD, YUSUF F, EIKELBOOM J, OLDGREN J, PAREKH A, POGUE J, REILLY PA, THEMELES E, VARRONE J, WANG S, ALINGS M, XAVIER D, ZHU J, DIAZ R, LEWIS BS, DARIUS H, DIENER HC, JOYNER CD, WALLENTIN L; RE-LY STEERING COMMITTEE AND INVESTIGATORS. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009; 361: 1139-1151.

10) GRAHAM DJ, REICHMAN ME, WERNECKE M, ZHANG R, SOUTHWORTH MR, LEVENSON M, SHEU TC, MOTT K, GOULDING MR, HOUSTOUN M, MACURDY TE, WORRALL C, KELMAN JA. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation 2015; 131: 157-164.

11) PROIETTI R, JOZA J, ARENSI A, LEVI M, RUSSO V, TZIKAS A, DANNA P, SAGONE A, VIECCA M, ESSEBAG V. Novel nonpharmacologic approaches for stroke prevention in atrial fibrillation: results from clinical trials. Med Devices (Auckl) 2015; 8: 103-114.

12) DANNA P, PROIETTI R, SAGONE A, ARENSI A, VIECCA M, RAGO A, RUSSO V. Does left atrial appendage closure with a cardiac plug system reduce the stroke risk in nonvalvular atrial fibrillation patients? A single-center case series. Pacing Clin Electrophysiol 2013; 36: 347-353.

13) OLDGREN J, EZEKOWITZ MD, ALINGS M, DIENER HC, REILLY PA, YUSUF S, WALLENTIN L, CONNOLLY S. Dabigatran versus warfarin and inpact od CHAD2-Vasc score on outocome in atrial fibrillation patients: a RE-LY subgroups analysis. J Am Coll Cardiol 2011; 57: E7-E7.

14) Eikelboom JW, Connolly SJ, Hart RG, Wallentin L, Reilly P, Oldgren J, Yang S, Yusuf S. Balancing the benefits and risks of 2 doses of dabigatran compared with warfarin in atrial fibrillation. J Am Coll Cardiol 2013; 62: 900-908.

15) Russo V, Ammendola E, De Crescenzo I, Docimo L, Santangelo L, Calabrò R. Severe obesity and P-wave dispersion: the effect of surgically induced weight loss. Obes Surg. 2008; 18: 90-96.

16) Nigro G, Russo V, Politano L, Della Cioppa N, Rago A, Arena G, Papa AA, Paoli LD, de Chiara A, Russo MG, Golino P, Calabrò R. Does Bachmann's bundle pacing prevent atrial fibrillation in myotonic dystrophy type 1 patients? A 12 months follow-up study. Europace 2010; 12: 1219-1223.

17) Russo V, Rago A, Palladino A, Papa AA, Di Meo F, Della Cioppa N, Golino P, Russo MG, Calabrò R, Politano L, Nigro G. P-wave duration and dispersion in patients with emery-dreifuss muscular dystrophy. J Investig Med 2011; 59: 1151-1154.

18) Nigro G, Russo V, Rago A, Antonio Papa A, Palladino A, Politano L. Right atrial preference pacing algorithm in the prevention of paroxysmal atrial fibrillation in myotonic dystrophy type 1 patients: a long term follow-up study. Acta Myol 2012; 31: 139-143.

19) Russo V, Rago A, Politano L, Della Cioppa N, Russo MG, Golino P, Calabrò R, Nigro G. The effect of atrial preference pacing on paroxysmal atrial fibrillation incidence in myotonic dystrophy type 1 patients: a prospective, randomized, single-bind cross-over study. Europace 2012; 14: 486-489.

20) Russo V, Nigro G, Rago A, Antonio Papa A, Proietti R, Della Cioppa N, Cristiano A, Palladino A, Calabrò R, Politano L. Atrial fibrillation burden in Myotonic Dystrophy type 1 patients implanted with dual chamber pacemaker: the efficacy of the overdrive atrial algorithm at 2 year follow-up. Acta Myol 2013; 32: 142-147.

21) Russo V, Rago A, Papa AA, Politano L, Golino P, Russo MG, Calabrò R, Nigro G. Does a high percentage of right ventricular pacing influence the incidence of paroxysmal atrial fibrillation in myotonic dystrophy type 1 patients? Kardiol Pol 2013; 71: 1147-1453.

22) Russo V, Nigro G, Di Meo F, Papa AA, Cioppa ND, Proietti R, Russo MG, Calabrò R, Politano L. The effect of atrial preference pacing on atrial fibrillation electrophysiological substrate in Myotonic Dystrophy type 1 population. Acta Myol 2014; 33: 127-135.

23) Russo V, Di Meo F, Rago A, Papa AA, Molino A, Mosella M, Politano L, Russo MG, Nigro G. Paroxysmal atrial fibrillation in myotonic dystrophy type 1 patients: P wave duration and dispersion analysis. Eur Rev Med Pharmacol Sci 2015; 19: 1241-1248.

24) Russo V, Rago A, Pannone B, Di Meo F, Papa AA, Mayer MC, Spasiano A, Russo MG, Golino P, Calabrò R, Nigro G. Early electrocardiographic evaluation of atrial fibrillation risk in beta-thalassemia major patients. Int J Hematol 2011; 93: 446-451.

25) Russo V, Rago A, Pannone B, Papa AA, Mayer MC, Spasiano A, Calabrò R, Russo MG, Nigro G. Atrial fibrillation and beta thalassemia major: the predictive role of the 12-lead electrocardiogram analysis. Indian Pacing Electrophysiol J 2014; 14: 121-132.

26) Russo V, Rago A, Di Meo F, Papa AA, Ciardiello C, Cristiano A, Calabrò R, Russo MG, Nigro G. Atrial septal aneurysm and supraventricular arrhythmias: the role of atrial electromechanical delay. Echocardiography 2015; 32: 1504-1514.

27) Proietti R, Russo V, Sagone A, Viecca M, Spodick DH. Interatrial block: an under-recognized electrocardiographic diagnosis with important clinical-therapeutic implications. G Ital Cardiol (Rome) 2014; 15: 561-568.

28) Stabile G, Russo V, Rapacciuolo A, De Divitiis M, De Simone A, Solimene F, D'Onofrio A, Iuliano A, Maresca G, Esposito F, La Rocca V, Schillaci V, De Crescenzo I, Losi MA, Librera M. Transesophageal echocardiography in patients with persistent atrial fibrillation undergoing electrical cardioversion on new oral anticoagulants: A multi center registry. Int J Cardiol 2015; 184: 283-284.

29) Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation 2011; 123: 131-136.