International Blood Research & Reviews
2(2): 56-68, 2014, Article no. IBRR.2014.002

SCIENCEDOMAIN *international*
www.sciencedomain.org

Type the Characteristics of Pacemaker (PM) Patients Admitted in Stroke Unit: The Stroke Pacemaker Study (SPACES)

M. Spinelli[1], G. Silvestrelli[2], S. Micheli[3], M. Paciaroni[4], G. Agnelli[4], A. Lanari[2] and F. Corea[5*]

[1]Stroke Unit, IRCCS C. Mondino, Pavia and IRCCS San Raffaele, Milano, Italy.
[2]Stroke Unit, Division of Neurology, C. Poma Hospital, Mantova, Italy.
[3]Neurofisiologia, Spoleto, Italy.
[4]Stroke Unit, University of Perugia, Italy.
[5]Brain Injury Unit, San Giovanni Battista, Foligno, Italy.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MS and FC designed the study and wrote the first draft of the manuscript. Authors MS, GS, AL, MP, SM and GA selected the patients, developed the database and reviewed the draft. Author FC made the statistical analysis. All authors read and approved the final manuscript.

Original Research Article

Received 18th June 2013
Accepted 20th October 2013
Published 13th January 2014

ABSTRACT

Aims: According to recent surveys, despite health care authority's budget reductions, the total amount of PM implants increased worldwide. Even if the diffusion of these devices is large no data are available concerning the characteristics of PM patients hospitalized for stroke.
Study Design: The SPACES study is a retrospective observational study conducted in 3 hospital centres including paced patients consecutively admitted for acute stroke. The objective is to determine the characteristics of patients with PM admitted in the stroke units.
Place and Duration of Study: In 3 Italian general hospital (Perugia, Milano, Mantova), from January 2005 to September 2008.
Method: At admission all patients underwent non-contrast computed tomography (CT), routine biological tests, 12-lead ECG. The ECG was categorized in following subgroups:

**Corresponding author: E-mail: francesco.corea@uslumbria2.it;*

a) sinus rhythm; b) AF rhythm; c) PM-induced activity (when was not possible to state the underlying rhythm).
Results: In the study population were recorded 73 ischemic strokes, 10 hemorrhagic events and 19 TIA. At the basal ECG a “pacemaker-induced” rhythm was diagnosed in 37 cases, sinus rhythm in 28, AF in 32 subjects. At the univariate analysis patients with an ECG-detected AF rhythm at admission were more often those with positive AF medical history (p<.001) and treated with aspirin prior to the index event (p=.023). Patients with an ECG-detected AF at admission more often suffered a Total Anterior Cerebral Infarction (TACI) subtype of stroke (p=.038) having cardioembolism as cause (p<.001).
Conclusions: Our survey suggests that paced patients suffer more often, than unselected case-series, of ischemic strokes due to cardioembolic events. Moreover AF is the leading risk factor in PM subjects. Probably PM-induced electric activity may further confound the detection of the baseline ECG, with an underestimation of AF.

Keywords: Stroke; pacemaker; atrial fibrillation.

1. INTRODUCTION

The first successful cardiac resuscitation by external stimulation was reported in the 1950s, and the medical importance of electrical cardiac stimulation grew rapidly. Millions of people with cardiac arrhythmias have been treated with pacemakers. Virtually all countries that participated in the 1997 survey showed significant increases in implant numbers over the 4-year survey [1-3].

High degree atrioventricular block (AVB) and Sick Sinus Syndrome (SSS) remain the major Indications for implantation of a cardiac pacemaker. Dual-chamber pacing has steadily increased as a proportion of all pacemaker insertions in the past 10 years and accounted for 58.5% of the total in 2003. Use of dual-chamber devices has exceeded single chamber since 1995/96. Of dual chamber devices inserted in 2003, about half were rate responsive (DDDR) and half not (DDD). About 40% of implants were ventricular: 16.4% of the total was VVI and 24% VVIR.

According to the above mentioned survey, we extrapolated, a total of around 800 new implants per million of inhabitants in Europe, only in 2005. This large number of patients has specific needs and peculiar characteristics connected with the presence of the device (i.e. magnetic resonance imaging is not possible, need of closer cardiac follow-up, older age). Their characteristics have relevant influence in the stroke unit management, but no guidelines ever described which the best approach to use is.

Supra-ventricular arrhythmias are likely to be a major concern in these subjects. The incidence of AF after pacemaker implantation, as found by Bandit, was more than half of patients with sinus node dysfunction and almost one-fifth in those with AV block within a 6-year post-implant follow-up duration [4]. In the general population of patients receiving pacemakers it has been shown that approximately 18% have a prior history of AF, while 50% of patients with sinus node disease and 20% with AV block will eventually develop AF even without a history of AF prior to pacemaker implantation [4]. Previous studies suggested that atrial pacing decreased the risk of AF in patients who required the implantation of a permanent pacing system for primary sinus node dysfunction [5,6].

Theoretically, atrial pacing could prevent AF, but despite the commercial availability of many advanced pacing techniques the role of permanent pacing to prevent AF is controversial. At present, permanent pacing to prevent AF is not indicated. Additional studies are ongoing, which will help to clarify the role of permanent pacing for AF [7-13]. The Stroke Pacemaker Study (SPACES) study is a retrospective observational study conducted in 3 hospital centers (Perugia, Milano, Mantova) including paced patients consecutively admitted in the study period January 2005 to September 2008 for an acute stroke or transient ischemic attack (TIA). Objective of the SPACES study is to determine the characteristics of cerebrovascular events in PM patients, and the antithrombotic regimens used before and after hospitalization.

2. MATERIALS AND METHODS

The characteristic of the index event and more frequent risk factors in the study population were reported. All available data concerning the management of patients in the 3 centres were recorded with specific attention on both pre and post stroke antithrombotic treatment and cardiac rhythm. All patients, of any age and gender, admitted to the centres during the study period were eligible to enter the study, provided they were admitted for an acute stroke (ischemic or hemorrhagic) or Transient Ischemic Attack (TIA), and had an implanted pacemaker or defibrillator.

At admission all patients underwent non contrast computed tomography (CT), routine Biological tests, 12 lead ECG, and chest radiography. The 12 lead ECG was categorized in following subgroups: a) sinus rhythm; b) AF rhythm; c) PM-induced activity (when the cardiologist was not able to state the underlying rhythm). Other patients with ischemic stroke or TIA underwent cervical Doppler ultrasonography. All patients with an ischemic stroke or TIA, and most patients with haemorrhagic stroke, underwent a transthoracic echocardiography. Conventional angiography and transoesophageal echocardiography were performed in selected patients. Ischemic stroke was defined as clinical signs of focal disturbance of cerebral function lasting longer than 24 hours or leading to death, with no apparent cause other than of vascular origin, and no sign of relevant primary intracerebral haemorrhage on CT scan or at necropsy. Haemorrhagic stroke was defined as clinical signs of focal disturbance of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than vascular, and evidence of a relevant primary intracerebral haemorrhage on CT scan or at necropsy.

TIAs were defined as episodes of focal cerebral dysfunction, presumably ischaemic in origin, lasting less than 24 hours and followed by return to normality, without any relevant lesion on CT scan other than of ischemic origin. Medical history was determined from all available records (letter from their general practitioner (GP) or telephone call) and sources (patient, family, or GP). We collected the following data: age; sex; previous stroke or TIA; presence of arterial hypertension (defined as systolic blood pressure>160 mm Hg, or diastolic blood pressure>90 mm Hg, or treatment with antihypertensive drugs before stroke onset); diabetes mellitus (defined as fasting serum glucose concentration>120 mg/dl (6.7 mmol/l), or current use of antidiabetic drugs); hyperlipidaemia (defined as fasting serum triglycerides concentration>150 mg/dl (1.71 mmol/l), or fasting cholesterol serum concentration>230 mg/dl (6.0 mmol/l), or current hypolipidaemic treatment); history of peripheral artery disease with intermittent claudication; alcoholism (defined as a mean alcohol consumption>300 g/ week); cigarette smoking (>10 cigarettes/day or cessation less than five years earlier); high risk cardiopathies as defined according to the trial of org 10172 in acute stroke treatment (TOAST) criteria [14]; Oxfordshire community Stroke Project criteria were also used to

classify the index events. Partial Anterior Cerebral Infarcts (PACI), Total Anterior Cerebral Infarcts (TACI), Lacunar Cerebral Infarcts (LACI), Posterior Cerebral Infarcts (POCI)[15]. Significant stenosis of the internal carotid arteries defined as>50% narrowing of the lumen documented by Doppler ultrasonography, B mode echotomography, or conventional angiography. Treatments at entrance and at discharge were also recorded.

Pacemaker characteristics were recorded according to the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) jointly revised pacemaker nomenclature [16]. This established the Generic Code for Anti-bradycardia Pacing. The Generic Code is composed of elements ('positions') describing the chamber paced (position I), chamber sensed (position II), response to sensing (position III) and rate modulation (position IV). Position II indicates the chamber where spontaneous depolarization is detected if it occurs outside the pulse generator's preset refractory periods.

The action of the pacemaker in response to spontaneous cardiac depolarization is described by position III. Position IV describes the incorporation of an extrinsic sensor to provide 'rate modulation' or 'rate responsiveness'. Patients were divided in 3 groups according to their 12-lead ECG findings ad admission: a) sinus rhythm b) atrial fibrillation, c) PM induced rhythm. The statistical analysis comprised a univariate analysis comparing variables between the 3 patient's subgroups: a) sinus rhythm; b) AF rhythm; c) PM-induced rhythm. We used the Chi squared test with Yates correction or Fisher's exact test when appropriate. Variables were demographic details, characteristics of the index stroke, medical history, risk factors for stroke, potential causes of stroke other than atrial fibrillation, and past or current treatments. The last step of the statistical analysis was logistic regression assuming AF rhythm detected at admission ECG and OA at discharge as dependent variable.

3. RESULTS AND DISCUSSION

3.1 Study Population

We included 102 PM patients: 58 were males the median age was 78 ranging from 56 to 98. The 78.4% were hypertensive, 21.5 % had diabetes and 43% AF history. In the study population 46 subjects had dual chamber pacing (DDD) and 56 a single chamber type (VVI). The reason for the pacemaker implant was known in 48 subjects, 9 cases because a SSS, in 15 AVB, in 24 a symptomatic bradycardia. These subjects were admitted in the stroke unit in 73 (71.5%) cases for an ischemic stroke, in 10 (9.8%) because of an hemorrhagic event and 19 (18.6 %) for a TIA. Most of the ischemic events were considered having a clear cardiac cause (35.3%) while a large vessels disease was identified in 12 (11.7%) cases, small artery disease in 15 (14.7%) multiple causes in 11 (10.7%) and other known in 3 (2.9%). According to the OCSP classification 26 were PACI events (25,5%), 17 TACI (16,6%), 17 LACI (16,6%) and 11 POCI (9,8 %).

3.2 Cardiac Rhythm

At the basal ECG a "pacemaker-induced" rhythm was diagnosed in 37 cases, while sinus rhythm was detected in 28, and AF rhythm in 32 subjects (5 non classifiable). At the univariate analysis in the study population those with a clear sinus rhythm at admission were younger (73 vs. 78 $p<.05$), with smoke habit ($p<.001$) and more often suffered of an hemorrhagic stroke (prevalence in the group of 25% vs. 3.1% in AF group and 2.7% in PM induced rhythm) (Table 1). Patients with an ECG-detected AF rhythm at admission were also

those with positive AF medical history (p<.001). Moreover they were often treated with aspirin prior to the index event (p=.023) and admitted because of an ischemic stroke in 84.3% of cases. Patients with clear AF rhythm at admission were more frequently victims of a TACI subtype of stroke having a cardioembolic cause (p<.001) Table 1. These subjects were also older (p=.001) and suffered of more disabling strokes according to the modified Rankin (RM) scale scores (median scores of RM were 2 vs. 3 in AF patients; p=.02). The logistic regression analysis, assuming ECG-detected AF as dependent variable, found only AF medical history as independent variable (OR 22,5 IC95% 6,2-81,6) Table 2. The model was adjusted for age, gender and PM subtypes. An electrically induced rhythm was reported mostly in subjects with history of atrioventricular block (AVB) as indication to PM implant (p=.04) and having a DDD device (p<.05) Table 1.

Table 1. Characteristics of the patients with regard to the report 12-lead ECG performed at admission. §In 2 cases the ECG report was not classifiable in one of the 3 categories, in 2 cases not available, In 1 case with artefacts. Univariate analysis with Chi squared test or Mann Whitney U test. Level of significance: *p<0.05; ** p<0.01; ***p<0.001. PM: Pacemaker; AVB: Atrioventricular block

Demographic data	Total (n=102§)	AF Rhythm (n=32)	Sinus Rhythm (n=28)	PM-induced (n=37)
Age (median and range)	78 (56-98)	82 (58-98) ***	73 (56-87)*	77 (60-92)
Male gender	56(54.9%)	14* (43.7%)	18 (64.3%)	24 (64.8%)
Diabetes	21(20.5%)	6 (18.7%)	6 (21.4%)	9 (24.3%)
Hypertension	80 (78.4%)	27 (84.4%)	22 (78.6%)	30 (81%)
Current smoking	15 (14.7%)	3 (9.4%)	12***(42.8%)	0***
Hyperlipidemia	25 (24.5%)	3** (9.4%)	13** (46.4%)	8 (21.6%)
Atrial fibrillation history	44 (43.1%)	28*** (87.5%)	1*** (3.5%)	15 (40.5%)
Indication to PM implant				
Sick Sinus Syndrome	9 (8.8%)	4 (12.5%)	1(3.5%)	3 (8.1%)
AVB	15 (14.7%)	2 (6.3%)	2 (7.1%)	11* (29.7%)
Bradycardia	24 (23.5%)	7 (21.9%)	6 (21.4%)	11 (29.7%)
Dual chamber pacing	45 (44.1%)	13 (40.6%)	9 (32.1%)	22* (59.4%)
Single chamber pacing	54 (52.9%)	19 (59.4%)	19 (67.8%)	15* (40.5%)
Index event				
Ischemic stroke	73 (71.5%)	27 (84.3.%)	13*** (46.4%)	30 (81%)
TIA	19 (18.6%)	5 (15.6%)	8 (28.5%)	6 (16.2%)
Hemorrhage	10 (9.8%)	1 (3.1%)	7** (25%)	1* (2.7%)
Rankin score (median)	3 (0-6)	3 (0-5)*	2 (0-5)*	3 (0-6)
Cause				
Atherosclerosis	12 (11.7%)	1* (3.1%)	3 (10.7%)	8*(21.6%)
Small vessel disease	15 (14.7%)	1**(3.1%)	8*(28.5%)	6 (16.2%)
Cardioembolism	36 (35.3%)	23***(71.9%)	1***(3.5%)	11(29.7%)
Other cause	3 (2.9%)	0	1(3.5%)	2 (5.4%)
Multiple possible causes	11 (10.7%)	3 (9.4%)	1(3.5%)	7*(18.9%)
Subtype				
TACI	17 (16.6%)	9* (28.1%)	0**	8 (21.6%)
PACI	26 (25.5%)	10 (31.2%)	3*(10.7%)	13 (35.1%)
LACI	17 (16.6%)	6 (18.7%)	6 (21.4%)	5 (13.5%)
POCI	10 (9.8%)	1 (3.1%)	4 (14.2%)	4 (10.8%)

Table 1 Continue…….

Treatment at admission				
Aspirin	40 (39.2%)	18* (56.2%)	4***(14.2%)	17 (45.9%)
Oral anticoagulants	11 (10.7%)	4 (12.5%)	1(3.5%)	6 (16.2%)
Other antiplatelet	9 (8.8%)	2 (6.2%)	2 (7.1%)	5 (13.5%)
Treatment at discharge				
Aspirin	42 (41.2%)	12 (37.5%)	13 (46.4%)	17(45.9%)
Oral anticoagulants	20 (19.6%)	9 (28.1%)	3 *(10.7%)	7 (18.9%)
Other antiplatelet	10 (9.8%)	3 (9.4%)	1 (3.5%)	6 (16.2%)
Clopidogrel	17 (16.6%)	7 (21.9%)	5 (17.8%)	5 (13.5%)
Any antithrombotic	88 (86.3%)	30 (93.7%)	21*(75%)	34 (91.8%)
	Total (n=102[§])	AF Rhythm (n=32)	Sinus Rhythm (n=28)	PM-induced (n=37)

Table 2. Logistic regression analysis: AF history is independently associated with presence of AF on 12 lead-ECG

variable	OR	CI 95%
AF history	22,5	6,22-81,6
Age	1,04	0,98-1,12
Male	0,39	0,12-1,28
Type of device	0,5	0,56-3,13

3.3 Antithrombotic Regimens

Before the index event the use any-antithrombotic drug was below 60%, in the study population 41% were treated with aspirin, 11% with OA, 8.8% with other antiplatelet agents (aspirin/extended-release dipiridamole or clopidogrel). At discharge from the stroke unit the use of any-antithrombotic raised to 86.3%, aspirin was stable to 42.2%; OA raised to 19.6% other antiplatelet drugs triplicate to 26.4%. At the univariate analysis the administration of any anti-thrombotic drug at discharge was associated to male gender (p=.02), to ischemic stroke as reason for hospitalization (p<0.001) and known AF medical history (p=.01). The logistic regression analysis assuming OA treatment at discharge as dependent variable found known AF (p<.05 OR 4 IC95% 1.3-11.2), previous OA treatment (p <.01 OR 11 IC95% 2.3-51) and lower MR score (p<.05 OR 0.7 IC95% 0.5-0.9) as independent variables Table 3.

Table 3. Factors independently associated with oral anticoagulant administration at discharge, on logistic regression analysis Rankin Scale (RS), Atrial Fibrillation (AF), Oral anti coagulants (OA)

Variable	OR	CI 95%
AF history	4	1,3 – 11,2
OA prior-stroke	11	2,3 – 51
RS post-stroke	0,7	0,5 - 0,9

4. DISCUSSION

Paced patients admitted in the stroke unit suffered frequently of major ischemic strokes due to cardio embolism. No previous study has examined AF prevalence, etiology of the event and antithrombotic regimens in a similar setting. Our study as shown that in consecutive PM-stroke patients AF is the leading risk factor with a prevalence of 32.6%. The study of Tse and colleagues, in the general population, studied 226 unselected paced patients with dual DDDR. During a mean follow-up of 84 months, 99 patients (44%) had at least one episode of AF, compared with 0.4% in the general population. Patients with AF had 2·5 times more cardiovascular events and a ten times greater incidence of persistent AF than the other patients in the study [17]. Sparks and colleagues reported a similar prevalence of AF (48%) in a smaller series of outpatients with pacemakers. [18].

Stroke in sick sinus syndrome after pacemaker insertion is not rare, as found by Fisher et al. and pacing does not appear to be protective. Sick sinus syndrome patients who convert to atrial fibrillation or who have a ventricular-demand pacemaker might represent high-risk groups for stroke [19].

We found a relevant disproportion between the medical history of permanent/persistent AF (43%) and ECG-detected AF rhythm (31%). The type of PM implanted may have a role in the diagnosis of AF? Several prospective randomized controlled trials comparing single- (atrial or ventricular) or dual-chamber pacing have evaluated the incidence of AF, usually as a secondary end point, in patients with a history of bradycardia [20-32]. In the Mode Selection Trial (MOST), 2000 patients with SSS were randomized to either dual-chamber DDDR pacing or ventricular VVIR pacing. AF developed in 24% of the study population over a median follow-up of 3 years, and 22% of these patients progressed to permanent.

Dual chamber pacing was associated with a lower rate of progression to chronic AF as compared with ventricular pacing (15% vs. 27%; hazard ratio 0.44). Therefore, it was concluded that patients, irrespective of the initial indication for pacing, if implanted with AAI or DDD pacing systems, are more likely to remain free of AF (29). In the Canadian Trial of Physiological Pacing (CTOPP), 2600 patients undergoing initial pacing system implant were randomized to a VVIR device or a DDDR device. DDDR pacing was associated with a 27% relative risk reduction of permanent AF, over a mean follow-up of 3 years, compared with ventricular pacing; 2.8% per year vs 3.8% per year. However, the advantage of physiological pacing was demonstrated after 2 years of the implantation [30,31].

Guidelines from international scientific societies stated how at present, permanent pacing to prevent AF is not indicated. Additional studies are ongoing, which will help to clarify the role of permanent pacing for AF [6-7]. In our study the more physiological type of pacing (DDD) demonstrated a lower prevalence of ECG-detected AF (40.6% in DDD vs. 59.4% in VVI). But in a large number of subjects the standard 12-lead ECG was not able to distinguish between sinus rhythm and AF (37 cases 36.2%). The ratio between DDD and VVI pacing was 0.8 in the all study population, 0.7 in AF rhythm group, 0.5 in the sinus rhythm group and surprisingly inverted in the PM-induced rhythm group with 1.5 ($p<.05$). Many data support the hypothesis that PM-induced electric activity may confound the report of the baseline 12-lead ECG; paced patients are not spared by AF episodes, during in-hospital staying; they simply need a reprogramming of the device to assess the real underlying rhythm. Reprogramming to VVI 30 beats/min appeared to be most useful in patients with VVI pacemakers where ventricular rates were regular and no discrete P waves or fibrillation waves were visible between pacing arte facts on the 12-lead ECG [18]. Pacemaker

reprogramming in this way has been reported in few studies, and the frequency of its use or the reasons for its use are not described. We believe that a specific examination for AF should be a routine part of pacemaker patient's evaluation in a Stroke Unit. In 37.7% of cases included in the SPACES study the standard ECG was not sufficient to state whether the patients was in sinus rhythm or not. In our study only 16 patients underwent to aritmological evaluation of the device. Pacing in DDD mode was more often associated to PM-induced rhythm ($p<.05$) on the baseline ECG, presumably because of more electrically induced artifacts [33]. In all cases, without other contraindications, once AF is diagnosed OA should be considered for primary and secondary stroke prevention. Many large prospective randomised trials have shown that OA therapy lowers the risk of thromboembolic stroke by 70% in patients with AF [34-52]. Even if these trails did not involve paced subjects, there is no reason for excluding "a priori" them from prophylaxis with cumarins. Moreover despite clear guidelines anticoagulation is underused in patients with AF in various clinical settings [53-56]. Also in pacemaker patients the rate of anticoagulation seems far from being satisfactory [17,18,33]. The prevalence of AF seems particularly high in patients with permanent pacemaker therapy for SSS [17,18,33]. These patients, in part due to their old age, have a very high risk of stroke and might therefore benefit from an appropriate antithrombotic therapy. Patel and McLellan reported a rate of anticoagulation in AF paced patients of 60%, while Sparks and colleagues' survey showed that only 15% of paced patients had received cumarins [33,57]. New onset AF and contraindications do not account for all patients not receiving stroke prevention. Many patients with pacemakers are unlikely to have a previously diagnosed AF, and most have no symptoms suggesting cardiac diseases. The use of antithrombotic agents, prior to stroke in the study population was large (58.8%), and mainly based on antiplatelet drugs. OA were administered in 11% of cases. But this is insufficient taking into account a known medical history of AF in so many cases. Also at discharge, even if doubled, the use of OA seems low (20%) and mostly based on the medical history of AF and a previous treatment with cumarins. A part of non prescriptions may be to potential contra-indications due to the vascular index event (i.e. post-stroke dementia, severe disability (mRS≥3), large cerebral infarction, haemorrhagic transformations). But also in this case the rate of nonprescriptions of OA seems to be too high to be explained just by contraindications.

We found a large use of thyenopiridines (ticlopidine and clopidogrel) to prevent stroke in paced patients. International guidelines only recommended aspirin to prevent stroke in patient with cardioembolism who cannot tolerate oral anticoagulants. At our knowledge, no data are available on thyenopiridines efficacy for secondary prevention of cardioembolic stroke [34,58-60]. Our study has some limits, mostly due to the small sample analyzed and the lack of a detailed aritmological assessment in the study population. But has also some strengths. We prospectively enrolled consecutive subjects, all admitted in well established stroke centers and managed according to guidelines. Thereby the picture obtained is likely to be representative of the management of PM patients, at least in continental European health care systems.

5. CONCLUSIONS

Our data suggest how the use of a pacemaker diagnostic counter or deeper aritmological assessment, can assist stroke specialists in identifying AF patients. Anticoagulation treatment for stroke prevention should be systematically considered in those patients who have a prior history of AF or device detected AF episodes [61-62]. Stroke prevention in PM patients can be further optimised this subjects are under close follow up, cardiac rhythm can be checked with feasible procedures thus guidelines needs to be better attended. We

strongly believe that a closer cooperation of cardiologist and the stroke neurologist is vital for implementing strategies to reduce the burden of stroke.

CONSENT

Not applicable. All patients gave written consent to enter personal data in the local stroke registries (Mantova, Milano and Perugia).

ETHICAL APPROVAL

Not applicable. Ethical commissions authorized each local stroke registry (Mantova, Milano and Perugia) to collect prospective data.

COMPETING INTERESTS

FC received modest grants from Merck-Serono and Biogen-Idec. Partial data of the study were submitted in 2011 to the “One mission one million” expert panel initiative sponsored by Boehringer Ingelheim.

REFERENCES

1. Ector H, Rickards AF, Kappenberger L, Linde C, Vardas P, Oto A et al. Working Group on Cardiac Pacing. The world survey of cardiac pacing and implantable cardioverter defibrillators. Europe. 2001;24:863-68.
2. Mond HG, Irwin M, Ector H. The world survey of cardiac pacing and implantable cardioverter defibrillators. 2004;27:955-64.
3. Ector H, Vardas P. Current use of pacemakers, implantable cardioverter defibrillators, and resynchronization devides data from the registry of the European Heart Rhythm Association. European Heart Journal. 2007;9(1):144-49.
4. Benditt DG, Mianulli M, Gorski J, Carr L, Neels K. Emergence of atrial fibrillation as a new Comorbidity in pacemaker patients. A natural history study. 1999;22:809.
5. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T et al. Long-term follow-up of patients from a randomized trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet. 1997;350:1210–6.
6. Irwin ME. Cardiac pacing device therapy for atrial dysrhythmias. AACN Clinical. 2004; 377-390.
7. Knight BP, Gersh BJ, Carlson MD, Friedman PA, Gersh BJ, Carlson MD et al. Role of permanent pacing to prevent atrial fibrillation. Circulation 2005;111:240-243.
8. De Voogt W, De Vusser P, Lau CP, Van den Bos A, Koistinen Y, Mairesse G et al. Overdrive atrial septum stimulation in patients with paroxysmal atrial fibrillation (AF) and class 1 and 2 pacemaker indication (OASES). Paper presented at: Annual Scientific Sessions of the Heart Rhythm Society; 2003.
9. Carlson M, Ip J, Messenger J, Beau S, Kalbfleisch S, Gervais P, Cameron DA et al. A new pacemaker algorithm for the treatment of atrial fibrillation results of the Atrial Dynamic Overdrive Pacing Trial (ADOPT). J Am Coll Cardiol. 2003;42:627–633.
10. Savelieva I, Camm AJ. The results of pacing trials for the prevention and termination of atrial tachyarrhythmias is there any evidence of therapeutic breakthrough? J Interv Cardiol Electrophysiol. 2003;8:103–115.

11. Friedman P, Dijkman B, Warman EN, Xia HA, Mehra R, Stanton M, Hammill SC. Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. Circulation. 2001;104:1023–1028.
12. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003;107:2932–2937.
13. Lee MA, Weachter R, Pollak S, Kremers MS, Naik AM, Silverman R et al. The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency results of a randomized trial in patients with bradycardia and atrial tachyarrhythmias. J Am Coll Cardiol. 2003;41:1926 –1932.
14. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL et al. 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment Stroke. 1993;24(1):35-41.
15. BMJ. Oxfordshire Community Stroke Project Incidence of stroke in Oxfordshire first year's experience of a community stroke register. 1983;287:713-717.
16. Zipes, in Braunwald's Heart Disease A Textbook of Cardiovascular Medicine, 7ª ed., Philadelphia, Saunders; 2005.
17. Tse HF, Lau CP. Prevalence and clinical implications of atrial fibrillation episodes detected by pacemaker in patients with sick sinus syndrome. 2005;91:362.
18. Sparks PB, Mond HG, Kalman JM, Jayaprakash S, Lewis MA, Grigg LE. Atrial fibrillation and anticoagulation in patients with permanent pacemakers: implications for stroke prevention. Pacing Clin Electrophysiol. 1998;21:1258–67.
19. Fisher M, Kase CS, Stelle B, Mills RM. Jr. Ischemic stroke after cardiac pacemaker implantation in sick sinus syndrome Stroke. 1988;19(6):712-5.
20. Israel CW. The role of pacing mode in the development of atrial fibrillation. Europace. 2006;8:89–95.
21. Andersen HR. Prospective randomized trial of atrial versus ventricular pacing in sick-sinus syndrome. Lancet. 1994;344:1523-8.
22. Sgarbossa EB, Pinski SL, Maloney JD, Simmons TW, Wilkoff BL, Castle LW et al. Chronic atrial fibrillation and stroke in paced patients with sick sinus syndrome.Relevance of clinical characteristics and pacing modalities. Circulation. 1993;88:1045–53.
23. Lamas GA, Orav J, Stambler BS, Ellenbogen KA, Sgarbossa EB, Huang SK et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. N. Engl. J. Med. 1998;338:1097–104.
24. Saccomanno G, Fraticelli A, Marini M, Spazzafumo L, Paciaroni E. Permanent ventricular and dual chamber cardiac stimulation: role of pacing mode in relation to chronic atrial fibrillation risk and stroke development. Archives of gerontology and geriatrics. 1999;(29):61-74.
25. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R et al. Mode Selection Trial in Sinus-Node Dysfunction. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N. Engl. J. Med. 2002;346:1854-62.
26. Greenspon AJ, Hart RG, Dawson D, Hellkamp AS, Silver M, Flaker GC et al. Predictors of Stroke in patients paced for sick sinus syndrome J Am Coll Cardiol. 2004;43:1617-22.
27. Connolly SG, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. N Engl J Med. 2000;342:1385-91.

28. Fored CM, Granath F, Gadler F, Blomqvist P, Rynder J, Linde C et al. Atrial vs dual-chamber cardiac pacing in sinus node disease a register-based cohort study Europace. 2008;10:825-831.
29. Lamas GA, Lee K, Sweeney M, Leon A, Yee R, Ellenbogen K et al. The Mode Selection Trial (MOST) in sinus node dysfunction: Design, rationale, and baseline characteristics of the first 1000 patients. Am Heart J. 2000;140:541-51.
30. Stambler BS, Ellenbogen KA, Orav EJ, Sgarbossa EB, Estes NA, Rizo-Patron C et al. Pacemaker Selection in the Elderly Trial Investigators. Predictors and clinical impact of atrial fibrillation after pacemaker implantation in elderly patients treated with dual chamber versus ventricular pacing. 2003;26:2000-7.
31. Skanes AC, Krahn AD, Yee R, Klein GJ, Connolly SJ, Kerr CR et al. Canadian Trial of Physiologic Pacing. Progression to chronic atrial fibrillation after pacing the Canadian Trial on Physiologic Pacing. J Am Coll Cardiol. 2001;38:167-172.
32. Padeletti L, Purerfellner H, Adler S, Waller TJ, Harvey M, Horvitz L et al. Atrial septal lead placement and atrial pacing algorithms for prevention of paroxysmal atrial fibrillation. ASPECT study results. 2002;25(4):687.
33. Patel AM, Westveer DC, Man KC, Stewart JR, Frumin HI. Treatment of underlying atrial fibrillation paced rhythm obscures recognition. J Am Coll Cardiol. 2000;36:784–87.
34. Kirshner HS. Therapeutic Interventions for Prevention of Recurrent Ischemic Stroke. Am J Manag Care. 2008;14:212-S226.
35. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS et al. Selecting patients with atrial fibrillation for anticoagulation stroke risk stratification in patients taking aspirin. Circulation. 2004;110:2287-92.
36. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFaSAK study. Lancet. 1989;1:175-9.
37. Stroke prevention in Atrial Fibrillation study. Final results. Circulation. 1991;84:527-39.
38. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation Stroke Prevention in Atrial Fibrillation II study. Lancet. 1994;343:687–91.
39. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet. 1996;348:633–8.
40. Engl N, Med J. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. 1990;323:1505–11.
41. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation (CAFA) study. J Am Coll Cardiol .1991;18:349 –55.
42. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation Stroke Prevention in Atrial Fibrillation II study. Lancet. 1994;343:687–91.
43. Marmagkiolis K, Nikolaidis IG, Politis T, Goldstein L. Approach to and management of the acute stroke patient with atrial fibrillation: a literature review. Journal of Hospital Medicine. 2008;3:326-32.
44. SPAF, JAMA. Committee Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin. 1998;279:1273-77.

45. Segal JB, McNamara RL, Miller MR, Powe NR, Goodman SN, Robinson KA. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation Stroke Prevention in Atrial Fibrillation II study. Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter (Review) 2006. Cochrane Database of Systematic Reviews Lancet. 1994;343:687–91.
46. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S et al. Active Writing Group of the active Investigators, Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) a randomised controlled trial. Lancet. 2006;367:1903-12.
47. Healey Js, Hart RG, Pogue J, Pfeffer MA, Hohnloser SH, De Caterina R et al. Risks and Benefits of Oral Anticoagulation Compared With Clopidogrel Plus Aspirin in Patients with atrial Fibrillation According to Stroke Risk. The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W) Stroke. 2008;39(5):1482-6.
48. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA) a randomised controlled trial Lancet. 2007;370:493-503.
49. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomized controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO) Age and Ageing. 2007;36:151-156.
50. Hughes M. Lip GY on behalf of the Guideline Development Group for the NICE national clinical guideline for management of atrial fibrillation in primary and secondary care. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation a systematic review. QJM. 2007;100:599–607.
51. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007;115:2689–2696.
52. Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the generale Medicare population a 10-year perspective (1992-2002). Stroke. 2006;37:1969-1974.
53. Waldo AL, Becker RC, Tapson VF, Colgan KJ. NABOR Steering Committee Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adeguate anticoagulation. J Am Coll. Cardiol. 2005;46(9):1729-36.
54. Friberg L, Hammar N, Ringh M, Pettersson H, Rosenqvist M. Stroke prophylaxis in atrial fibrillation who gets it and who does not? Report from the Stockholm Cohortstudy on Atrial Fibrillation (SCAF-study). European Heart Journal. 2006;27:1954-64.
55. Deplanque D, Corea F, Arquizan C, Parnetti L, Mas JL, Gallai V et al. Stroke and atrial fibrillation is stroke prevention treatment appropriate beforehand? Heart. 1999;82:563–569.
56. Deplanque D, Leys D, Parnetti L, Schmidt R, Ferro J, De Reuck J et al. Stroke prevention and atrial fibrillation reasons leading to an inappropriate management. Main results of the SAFE II study Br J Clin Pharmacol. 2004;57:(6)798-806.
57. McLellan CS, Abdollah H, Brennan FJ, Simpson CS. Atrial fibrillation in the pacemaker clinic. Can J Cardiol. 2003;19:492–94.
58. ESO. European Stroke Organisation Guidelines. Ischaemic stroke. Preventiontreatment-rehabilitation January 2009 downloaded at http://www.eso-stroke.org/ ; 2012.

59. Lakshminarayan K, Anderson DC, Herzog CA, Qureshi AI. Clinical epidemiology of atrial fibrillation and related cerebrovascular events in the United States. Neurologist. 2008;14(3):143-50.
60. Savelieva I, Camm J. Update on atrial fibrillation part I. Clin Cardiol. 2008;31(2):55-62.
61. Corea F, Tambasco N. Cardiac pacing: atrial fibrillation may go unrecognised. Lancet Neurol. 2005;4(5):265.
62. Giacalone G, Abbas MA, Corea F. Prevention strategies for cardioembolic stroke present and future perspectives. Open Neurol J. 2010;15(4):56-63.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=391&id=28&aid=3299