Bleeding complications after pacemaker or cardioverter-defibrillator implantation in patients receiving dual antiplatelet therapy

Results of a prospective, two-centre registry

A. Przybylski, P. Derejko, W. Kwaśniewski, D. Urbańczyk-Świąć, J. Zakrzewska, W. Orszulak, M. Orczykowski, A. Filipecki, Ł. Szumowski, F. Walczak, M. Trusz-Gluza

Introduction. The aim of the study was to define the prevalence of bleeding events in patients treated with dual antiplatelet therapy (DAT) in comparison with patients receiving only acetylsalicylic acid (ASA).

Methods. Prospective two-centre registry of all first implantations of pacemakers, cardioverter-defibrillators and cardiac resynchronisation therapy units in patients receiving ASA (n=194) or DAT (n=53).

Results. Bleeding complications were detected in 27 (16.2%) patients in the ASA group and in 13 (24.5%) in the DAT group. There was no significant difference in the overall number of complications between the patients receiving ASA or DAT, although there was a trend towards a higher incidence of overall complication rates in the DAT group (p=0.0637). The incidence of major complications (requiring blood transfu-

sion or surgical intervention or prolonging hospital stay) was low (3.6%), and similar in both groups (3.6 and 3.8% respectively, ns). The rate of minor complications (subcutaneous haematoma) was greater in the DAT group (p=0.015).

Conclusions. Treatment with DAT does not increase the risk of major bleeding complications as a result of device implantation; however, minor complications are significantly more frequent. Our results suggest that DAT could be continued in patients undergoing device implantation with a moderate risk of bleeding complications. (Neth Heart J 2010;18:230-5.)

Keywords: Platelet Aggregation Inhibitors; Drug Therapy; Adverse Effects; Pacemaker; Defibrillators, Postoperative Complications

A. Przybylski

P. Derejko

J. Zakrzewska

M. Orczykowski

Ł. Szumowski

F. Walczak

Cardiac Arrhythmias Department, Institute of Cardiology,
Warsaw, Poland

W. Kwaśniewski

D. Urbańczyk-Świąć

W. Orszulak

A. Filipecki

M. Trusz-Gluza

Department of Cardiology, Medical University of Silesia,
Katowice, Poland

Correspondence to: A. Przybylski

Cardiac Arrhythmias Department, Institute of Cardiology,
Alpejska 42, 04-637 Warsaw, Poland

E-mail: aprzybylski@ikard.pl

Pocket haematoma and non-pocket bleeding are frequent and potentially dangerous complications of an implantation of a pacemaker, implantable cardioverter-defibrillator (ICD) or cardiac resynchronisation therapy device (CRT).¹⁻³ Moreover, a large number of patients receive either antiplatelet or anticoagulation therapy for the treatment of co-existing morbidities. According to the contemporary guidelines, the majority of patients with acute coronary syndromes (ACS) and after percutaneous coronary interventions (PCI) require treatment with a combination of two antiplatelet drugs (dual antiplatelet therapy, DAT). In addition, a temporary or permanent withdrawal of DAT is discouraged due to the risk of stent thrombosis.⁴⁻⁸ On the other hand, increased postoperative bleeding and morbidity after coronary artery bypass surgery (CABG) or noncardiac surgical procedures in patients receiving DAT have been reported.⁹⁻¹¹ Nowadays, the number of patients undergoing a pace-

maker, ICD or CRT implantation and receiving two antiplatelet drugs in the perioperative period has not been assessed. Moreover, the risk of bleeding complications in this group of patients has not been sufficiently elucidated.

The study was carried out to assess the prevalence of bleeding complications in patients receiving DAT in comparison with patients treated with acetylsalicylic acid (ASA).

Materials and methods

We prospectively analysed all the primary implantations (n=626) of cardiovascular implantable electronic devices (CIED) performed in two tertiary referral centres in the period of 12 months (1 January 2007 to 31 December 2007). All patients undergoing a primary implantation and receiving only ASA or dual antiplatelet therapy were included in the analysis. The patients treated with either oral anti-coagulants or heparin (both unfractionated and low-molecular-weight) were excluded from the study, as well as those treated with heparin or oral anti-coagulants in combination with antiplatelet drugs. Patients who underwent a device replacement or revisions were not included in the analysis. All patients had previously provided signed consent for use of their medical records for research purposes.

Implantation

All implantations were performed in the operating rooms equipped according to the guidelines of the European Society of Cardiology and hospital routine.¹² In all cases, the pocket was developed between the subcutaneous tissue and the pectoral fascia. Whenever possible, cephalic vein cutdown was preferred. If the preparation of the vein failed or if the vessel was too small to accommodate all the required leads, the axillary or subclavian vein was punctured with a standard technique. Prophylactic antibiotic treatment with a single dose of cephalosporin or vancomycin was routinely given before the implantation. The electrocautery was used at the operator's discretion in only six procedures.

The operators were divided into two groups based on the number of previously performed implantations: frequent implanters (those who had performed more than 100 implantations and had at least five years' experience in cardiac pacing) and infrequent implanters.

After the implantation, the patients were asked to lie still for at least 12 hours, which is part of our hospital routine for all implants. Afterwards, they were allowed to return to their normal activities unless this was contraindicated by another medical condition. The patients were followed for the period of 12 months. They were assessed 24 to 48 hours after implantation, 7 to 10 days after the procedure and then at three-month intervals.

Antiplatelet therapy

Antiplatelet therapy was not discontinued before the implantation. The patients received ASA in a daily dose of 75 to 150 mg. Clopidogrel was given in a standard dose of 75g once daily. Two patients received a combination of ASA and ticlopidine (250 mg twice daily). DAT was required due to prior coronary stenting in all cases.

Classification of bleeding complications

Bleeding complications were classified as major or minor on the basis of the clinical symptoms. The following complications were regarded as major:

- Bleeding complications requiring blood transfusion;
- Complications requiring cardiosurgical intervention or pericardiocentesis (e.g. cardiac tamponade);
- Haematomas requiring pocket revision;
- Bleeding complications prolonging hospitalisation, requiring readmission to the hospital or additional outpatient visits.

Minor complications included:

- Small pocket haematomas not requiring any treatment or prolonging hospitalisation;
- Subcutaneous haematomas and local ecchymosis.

The indications for pocket revision included active bleeding, prolonged pain, organised large haematoma or imminent skin perforation. Needle aspiration was never performed due to the risk of introducing infection. The complications were classified by the responsible physician with the advice of the head of the department, if necessary.

Statistical analysis

Statistical analysis were performed using Statistica 5.0 (StatSoft, Inc.). Data are reported as mean $\pm$ standard deviation and percentages as appropriate. Chi-square statistics with appropriate corrections (Yates' correction, V-square) were used for the evaluation of possible associations between variables. Differences between two percentages were calculated as appropriate. Two-tailed tests of significance are reported and p values <0.05 were considered statistically significant.

Results

Out of 626 consecutive patients undergoing first endocardial CIED implantation in our hospitals during the period of 12 months, 247 (39.5%) met the inclusion criteria; that is to say, they received either ASA (n=194) or DAT (n=53) in the perioperative period (table 1). Clinical characteristics of the patients are shown in table 2. In our series, 53 patients were treated with DAT, representing 8.5% of all patients undergoing CIED implantation in the indicated period. Among the defibrillator and

pacemaker recipients, there were no significant differences in the number of patients receiving DAT (9.8 and 8.4% respectively, ns). There were no differences between the ASA and the DAT group as far as gender, age, prior coronary artery bypass grafting, NYHA class, indications for implantation, venous access and implanters experience are concerned (table 3). There were significantly more patients with diagnosed coronary artery disease and previous PCI in the DAT group (77.3 vs. 100%; $p=0.00013$; 24.7 vs 100%, $p<0.0001$, respectively).

Bleeding complications

The bleeding complications (both major and minor) occurred in 40 patients. Using the univariate analysis, we did not find any differences in the overall complication rate with respect to venous access, implanter experience and the volume of a device (ICD and CRT versus pacemakers) (table 3). Bleeding complications were detected in 27 (13.9%) patients in the ASA group and in 13 (24.5%) in the DAT group. There was no significant difference in the number of complications between the patients receiving ASA or DAT (figure 1), although there was a trend towards a higher incidence of complications in the DAT group ($p=0.06$). In four patients, both major and minor complications were diagnosed. Three patients had pericardial effusion and one had a pocket haematoma as well as a subcutaneous haematoma.

Major complications

Major complications were detected in nine patients (3.6%), seven (3.6%) in the ASA group and two (3.8%) in the DAT group ($p=0.7$, n.s.) (table 4). There were no intraoperative bleeds requiring blood transfusion or pocket drainage. None of the pocket haematomas required a pocket revision. The development of a pocket haematoma prolonged hospital stay in all five cases.

Figure 1. Bleeding complications (in percentages) among all study patients and in the acetylsalicylic acid (ASA) and in the dual antiplatelet therapy (DAT) group. * In four patients (two in the ASA group and two in the DAT group) both major and minor complications occurred. See the text for details. ns=non significant.

In four cases (three in the ASA and one in the DAT group), a pericardial effusion occurred (table 4). In one case (in a patient receiving only ASA), a surgical intervention was necessary because of the signs of cardiac tamponade. In the remaining three cases the effusion resolved without any treatment within 48 to 72 hours. In all cases of pericardial effusion the active fixation leads were implanted.

Minor complications

Subcutaneous haematomas and ecchymoses occurred in 35 patients (14.2%). The incidence of minor complications was significantly greater among patients receiving DAT (24.5%) compared with those treated with ASA (11.3%, $p=0.015$). All those complications resolved without any treatment and had no clinical implications.

Discussion

A prolonged, dual antiplatelet therapy is recommended for all patients after stent implantation and the majority of patients presenting with acute coronary syndromes.⁴⁻⁷ The DAT should be administered for 12 months to patients who have received DES, for at least one month after bare-metal stent implantation and for 12 months in patients presenting with ACS.⁴⁻⁷ At the same time, a significant number of patients required another surgical procedure. There are several reports on the increased rate of bleeding complications in patients receiving clopidogrel or DAT who undergo CABG, general surgery or transbronchial biopsy.^{9,10,11,13} Although the consequences of bleeding complications after CIED implantation are usually lower than those associated with cardiosurgery or neurosurgery, pocket bleeding may result in pocket infection or endocarditis. On the other hand, the indications for CIED implantation have expanded.¹⁴ Not surprisingly, many CIED candidates are receiving DAT because of recently implanted stents. Moreover, since a vast majority of CIED implantations are potentially life-saving, they cannot be postponed until the completion of DAT therapy. What is more, a temporary interruption of DAT is not recommended unless a massive bleed occurs or there is a necessity for a major surgical procedure (i.e. neurosurgery).⁴⁻⁶ The number of patients receiving DAT at the time of CIED implantation has not been well assessed in the era of expanded indications for DAT. In a single-centre study on 3164 implantations or reimplantations performed in the years 1990 to 2002, only 0.7% (30 patients) received DAT.² However, in another single-centre study conducted in years 2004 to 2007, about 16% of the ICD recipients received DAT.¹⁵ In our study 8.5% of patients received DAT. This percentage does not differ significantly between the group of ICD and pacemaker recipients.

Table 1. Type of device implanted.

Type of device implanted	All procedures	ASA only (%)	Dual antiplatelet therapy (%)
Single chamber pacemakers	114	4 (2)	3 (5.7)
Dual chamber pacemakers	219	76 (39.2)	21 (39.6)
Cardiac resynchronisation therapy pacemakers (CRT-P)	9	3 (1.5)	1 (1.9)
All pacemakers (%)	342	83 (24.3)	25 (7.3)
Single chamber ICD	183	74 (38.1)	22 (41.5)
Dual chamber ICD	73	28 (14.4)	5 (9.4)
Cardiac resynchronisation therapy combined with ICD (CRT-D)	28	9 (4.64)	1 (1.9)
All defibrillators (%)	284	111 (35.6)	28 (9.8)
Total	626	194 (30.1)	53 (8.5)

ICD=implantable cardioverter defibrillators, CRT=cardiac resynchronisation therapy, ASA=Acetylsalicylic acid.

Table 2. Patient and implantation characteristics.

	ASA (n=194)	DAT (n=53)	P
Age (years)	65 ±14.7	69 ±10.2	ns
Male (%)	146 (59)	43 (75.5)	ns
Coronary artery disease (%)	150 (77.3)	53 (100)	0.00013
Previous CABG (%)	37 (19.1)	11 (20.7)	ns
Previous PCI (%)	48 (24.7)	53 (100)	<0.0001
NYHA functional class I or II (%)	159 (81.9)	42 (79.2)	ns
NYHA functional class III or IV	35 (18)	11 (20.7)	ns
ICD/CRT-D indications*			
- Primary prophylaxis (%)	47 (24.2)	8 (15.1)	ns
- Secondary prophylaxis (%)	64 (33)	23 (43.4)	
Pacemaker indications*			
- Sinus node disease (%)	46 (23.7)	15 (28.3)	ns
- Atrioventricular block (%)	15 (7.7)	10 (18.87)	
- Heart failure (%)	3 (3.6)	1 (1.9)	
Venous access			
- Subclavian vein puncture	107 (55.1)	30 (56.6)	ns
- Cephalic vein cut down	57 (29.4)	16 (30.2)	ns
- Both techniques	30 (15.5)	7 (13.2)	ns
Implanters' experience			
- Frequent implanters	140 (72.2)	42 (79.2)	ns
- Infrequent implanters	54 (27.8)	11 (20.8)	ns

CABG=coronary artery bypass grafting, ICD=implantable cardioverter defibrillator, NYHA=New York Heart Association, PCI=percutaneous coronary intervention, CRT-D=cardiac resynchronisation therapy combined with ICD, ASA=acetylsalicylic acid, DAT=dual antiplatelet therapy, ns=not significant. *Some patients had indications for both pacemaker and ICD implantation.

Table 3. Univariate analysis of overall complication rate. Comparison by implantation-related factors.

	All patients	Patients without complications	Patients with complications (%)	P
Venous access				ns
- Subclavian vein puncture	137	111	26 (19)	
- Cephalic vein cut down	73	66	7 (9.5)	
- Both techniques	37	30	7 (18.9)	
Implanter experience				ns
- Frequent implanters	182	156	26 (14.3)	
- Infrequent implanters	65	51	14 (21.5)	
Device volume				ns
- ICD/CRT*	143	120	23 (16.1)	
- Pacemakers	104	87	17 (16.3)	

*Both CRT-P and CRT-D.

The overall number of complications in our study (16.2%) seems to be high, but it should be noted that the definition of bleeding complications applied in our study is broader than that used in other studies.^{1-3,15} We decided to recognise local ecchymosis and subcutaneous haematoma as minor complications, because they may cause patient anxiety and thereby influence their well-being after implantation.

Although there is no evidence for the correlation between antiplatelet therapy and cardiac perforations during a lead placement,^{16,17} we decided to consider perforation and its consequences (i.e. surgical intervention, pericardiocentesis) as major events in the study design. Some physicians postpone the implantation due to a potential risk of bleeding during emergent cardiosurgical intervention in patients receiving DAT.

There were two main reasons for choosing patients receiving ASA as a reference group. Firstly, previous studies have shown that ASA does not increase the number of implantation-related bleeds.² Secondly, we presumed that patient characteristics would be similar in the ASA and the DAT group.

The dominant finding of our study is a low incidence of major complications (defined as those requiring blood transfusion, drainage, surgical intervention, pocket revision, prolonging hospitalisation or the necessity of hospital readmission) in patients receiving DAT. The number of major bleeding complications in our study did not differ statistically between the two groups of patients. Moreover, there was only one pocket haematoma in the DAT group that was considered a major complication as it prolonged hospitalisation. The second major complication was pericardial effusion, which did not require therapy in three cases.

Our results are contrary to the previous reports, in which treatment with DAT during the perioperative period in patients undergoing a pacemaker or ICD implantation was associated with a more than tenfold increase in bleeding complications in comparison with patients receiving only low-dose heparin.² The reported complication rate in this group of patients was 20%. In another report, pocket haematoma also occurred more frequently in patients receiving DAT after ICD implantation.¹⁵ We are not able to give a convincing explanation for the

Table 4. Bleeding complications.

	All patients (n=247)	ASA	DAT	P
All complications (number of patients, %)	40 (16.2)	27 (13.9)	13 (24.5)	0.06
Major complications				
- Number of complications* (%)	9 (3.6)	7 (3.6)	2 (3.8)	ns
- Cardiac perforation requiring surgery	0	1	0	
- Pericardial effusion	1	2	1	
- Pocket haematoma prolonging hospitalisation	1	4	1	
Minor complications (%)	35 (14.2)	22 (11.3)	13 (24.5)	0.015

ASA=acetylsalicylic acid, DAT=dual antiplatelet therapy. *In four patients (two in the ASA and two in the DAT group) both major and minor complications occurred (see text for details).

low incidence of serious complications in our study. Nevertheless, operator experience and the recommendation to lie still after the procedure may be contributing factors to our results. However, there is no statistical correlation between operator experience and the overall number of complications.

The frequency of minor complications was significantly greater in the DAT group. All of these complications resolved without interruption of the antiplatelet therapy and without any consequences. On the basis of our study, we are not able to recommend any method to diminish the number of subcutaneous haematomas. We suggest to inform the patients treated with DAT about the probability of developing ecchymosis close to the implantation site.

Limitations of the study

The number of patients in the DAT group was too small to draw major conclusions from the study. There are no uniform definitions of bleeding complications or pocket haematoma after a pacemaker or ICD implantation. Therefore, it is difficult to precisely assess the complication rate and compare the results of different studies. There are also no guidelines on pocket haematoma treatment. The decision on how aggressive the treatment should be depends mainly on the physician's discretion and institutional standards. Our data derive from two tertiary referral centres with a 24-hour haemodynamic emergency service and thus the percentage of the patients receiving DAT could be higher than in smaller hospitals. As the study was not blinded, we are not able to exclude the differences in surgical techniques between the ASA and the DAT group.

Conclusion

The treatment with DAT does not increase the risk of major bleeding complications as a result of device implantation; however, minor complications are significantly more frequent. Our results suggest that DAT could be continued in patients undergoing device implantation with a moderate risk of bleeding complications.

Acknowledgements

The authors would like to thank Ms Magdalena Ingnot and Mr Marek Waszkiewicz for their help in the preparation of the manuscript.

Conflict of interests

Andrzej Przybylski is a member of the advisory board of Biotronik and Principle Investigator of a Medtronic sponsored trial. None of the other authors has any conflicts of interest to report. ■

References

- 1 Jamula E, Douketis JD, Schulman S Perioperative anticoagulation in patients having implantation of a cardiac pacemaker or defibrillator: a systematic review and practical management guide. *J Thromb Haemost*. 2008;6:1615-21.
- 2 Wiegand UK, Le Jeune D, Boguschewski F, Bonnemeier H, Eberhardt F, Schunkert H, et al. Pocket hematoma after pacemaker or implantable cardioverter defibrillator surgery: influence of patient morbidity, operation strategy, and perioperative antiplatelet/anticoagulation therapy. *Chest*. 2004;126:1177-86.
- 3 Marquie C, De Geeter G, Klug D, Kouakam C, Brigadeau F, Jabourek O, Trillot N, et al. Post-operative use of heparin increases morbidity of pacemaker implantation. *Europace*. 2006;8:283-7.
- 4 Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, et al. European Society of Cardiology. Percutaneous coronary interventions. Guidelines of the European Society of Cardiology-ESC. *Kardiol Pol*. 2005;63:265-320.
- 5 Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, et al. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007;28:1598-660.
- 6 Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2008;29:2909-45.
- 7 King SB III, Smith SC Jr, Hirshfeld JW Jr, Jacobs AK, Morrison DA, Williams DO. 2007 focused update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: (2007 Writing Group to Review New Evidence and Update the 2005 ACC/AHA/SCAI Guideline Update for Percutaneous Coronary Intervention). *Circulation*. 2008;117:261-95.
- 8 Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med*. 2006;166:1842-7.
- 9 Yende S, Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. *Crit Care Med*. 2001;29:2271-5.
- 10 Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol*. 2000;35:1288-94.
- 11 Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. *Chest*. 2006;129:734-7.
- 12 Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Europace*. 2007;9:959-98.
- 13 Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. *Pharmacotherapy*. 2008;28:376-92.
- 14 Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace*. 2006;8:746-837.
- 15 Robichaux R, Jennings J, Osorio J, Doppalapudi H, McEl-derry T, Epstein A, et al. Antiplatelet Effect on Pocket Hematoma Rate in ICD Implantation. *Circulation*. 2008;118:S.987-S.988.
- 16 Mahapatra S, Bybee KA, Bunch TJ, Espinosa RE, Sinak LJ, McGoon MD, et al. Incidence and predictors of cardiac perforation after permanent pacemaker placement. *Heart Rhythm*. 2005;2:907-11.
- 17 Sterlinski M, Przybylski A, Maciag A, Syska P, Pytkowski M, Lewandowski M, et al. Subacute cardiac perforations associated with active fixation leads. *Europace*. 2009;11:206-12.