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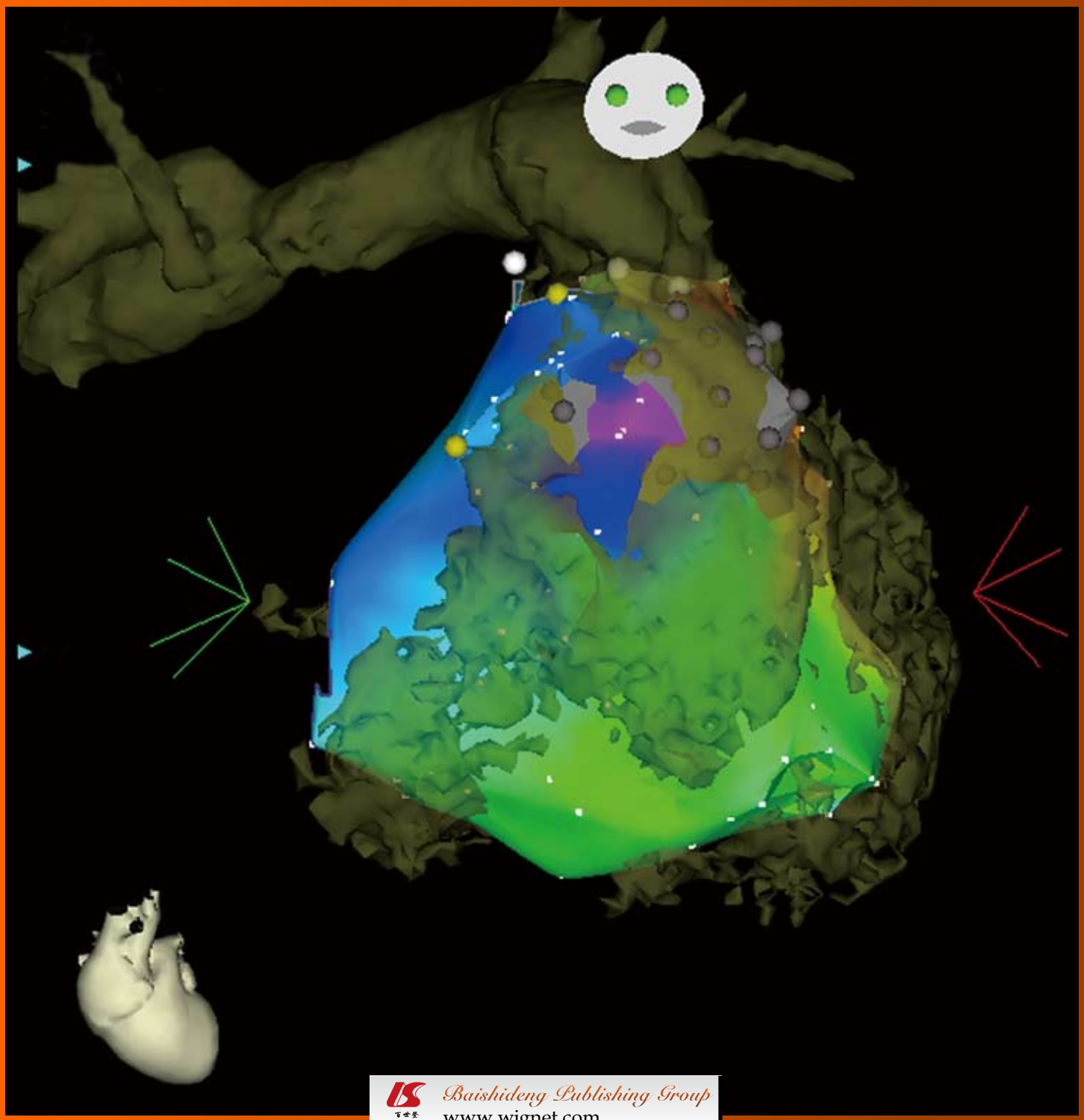

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EDITORIAL

Role of catheter ablation of ventricular tachycardia associated with structural heart disease

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Abstract

In patients with structural heart disease, ventricular tachycardia (VT) worsens the clinical condition and may severely affect the short- and long-term prognosis. Several therapeutic options can be considered for the management of this arrhythmia. Among others, catheter ablation, a closed-chest therapy, can prevent arrhythmia recurrences by abolishing the arrhythmogenic substrate. Over the last two decades, different techniques have been developed for an effective approach to both tolerated and untolerated VTs. The clinical outcome of patients undergoing ablation has been evaluated in multiple studies. This editorial gives an overview of the role, methodology, clinical outcome and innovative approaches in catheter ablation of VT.

Key words: Catheter ablation; Electroanatomic mapping; Implantable cardioverter-defibrillator; Radiofrequency energy; Sudden cardiac death; Ventricular tachycardia

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INTRODUCTION

Ventricular arrhythmias may occur in patients with or without structural heart disease. A dissertation on ablation of the different forms of ventricular arrhythmias in different patient settings may be too long. Therefore, this editorial will focus only on catheter ablation of ventricular tachycardia (VT) associated with structural heart disease. A list of diseases possibly associated with VT is shown in Table 1.

Catheter ablation is a therapeutic option aimed at the prevention of recurrences of ventricular arrhythmias. Other options used for the same purpose are antiarrhythmic drugs and antiarrhythmic surgery, while an implantable cardioverter-defibrillator (ICD) terminates ventricular arrhythmias and prevents sudden cardiac death. Class Ⅲ antiarrhythmic agents, such as amiodarone (especially in combination with β-blockers) or sotalol, can be used to reduce recurrences of ventricular arrhythmias and, therefore, appropriate ICD interventions[1,2]. However, their use is associated with a significant risk of detrimental adverse effects, including proarrhythmia. Moreover, in patients with structural heart disease and life-threatening ventricular arrhythmias, antiarrhythmic drug therapy, used alone, is inferior to ICD for secondary prevention of sudden death[3]. Mapping-guided antiarrhythmic surgery is still a valuable option in abolishing ventricular arrhythmias, which can be used especially in patients who require concomitant cardiac surgery. However, surgical treatment

achieves the best results only in a selected patient population, implies open-chest intervention and requires an experienced center/surgeon[4]. Finally, although undoubtedly valuable to decrease arrhythmic and all-cause mortality, ICDs represent a suppressive therapy and do not prevent recurrences of ventricular arrhythmias. Repeated shocks for the termination of multiple episodes of ventricular arrhythmias may affect both quality of life[5] and survival[6], while inappropriate shocks for supraventricular arrhythmias represent a clinical problem, especially in patients receiving an ICD for primary prevention[7].

In this scenario, a single therapy might not be the best option for every patient. Hybrid treatments including more than one therapy, far from representing an overtreatment, are the best strategy to improve both survival and quality of life in the cohort of patients with structural heart disease and ventricular arrhythmias. Catheter ablation is currently an effective treatment to abolish or minimize recurrences of ventricular arrhythmias and ICD interventions. New techniques and sophisticated technologies have contributed to improve acute and mid-term outcomes of catheter ablation. Peculiarly, it becomes of crucial importance in the case of storms of intractable VTs, when all the other options are ineffective or may not be applicable.

CATHETER ABLATION OF VT ASSOCIATED WITH STRUCTURAL HEART DISEASE: METHODS AND RESULTS

Pathophysiological considerations

In patients with structural heart disease, the VT can be macroreentrant or focal. If focal in origin, the arrhythmogenic mechanisms can be either enhanced automaticity or macroreentry. In the vast majority of cases, VT associated with large areas of fibrosis/necrosis surrounded by a border zone of slow conduction is sustained by a macroreentrant mechanism[8,9]. This is the case in ischemic cardiomyopathy with an old myocardial infarction, arrhythmogenic right ventricular dysplasia, and some forms of dilated cardiomyopathy. In other cardiomyopathies, an arrhythmogenic focus able to generate and sustain VT is located in a discrete area of the ventricular myocardium in strict anatomical relationship with an area of minimal, moderate, or extensive fibrosis[10]. The mechanism of the VT is clarified in the diagnostic phase of the procedure and determines the electrophysiologic criteria used to identify the ablation target. Some other variables, such as VT inducibility by ventricular stimulation and hemodynamic tolerance, determine the approach for catheter ablation of VT in a given patient.

Methods

Figure 1 shows the different approaches for VT ablation. The presence of left ventricular or atrial[11] thrombi and of inducible myocardial ischemia should be ruled out before the procedure. The left ventricle can be approached transaortically or transmitrally, after transseptal catheterization has been performed. This second option is preferable when critical peripheral vasculopathy or aortic disease is found and necessary when a prosthetic mechanical aortic valve is present. As mentioned before, the major determinants of the ablation strategy are arrhythmia inducibility by programmed electrical stimulation and hemodynamic tolerance. The latter very much depends on ventricular rate during tachycardia and the degree of left ventricular impairment.

Table 1 Diseases frequently associated with sustained ventricular tachycardia

Ischemic heart disease
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Hypertensive heart disease
Congenital heart disease (with or without prior surgical correction)
Noncompaction of ventricular myocardium
Sarcoidosis
Systemic sclerosis
Chagas disease
Myotonic dystrophy type I

If a VT is easily inducible, hemodynamically well tolerated and shows a stable morphology (left hand side of Figure 1), then detailed activation mapping during tachycardia can be performed to clarify the arrhythmogenic mechanism. In the case of macroreentrant VTs[12], the attention is focused on identification of the critical isthmus of slow mid-diastolic conduction with the help of entrainment techniques[9]. In this area, low-amplitude, fragmented, long-lasting bipolar signals, which are a clear expression of slow conduction, are usually recorded. Ablation in this area is aimed at abatement of electrical signals and VT termination and, eventually, at conduction block over the critical isthmus. This procedure endpoint is a prerequisite to minimize recurrences of the same VT morphology during follow-up. Three-dimensional electroanatomic mapping precisely visualizes the reentrant circuit and, in particular, the critical isthmus of slow conduction[12-14]. Figure 2 shows an example of activation mapping using an electroanatomic system to reconstruct the circuit of a macroreentrant VT and identify the ablation target. A particular form of macroreentrant VT is represented by the bundle branch reentrant VT, which results from macroreentry within the bundle branches. This tachycardia occurs more frequently in patients with non-ischemic dilated cardiomyopathy in the presence of retrograde conduction delay over the left bundle branch. The easiest way to abolish this VT is radiofrequency ablation of the right bundle branch[15].

When the VT mechanism is focal, usually a centrifugally spreading activation pattern from the site of earliest activation is observed in the map generated by the electroanatomic system. Here, the earliest bipolar signal is recorded and, concomitantly, a fast negative intrinsicoid deflection is also recorded in the unipolar recording from

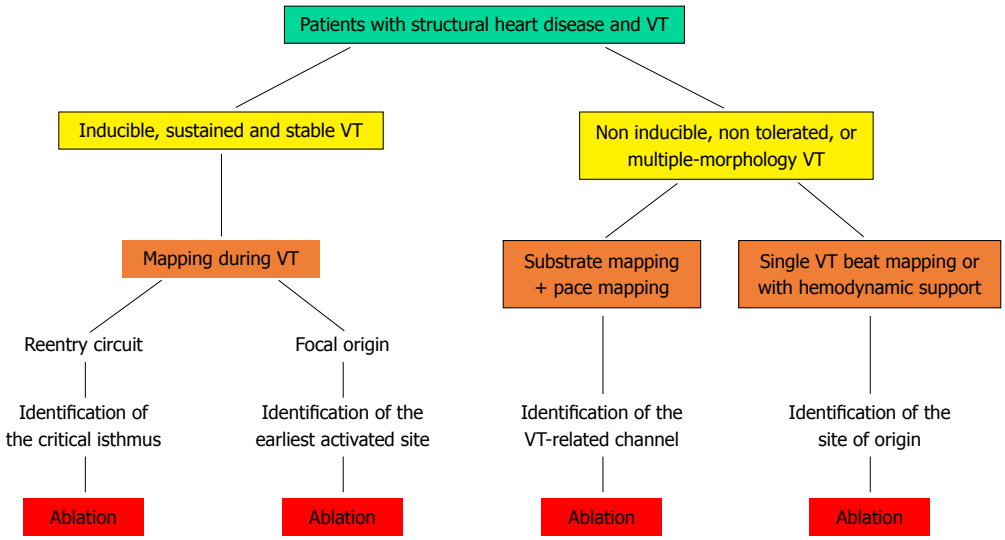

Figure 1 Strategies for catheter ablation of ventricular tachycardia. Flow-chart of the possible strategies for catheter ablation of ventricular tachycardia (see text for further explanation). VT: Ventricular tachycardia.

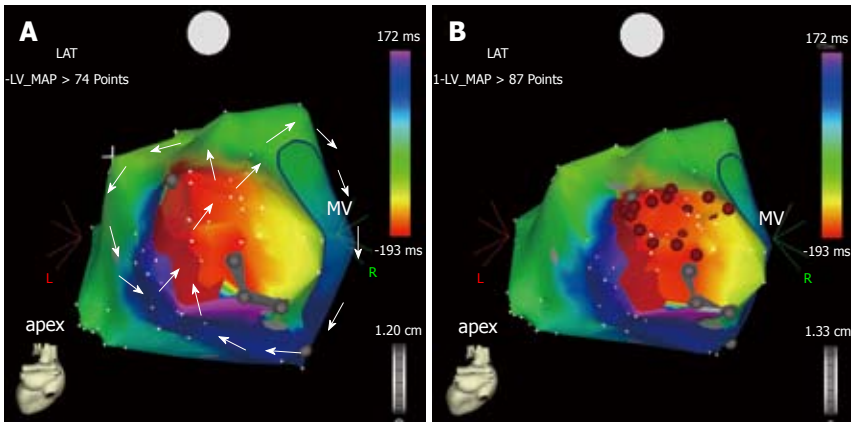

Figure 2 Three-dimensional electroanatomic map during macroreentrant ventricular tachycardia (A, B). Postero-anterior view of the electroanatomic activation map of the left ventricular endocardium, reconstructed during ventricular tachycardia with a cycle length of 380 ms in a patient with postinfarction ischemic cardiomyopathy. A: The ventricular tachycardia is sustained by a reentry circuit, which has been fully reconstructed during point-by-point mapping. The reentry course is shown by the sequence of colors from red to purple (arrows). There are two reentrant loops: one rotates clockwise around the mitral annulus, whereas the other has a counter-clockwise course in the lateral wall of the left ventricle. Both loops share the mid-diastolic isthmus, the dark red area between two electrically silent areas (gray dots) where the two arrowed circles meet each other; B: Sequential radiofrequency energy applications (red dots) were delivered linearly to transect the critical isthmus and produce a line of block between the two electrically silent areas and the mitral annulus. No arrhythmia was inducible at the end of the procedure and the patient had no recurrence at the mid-term follow-up. MV: Mitral valve.

the distal electrode of the mapping catheter. Ablation of this area usually results in early tachycardia termination. If the VT is subsequently no longer inducible then the procedure endpoint is met[16,17]. A rare but interesting form of focal VT has been described in patients with postinfarction ischemic cardiomyopathy[18,19]. In this form, the arrhythmogenic focus originates from surviving Purkinje fibers at the border zone of myocardial necrosis. Usually, the VT shows a relatively narrow QRS complex with right bundle branch block morphology and superior axis deviation and a heart rate of approximately 150 beats per minute. Ablation of the earliest activated site, where a high frequency Purkinje potential is recorded, results in permanent abolition of the VT, without the appearance of new conduction disturbances.

The approach based on activation mapping during VT is undoubtedly effective and time-tested. It has been used since the early phase of the experience in catheter ablation of VT[20,21]. Nevertheless, this approach has clear limitations. It can be applied only to a minority of patients with inducible and stable VTs, which has been estimated to account for no more than 30% of patients referred for recurrent VTs[20,22]. In some patients, even if recurrent VTs are clinically observed before the procedure, no arrhythmia is inducible during the procedure. Moreover, several patients have untolerated VTs, which trigger frequent ICD interventions. Finally, in particular cases, multiple morphologies of stable VT are observed and the arrhythmia may convert from one morphology to another during mapping. All these situations make it

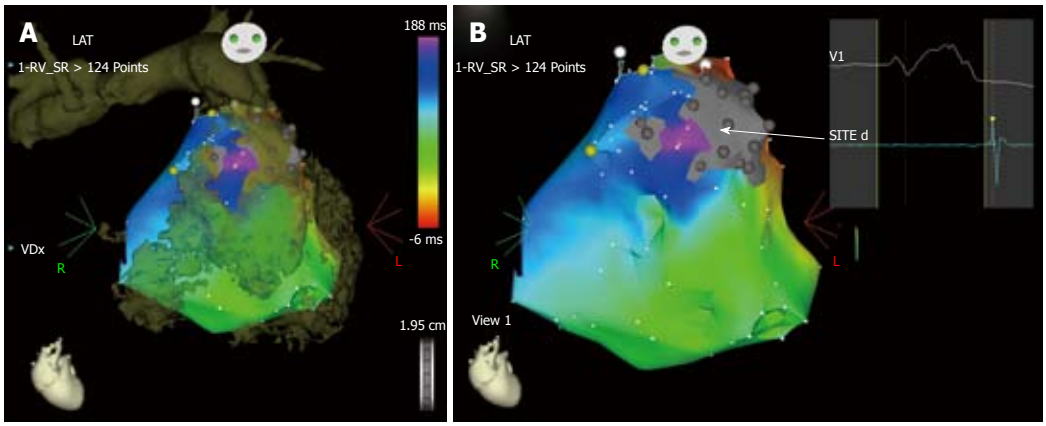

Figure 3 Imaging integration for ablation of ventricular tachycardia (A, B). Example of integration of a computed tomography image in the three-dimensional electroanatomic system. This patient had ventricular tachycardia years after multiple surgical corrections for tetralogy of fallot with pulmonary artery stenosis. He was referred for multiple recurrences of drug-refractory ventricular tachycardia with two morphologies, both with left bundle branch morphology and inferior axis deviation. However, no arrhythmia was inducible during the electrophysiology testing. Therefore, the ablation strategy was based on substrate mapping in sinus rhythm with imaging integration (Figure 4). A: The three-dimensional rendering of the computed tomography (image in brown) of the right ventricle and pulmonary artery is superimposed on the electroanatomic mapping of the right ventricle in sinus rhythm. The merging of the two images helps reconstruct the geometry of the heart chamber and, particularly in this case, clarifies the anatomy of the right ventricular outflow tract, identifying precisely the pulmonary valve annulus, an essential landmark for ablation. The right ventricle appears hypertrophic and markedly dilated; B: The activation map in sinus rhythm is shown in the antero-posterior projection without the integrated image. There is a markedly delayed activation in the anterior wall of the outflow tract (in purple), in a channel between two electrically silent areas (in gray) related to previous surgery (ventriculotomy and positioning of a prosthetic patch). This channel (arrow) shows late bipolar recordings, after the end of the surface QRS (panel on right hand side) and could possibly be related to one morphology of ventricular tachycardia. During sinus rhythm, the earliest activated site (in red) of the right ventricular endocardium is the ventricular septum, consistent with a breakthrough of activation from the left bundle branch in the presence of a complete right bundle branch block.

difficult or even impossible to use a strategy based on activation mapping to identify the ablation target. Consequently, over the years, alternative approaches to activation and entrainment mapping have been developed to treat these "unmappable" forms using catheter ablation. This has moved ahead the frontier of catheter ablation of VT, expanding this treatment option to a wider patient population. As shown in the right hand side of Figure 1, these strategies are necessarily based on the use of new technologies, such as three-dimensional mapping systems.

In "unmappable" VTs, the approach most frequently used is substrate mapping during sinus rhythm or right ventricular pacing combined with pace-mapping techniques[23-25]. This method aims at localizing the substrate for possible reentry circuits based on identification of areas of low voltage and slow conduction, assuming that the clinical "unmappable" arrhythmia is sustained by reentry. Using a three-dimensional electroanatomic mapping system, bipolar voltage mapping is performed in the ventricles to identify areas of low voltage related to an old myocardial infarction or, in general, fibrosis. According to a preliminary evaluation[23], areas with bipolar voltage $\geqslant$ 1.5 mV are normal, those with bipolar voltage $\leqslant$ 0.5 mV are areas of dense scar, whereas areas with a voltage between 0.5 and 1.5 mV are the border zone between necrosis/fibrosis and the normal myocardial tissue. In a post-mortem study, these voltage thresholds correlated very well with histology, since massive (> 80%) fibrosis has been found in areas with voltage < 0.5 mV, while intermediate (21%-79%) and minimal (< 20%) fibrosis has been observed in areas with voltage 0.5-1.5 mV and > 1.5 mV, respectively[26]. Once voltage mapping has been completed, pacing maneuvers are used in the area of dense scar and along the border zone to identify a channel of low voltage and slow conduction, possibly related to the VT. In fact, this may serve as the critical diastolic isthmus of the reentry circuit. Ventricular pacing is finalized to: (1) reproduce a QRS complex morphology identical or similar to the target VT; and (2) identify an area of slow conduction as assessed by a long interval between the pacing stimulus and the paced QRS complex. In the majority of cases, a slow conducting channel related to a VT can be identified in a discrete area, so that limited ablation can be performed to transect this channel[24]. An example of a non inducible VT ablated using this strategy is shown in Figures 3 and 4. These VT-related channels are usually found in the area of dense scars with a bipolar voltage of 0.1-0.3 mV and a length of 33 ± 22 mm, on average[24,27]. Ablation aims to render unexcitable the identified VT-related channel. After ablation, stimulation protocols are used to assess the non inducibility of VT. Although every effort is made to ablate a limited area, this strategy may be more aggressive than the one based on activation mapping during a stable VT, since in some cases this technique may overestimate the ablation target. However, this does not result in worsening of ventricular function, because ablation is performed in an area of massive fibrosis, which does not contribute to ventricular contraction. In fact, a study[28] showed that the value of left ventricular ejection fraction is unchanged before and after ablation, even if a considerable amount of radiofrequency energy was applied (25 applications on average, ranging from 3 to 98). Finally, this strategy, proposed to approach "unmappable" ventricular arrhythmias both in

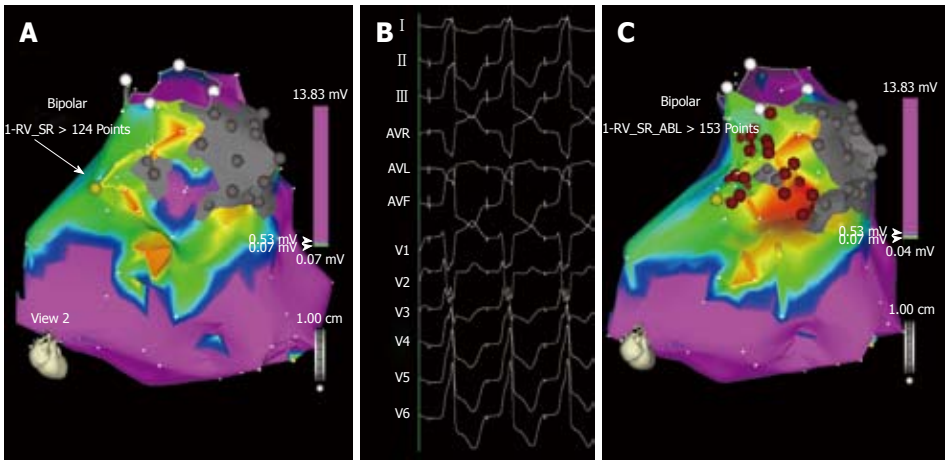

Figure 4 Ablation of "unmappable" ventricular tachycardia based on substrate mapping and pace-mapping (A, B). Bipolar voltage mapping of the right ventricle in the same patient as in Figure 3. A: According to the settings used for this map, shown in antero-posterior view, the purple area has a bipolar voltage > 0.53 mV, while in the myocardium surrounding the two scars (in gray) the voltage is low, between 0.05 and 0.52 mV (colors from red to blue). In this area, pace-mapping is used to identify channels of low voltage and slow conduction possibly related to the two ventricular tachycardia morphologies clinically documented. In addition to the channel of slow conduction identified between the two scars during sinus rhythm (Figure 3), a second channel of low voltage and slow conduction is now identified by pacing at 600 ms cycle length in the area marked by the yellow dot (arrow); B: In this site, pacing reproduces one of the two ventricular tachycardia morphologies. Interestingly, the interval between the stimulus artifact and the onset of the QRS complex is markedly prolonged (125 ms) and this demonstrates the presence of slow conduction in this area; C: The same map is now shown in right anterior oblique view with two lines of radiofrequency energy applications (red dots) delivered to transect the two channels: one line is deployed between the two scars and the other between one scar and the pulmonary artery annulus (circle marked by white dots). No arrhythmia was inducible at the end of the procedure and the patient had no recurrences during follow-up.

ischemic and non-ischemic cardiomyopathy, may have some limitations in the non-ischemic cardiomyopathy setting. In these cases, the distribution of the areas of fibrosis identified by voltage and slow conduction shows a patchy pattern and fewer protected channels/isthmi, definitely different from a postinfarction scar. This undermines the feasibility and efficacy of this approach in non-ischemic cardiomyopathy patients[29,30].

As reported in Figure 1, activation mapping of only a few tachycardia beats using noncontact mapping[31-33] or using a ventricular assist device for temporary hemodynamic support[34] is another possible, but rarely used, strategy to approach "unmappable" VT. Using a multi-electrode array mounted on an inflatable balloon, noncontact mapping reconstructs isopotential activation maps of a single VT beat[31]. Analysis of the map allows identification of the arrhythmogenic substrate, which, subsequently, can be ablated. Suppression of arrhythmia inducibility correlates with a favorable outcome during follow-up[31-33]. The limitation of this approach mainly consists of possible sub-optimal identification of the diastolic pathway in the reentry circuit. Especially in cases with enlarged heart chambers, noncontact mapping may be unable to detect low amplitude potentials, which are typically found in the critical isthmus of slow conduction. When this isthmus is not localized, ablation in the exit site from the critical isthmus where higher voltage is present is a possible alternative, but usually less effective[31].

As previously mentioned, activation and entrainment mapping to localize the arrhythmogenic substrate of untolerated VT is also possible using a ventricular assist device[34]. Currently, limited experience has been gathered in this field. However, this approach is feasible. The left ventricular assist device is percutaneously positioned before the procedure and is able to maintain a cardiac output during the VT for enough time to identify the arrhythmogenic substrate. Nevertheless, it is important to underline that some patients may require continuation of ventricular assistance after the procedure for a prolonged time period. Therefore, these cases should be managed in cooperation with a heart failure specialist and a cardiothoracic surgeon[34].

Finally, frequently recurrent very fast VT and even ventricular fibrillation can be completely or partially suppressed by catheter ablation, if their recurrence is invariably triggered by a specific ventricular ectopy. Both in patients with ischemic heart disease and in patients apparently without structural heart disease[35,36], when the origin of the triggering premature ventricular beat can be localized, ablation of this area results in long lasting suppression of the fast VT or fibrillation, minimizing ICD interventions during follow-up.

Results

It may be complex to evaluate the results of catheter ablation of VT in patients with structural heart disease. The reasons are multiple: (1) there is still a paucity of data and the published studies include a limited number of cases with non uniform underlying heart disease and, usually, only short- or mid-term follow-up data; (2) the clinical outcome in terms of prevention of VT recurrences may differ from the success of the procedure, defined as acute suppression of the inducible VT; long-term clinical outcome may also depend on the type of underlying heart disease; (3) new techniques and technologies have been introduced and applied over the last 10 years; there-

fore, early studies may underestimate the results now achievable, while the latest studies might overestimate the results because of the limited follow-up; (4) a given technique (e.g., ablation based on substrate mapping) can achieve good results in a subset of patients (ischemic cardiomyopathy), but sub-optimal results in other patients (non-ischemic cardiomyopathies); (5) single-center studies involving experienced operators may report better results, but in a limited patient population and for multicenter studies the opposite may be true; and (6) currently, meta-analyses include a limited number of studies with inhomogeneous patient populations and different ablation techniques with limited data on mortality. In the following section, data on the largest and most significant studies on VT ablation will be reported, including single-center studies, multicenter observational studies and prospective multicenter randomized trials. It would take too long to report detailed results of each subset of patients with different heart diseases. These data have been extensively reported in two recently published consensus documents[37,38].

In general, catheter ablation is effective in terminating a target morphology of VT and limiting arrhythmia recurrences. Acute suppression of VTs by radiofrequency energy application has been reported in 75% to 95% of patients, with a recurrence rate of up to 35%[37,38]. Although the recurrence rate seems high, it is much lower than in patients receiving only antiarrhythmic drugs, according to a recent meta-analysis[39]. This meta-analysis considered 154 potential studies on catheter ablation of VT associated with structural heart disease and included only 5. These studies spanned 11 years with a total of 457 patients. When catheter ablation used as adjunctive therapy to antiarrhythmic drugs was compared to antiarrhythmic drugs only, there was a statistically significant 38% reduction in the number of patients with VT recurrences in the group undergoing catheter ablation. The difference in mortality between the two groups could not be demonstrated in this meta-analysis.

Catheter ablation of VT associated with structural heart disease has been a promising therapeutic option since the beginning. In the early phase, two studies[20,21] reported encouraging results on VT ablation in patients with structural heart disease (mainly ischemic cardiomyopathy), based on activation and entrainment mapping. The success rate was 73%-83%, recurrence rate about 25%, with a complication rate of 7% and limited use of ICD (20% of patients). These results seem surprisingly good considering that at that time the technology of three-dimensional mapping and irrigated tip ablation, now routinely used, was not available. The selection of patients and prior experience in antiarrhythmic surgery for VT in these centers could have been crucial in achieving good results.

In single center reports, ablation based on the substrate mapping strategy in patients with "unmappable" VT have produced similar results in terms of recurrence rate during a short/mid-[23,24,40,41] and long-[42] term follow-up. Although the percentage of patients with recurrences varied between 17% and 36% in these studies, a considerable reduction in the frequency of ICD interventions was observed post-ablation. In a single center non-randomized study[43], substrate mapping during sinus rhythm and activation mapping during VT was compared in patients with coronary artery disease. The results of the two strategies in term of clinical outcome were similar: success rate during follow-up was 80% and 71% for the activation and the substrate mapping groups, respectively. However, as previously mentioned, the results achieved using substrate mapping for ablation of "unmappable" VT very much depended on the type of underlying heart disease. In fact, the success rate of ablation based on substrate mapping in terms of prevention of recurrences during follow-up was 82% and only 50% in ischemic and non-ischemic cardiomyopathy patients, respectively[30]. The poorer clinical outcome in the latter group of patients mainly depended on the different characteristics of the arrhythmogenic substrate in patients with non-ischemic cardiomyopathy, which is more difficult to localize by substrate mapping.

Recently, two prospective multicenter observational studies have been published. They report the results on catheter ablation of postinfarction VT using electroanatomic three-dimensional mapping and irrigated-tip radiofrequency energy ablation[44,45]. In the first study[44], 231 patients in 18 centers over a period of approximately 4 years were enrolled. They had a median left ventricular ejection fraction of 25% and a median of 11 VT episodes in the last 6 mo. The prevalence of heart failure and atrial fibrillation was 62% and 29%, respectively. Before ablation, amiodarone failed in 70% of patients and 94% of them had an ICD. During the ablation procedure, a median of 3 VT morphologies per patient were treated for a total of 864 morphologies ("unmappable" morphologies were present in 69% of patients). The primary end-point (freedom of VT in the following 6 mo) was reached in 53% of patients and a reduction in the frequency of VT recurrence of at least 75% was obtained in 67% of patients. Procedure-related mortality was 3% with an additional 7.3% of non fatal complications. The second study[45] achieved similar results in a smaller patient population. In 8 European centers during approximately 3 years, 63 patients underwent ablation of 164 mappable or "unmappable" VT morphologies. Two thirds of the patients had an ICD before ablation. Success was obtained in 81%, but 49% of patients had VT recurrences during follow-up. However, 79% of patients with recurrences had a significant reduction in episodes from 60 ± 70 prior to ablation to 14 ± 15 after ablation, during the same time period. Procedure-related complications were observed in 7.9% of patients. The results of these two studies suggest that suppression of postinfarction VT can be reproducibly obtained in different centers by catheter ablation during the procedure and results in a significant reduction of arrhythmia episodes during follow-up. It is important to take into account that these

studies included severely ill patients, with multiple and also unmappable tachycardia morphologies refractory to amiodarone. Considering the time period in which these studies were carried out (between 1999 and 2003), these results may possibly improve in the near future.

Two other prospective multicenter randomized trials were designed to assess the adjunctive benefit of catheter ablation in patients with previous myocardial infarction who received an ICD for secondary prevention of VT[46,47]. In both studies, enrolled patients were 1:1 randomly assigned to receive only an ICD or catheter ablation and an ICD. In the first study[46], named SMASH-VT, ablation was based on substrate mapping and the primary end-point was survival free from any appropriate ICD therapy. Over 46 mo, 128 patients with both mappable and "unmappable" VT were enrolled in three centers and followed up for 22 ± 5 mo. In the group of patients who received ablation + ICD, survival free from ICD therapy was significantly higher than that in the group who received only ICD and, interestingly, mortality was not increased in the first group compared to the second group. The second study[47], named VTACH, enrolled 107 patients with postinfarction mappable VT in 16 European centers. The ablation procedure was based on activation or substrate mapping with the use of three-dimensional mapping systems in all cases. During a mean follow-up of 22 ± 9 mo, time to recurrence of VT or VF, the primary end-point, was longer in the ablation + ICD group than in the ICD only group, with no deaths within 30 d of the procedure. Interestingly, at 2 years, survival free from VT or VF was better in the ablation group as compared to the control group. Moreover, the benefit of ablation was mainly observed in the group of patients with an ejection fraction between 30% and 50%, in which the difference in survival between the two groups reached high statistical significance. These two randomized studies confirm that, in patients with postinfarction mappable or "unmappable" VTs and impaired left ventricular function, early ablation based on activation or substrate mapping, far from being overtreatment, significantly reduces the appropriate ICD interventions with no impact on mortality related to the ablation procedure.

Catheter ablation of arrhythmic storms

Electrical storms are frightening events, characterized by multiple episodes in a relatively short time of intractable ventricular arrhythmias resulting in multiple appropriate ICD shocks with poor short- and long-term prognosis. Multiple reports highlight the crucial role of catheter ablation to control these arrhythmic storms and restore stable sinus rhythm[48-51]. Electrical storms usually occur in very sick patients with poor left ventricular function (ejection fraction < 30%), multiple co-morbidities, multiple morphologies of VT with heart rate of approximately 160 beats per minute. In some cases, these patients require immediate attention and the catheter ablation procedure is performed within the first 24 h after hospital admission[51]. During the same admission, multiple procedures (up to 3) may be necessary to control the electrical storm[48]. Electrical storms can be suppressed in 84%-100% of cases and during a mid-term follow-up the percentage of patients free from electrical storms and from any VT was 74%-94% and 48%-69%[48-51], respectively. Interestingly, the worst results in term of suppression of the electrical storm and, in general, of VT recurrences were obtained in patients presenting with an electrical storm associated with cardiogenic shock, despite the use in this subset of patients of the most sophisticated techniques and technologies[48]. Occasionally, inability to terminate the clinical incessant VT may result in electromechanical dissociation and death during the ablation procedure[51]. After the procedure, recurrence of electrical storm may require drastic countermeasures, such as implantation of ventricular assist device as a bridge to heart transplantation[50]. During follow-up, the mortality rate can be as high as 30%[49,50] and is mainly due to progression of heart failure. Low ejection fraction, increased left ventricular end-diastolic diameter and renal insufficiency are predictors of death[50].

Table 2 Common complications related to catheter ablation of ventricular tachycardia

Peripheral vascular injuries
Thromboembolic events
Pericardial effusion
Cardiac perforation and tamponade
Injuries to valve and subvalvular apparatus
Atrioventricular or bundle branch block
Injuries to coronary arteries and myocardial ischemia
New onset ventricular arrhythmias
Cardiogenic shock
Death

Complications

In several studies on catheter ablation of VT, the reported complication rate was about 7%, higher than that for ablation of supraventricular arrhythmias. This is mainly due to the associated severe underlying heart disease in many of these patients. Major and minor complications related to VT ablation are reported in Table 2. Importantly, procedure-related death has a non negligible prevalence, accounting for up to 3%[44]. In these patients, death is mainly related to the occurrence of uncontrollable fast VT leading to irreversible cardiogenic shock and cardiac arrest. Death can occur during or soon after the ablation procedure. Irreversible cardiogenic shock may also be observed after successful ablation for a long-lasting incessant VT, when the patient is in stable sinus rhythm and is related to the end-stage condition of the patient[20]. Clinical experience is required to select appropriate candidates for the procedure and to avoid ablation in those who are too sick to benefit. Moreover, expertise and team work with a heart failure specialist is needed to manage patients with critically depressed left ventricular function before, during and after the procedure.

NEW TECHNIQUES AND TECHNOLOGIES FOR CATHETER ABLATION OF VT

As previously mentioned the best results for catheter ablation of VT associated with structural heart disease are obtained using three-dimensional mapping and irrigated tip ablation. The first technology allows accurate characterization of the arrhythmogenic substrate during activation and/or substrate mapping, while the second is of crucial importance in delivering radiofrequency energy in an efficient and safe way and to abolish the arrhythmogenic substrate. Currently, these technologies are routinely used in the vast majority of centers. Over the last decade, new techniques and technologies have been developed and introduced in clinical practice. They have proved effective in improving procedure parameters and/or clinical outcomes and can be particularly useful in the management of cases refractory to standard ablation.

Epicardial approach

Percutaneous access to the pericardial space using a regular vascular sheath was originally described by Sosa[52]. Alternatively, the epicardial space can be accessed using a minimally invasive subxiphoid surgical approach[53,54]. An epicardial or sub-epicardial arrhythmogenic substrate is expected in approximately 10% and 30% of cases with ischemic and non-ischemic cardiomyopathies, respectively[55]. In a multicenter study, epicardial ablation was performed in 13% of patients undergoing VT ablation[56]. An epicardial origin of VT should be suspected when the QRS morphology shows a delta wave and/or a prolonged intrinsicoid deflection. Recently, it has been reported that in patients with a left ventricular cardiomyopathy, endocardial unipolar voltage mapping is able to identify a possible epicardial arrhythmogenic substrate for the greater field of view of the minimally filtered unipolar recordings as compared to bipolar recordings[57]. Epicardial access is clearly indicated when an endocardial approach including transvenous epicardial mapping through the coronary sinus and its sub-branches has failed. Percutaneous access to pericardial space is obtained usually under general anesthesia using a needle designed for epidural access. After positioning of a regular vascular sheath, an ablation catheter can be inserted and manipulated to map the epicardial surface of the heart. Irrigated-tip ablation is usually preferred, but this requires periodic aspiration of the saline used for irrigation, because it accumulates in the pericardial space. Epicardial fat, detected during mapping as a low voltage area, may affect the quality of mapping data and, at the same time, prevent radiofrequency energy delivery directly to the epicardial surface. In the case of intramural arrhythmogenic substrate, embedded deep in the layers of the left ventricular wall, a combined epi- and endocardial ablation may be required. Three publications focusing on epicardial access for VT ablation report data on a total of 247 epicardial procedures[56,58,59]. Success in abolishing VT was obtained in 76%-78%, and recurrences during follow-up were observed in 26%-47% of cases. Complications related to epicardial access were pericarditis and right ventricular puncture with pericardial bleeding, while complications related to epicardial ablation were phrenic nerve injury and coronary artery occlusion. To avoid these latter complications, it is mandatory to localize the phrenic nerves by pacing and coronary arteries by angiography before radiofrequency energy is delivered. It is important to underline that in these two studies[56,59] in roughly one fourth of cases undergoing or referred for an epicardial procedure, ablation was performed only at an endocardial site because it was eventually considered the most suitable site for ablation. For this reason, and due to the difficulties that can be encountered in accessing the pericardial space, and the complications including death[58,59] that may be observed, the need for an epicardial procedure should be carefully evaluated after failure of the endocardial approach.

Imaging integration

During the procedure, a pre-acquired three-dimensional rendering of a computed tomography or magnetic resonance scan of the heart can be imported in the electroanatomic system[60]. Once the three-dimensional image is correctly integrated, it is possible to navigate the mapping/ablation catheter in the high resolution image of a given heart chamber. In this way, complete reconstruction of the ventricular chamber is facilitated during activation or substrate mapping[61].

Integration of a computed tomography image is particularly useful, because it shows the course of the coronary artery, the size of the ventricular chamber and strategic landmarks. Visualization of the coronary vessels is necessary when an epicardial approach is performed and helps avoid ablation close to a coronary artery branch, which may result in acute myocardial ischemia[62-64]. In patients with peculiar anatomy, such as patients with multiple prior surgical intervention for correction of a congenital heart disease or with large aneurysms[64], a pre-acquired computed tomography image integrated into the electroanatomic map helps orient mapping. Figure 3 shows imaging integration of a computed tomography scan of the right ventricle in a case of post-Fallot VT. During substrate mapping in sinus rhythm, the computed tomography image guided reconstruction of the right ventricular outflow tract and allowed correct identification of the plane of the pulmonary valve, an essential landmark in the approach of this type of VT. This also facilitated localization of the channels of slow conduction related to the VT.

Delayed gadolinium-enhancement magnetic imaging identifies areas of fibrosis in the ventricular myocardium in patients with structural heart disease. When integrated in the electroanatomic systems, it provides topography and transmural extent of the fibrotic tissue and, hence, of the low voltage areas, simplifying the identification of the arrhythmogenic substrate during voltage mapping in sinus rhythm[65,66]. This is expected to significantly shorten mapping time, increase the success rate and reduce the

complication rate. In general, ICD and claustrophobia are considered contraindications for magnetic resonance imaging. However, using appropriate precautions this imaging modality is possible even in ICD patients, who represent a vast proportion of candidates for VT ablation[38,66].

Remote magnetic navigation

A sophisticated device which consists of two magnets on each side of the patient's torso makes it possible to maneuver a special catheter with magnetic sensors by changing the direction of the magnetic field around the patient's chest[67]. The ablation/mapping catheter is maneuvered by the operator *via* a computerized system, which can be located remote from the patient's bed, to avoid radiation exposure for the operator. One of the advantages of this system is the peculiar flexibility of the catheter, which therefore can be magnetically guided and stably positioned in sites difficult for standard catheters, such as the coronary cusps and the right ventricular outflow tract[68,69]. Single center studies show that in VT patients, endocardial and epicardial mapping and ablation using this system is safe and feasible with minimal radiation exposure for the patient[70,71]. It has been recently reported that remote magnetic navigation may be more effective than manual ablation[72]. On the other hand, the disadvantages of this system are mainly represented by costs and the need for appropriate location and magnetic shielding.

Alternative energy sources

As previously mentioned, irrigated tip ablation is a standard procedure both for endocardial and epicardial VT ablation. In antiarrhythmic surgery for VT, cryothermal energy was used to complement endocardial resection[4]. When applied percutaneously, cryothermal energy produces a more discrete lesion with less collateral damage to adjacent structures as compared to radiofrequency energy. Percutaneous cryoablation of VT associated with postinfarction ischemic cardiomyopathy has proved effective and safe, although a higher recurrence rate may be encountered, probably related to the smaller lesion size[73].

Ethanol injection in a coronary artery branch was proposed more than two decades ago to produce a controlled necrosis of the ventricular myocardium where the VT originates. This option can be used today[74], but it should be limited to very selected cases refractory to other approaches due to the high risk of complications including reflux of ethanol in other coronary branches, which results in a large necrosis of the ventricular myocardium.

Currently, ultrasound, laser, and radiation energy are under investigation to evaluate whether these energy sources can produce a larger lesion in a safe way, in order to treat patients refractory to conventional ablation. Gene therapy to modify the electrical properties of the arrhythmogenic substrate to prevent ventricular arrhythmias is currently under investigation, however, we are still far from having a clinical application[75].

CONCLUSION

Catheter ablation is effective and safe in abolishing recurrent VTs associated with structural heart disease, although it may not be a curative and stand-alone therapy. New techniques and technologies introduced over the last decade have made ablation possible even in cases of "unmappable" VT and, in general, they have improved the success rate of VT ablation. The complication rate, including death, is significantly higher than that for supraventricular arrhythmias. This is mainly due to the severity of the underlying heart disease and clinical conditions before the ablation procedure. Finally, in patients with a structural heart disease, VT ablation should not be the last resort after a long history of multiple ICD shocks despite high-dose amiodarone. Recent data show that the VT-free survival is significantly higher in patients who are referred early for ablation of recurrent VTs[76].

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REVIEW

Incidence, clinical impact and risk of bleeding during oral anticoagulation therapy

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Abstract

Bleeding is the most important complication of oral anticoagulation (OAC) with vitamin K-antagonists. Whilst bleeding is unavoidably related to OAC, it may have a great impact on the prognosis of treated subjects by leading to discontinuation of treatment, permanent disability or death. The yearly incidence of bleeding during OAC is 2%-5% for major bleeding, 0.5%-1% for fatal bleeding, and 0.2%-0.4% for intracranial bleeding. While OAC interruption and/or antagonism, as well as administration of coagulation factors, represent the necessary measures for the management of bleeding, proper stratification of the individual risk of bleeding prior to start OAC is of paramount importance. Several factors, including advanced age, female gender, poor control and higher intensity of OAC, associated diseases and medications, as well as genetic factors, have been proven to be associated with an increased risk of bleeding. Most of these factors have been included in the development of bleeding prediction scores, which should now be used by clinicians when prescribing and monitoring OAC. Owing to the many limitations of OAC, including a narrow therapeutic window, cumbersome management, and wide inter- and intra-individual variability, novel oral anticoagulants, such as factor Xa inhibitors and direct thrombin inhibitors, have been recently developed. These agents can be given in fixed doses, have little interaction with foods and drugs, and do not require regular monitoring of anticoagulation. While the novel oral anticoagulants show promise for effective thromboprophylaxis in atrial fibrillation and venous thromboembolism, definitive data on their safety and efficacy are awaited.

Key words: Bleeding; Oral anticoagulation; Vitamin K antagonists; Dabigatran; Apixaban; Rivaroxaban

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INTRODUCTION

The purpose of oral anticoagulation (OAC) therapy is to induce a controlled depression of blood coagulability in order to reduce the risk of thromboembolic complications in clinical conditions such as atrial fibrillation, mechanical heart valves, deep vein thrombosis and pulmonary embolism, and cardiogenic stroke. While newer oral anticoagulants, such as direct thrombin inhibitors (i.e., dabigatran) and direct factor Xa inhibitors (i.e., apixaban, rivaroxaban), have been recently evaluated in the clinical setting[1-5], vitamin K antagonists (VKAs), such as warfa-

rin, acenocoumarol, and phenprocoumon, currently represent the standard drugs for OAC therapy.

The anticoagulant effect of VKAs is a consequence of their interference with the cyclic interconversion of vitamin K and its epoxide, by means of the inhibition of the vitamin K epoxide reductase enzyme (VKORC1), which in turn, is essential for the gamma-carboxylation of vitamin K-dependent coagulation factors, including factor Ⅱ, Ⅶ, Ⅸ and Ⅹ[6] (Figure 1). While acenocoumarol and phenprocoumon are preferred in some countries, warfarin is the VKA most commonly used in clinical practice[6]. Warfarin is a racemic mixture of two optically active isomers, the R and S enantiomers[6]. It is rapidly absorbed from the gastrointestinal tract, has high bioavailability, and reaches its maximal blood concentration about 90 min after oral administration[6]. Racemic warfarin has a half-life of 36-42 h, as compared to 8-24 h for acenocoumarol, and 80-270 h for phenprocoumon, circulates bound to plasma proteins, and accumulates in the liver, where the two enantiomers are metabolized by different pathways[6]. The S enantiomer, which is about three times more potent than the R enantiomer, is primarily metabolized by the CYP2C9 enzyme of the cytochrome P450 system, whereas the R enantiomer is metabolized by the CYP1A2 and CYP3A4 enzymes[6].

In order to maximize protection against thromboembolic complications while minimizing the risk of bleeding associated with VKA therapy, the intensity of OAC should be maintained within a narrow therapeutic range (TTR). Apart from non-bileaflet mechanical heart valves and mechanical heart valves in the mitral position, where a higher intensity of OAC therapy is required, an international normalized ratio (INR) of 2.0-3.0 has long been identified as the optimal TTR for most clinical conditions at risk for thromboembolic events[6]. Nonetheless, bleeding represents the major complication of OAC therapy, even when OAC is properly prescribed[7].

INCIDENCE OF BLEEDING

The reported incidence of bleeding during OAC therapy with VKAs is highly variable in published studies. This variability may be accounted for by the differences in the definition and classification of bleeding (Table 1). More importantly however, the differences in the reported hemorrhagic rates are more likely to be attributed to differences in study design and patient population. In randomized clinical trials, where highly selected patients are enrolled, rates of bleeding are expected to be lower than in observational studies, where patients commonly encountered in clinical practice, including those with individual risk factors for bleeding, are included. As an example, in six pivotal trials evaluating the effect of warfarin compared to placebo in patients with atrial fibrillation, only 12.6% out of the 28 787 patients screened were finally included[8]. Whether or not monitoring of OAC therapy is carried out in specialized services, where a better and more stable control of the INR is generally achieved, may also have an impact on the occurrence of bleeding complications[9].

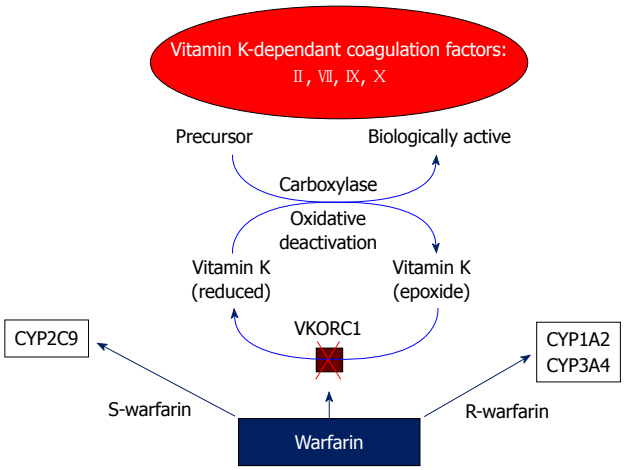

Figure 1 Mechanism of action and metabolism of warfarin. VKORC1: Vitamin K epoxide reductase enzyme.

The expected incidence of bleeding during long-term VKA therapy is about 10%-17% per year for all events, 2%-5% per year for major bleeding, and 0.5%-1% per year for fatal bleeding[10]. The reported occurrence of intracranial hemorrhage (ICH), which represents the mostly feared bleeding complication of VKA therapy because of its high disability and/or fatality rate, is in the range of 0.2%-0.4% per year[7,11].

CLINICAL IMPACT AND MANAGEMENT OF BLEEDING

The occurrence of bleeding during OAC therapy with VKAs has relevant prognostic and management implications. Major bleeding can be life-threatening, such as when occurring at critical sites like the head, the pericardium or the pleura, or when leading to the development of hemorrhagic shock. Also, major bleeding complications are generally associated with VKA discontinuation, which in turn, contributes to adverse outcomes by leaving the patient exposed to an increased risk of thromboembolism. In a recent meta-analysis of clinical trials reporting on OAC therapy with VKAs for venous thromboembolism, a case-fatality rate of major bleeding of 13.4% (95% CI: 9.4%-17.4%) has been reported in all patients, with a rate of ICH of 1.15% per year (95% CI: 2.5%-21.7%)[12]. Regardless of the severity however, hemorrhagic complications of OAC therapy with VKAs may be important for the related inconvenience to the patients. The perceived higher risk of bleeding of VKA therapy limits its more widespread use, therefore excluding many patients from the benefits of such therapy. It has been shown that the occurrence of VKA-associated adverse events has an impact on the prescribing of this treatment, since physicians are less likely to prescribe VKAs after observing a bleeding complication during VKA treatment in their patients[13].

Table 1 Different definitions of major bleeding in various studies

Ref.	Clinical setting	Definition
Landefeld *et al*[53]	Various	Fatal, life-threatening, potentially life-threatening, causing severe blood loss, leading to surgical treatment or moderate acute/subacute blood loss not explained by surgery/trauma
Palareti *et al*[32]	Various	Fatal intracranial (documented by imaging); ocular (with blindness); articular; retroperitoneal; requiring surgery/angiographic intervention; associated to Hb decrease ≥ 2 g/dL or need for ≥ 2 blood units transfusion
Beyth *et al*[54]	Various	Overt bleeding leading to ≥ 2 blood units loss in ≤ 7 d, or life-threatening
Gage *et al*[55]	AF	ICD-9CM codes for bleed in any location
Shireman *et al*[56]	AF	Hospitalization for "major acute bleeding" (including gastrointestinal or intracranial hemorrhage)

AF: Atrial fibrillation; Hb: Hemoglobin.

Management of bleeding occurring during OAC therapy with VKAs generally consists of discontinuation and/or antagonism of VKAs, as well as of local measures (i.e. endoscopic treatment and/or surgical hemostasis) and proper transfusion procedures. Discontinuation of VKAs allows for subsequent normalization of INR, which may require several hours owing to the prolonged half-life of VKAs. According to available data, temporary interruption of VKA therapy because of major bleeding or trauma appears not to be associated with an increased risk of subsequent thromboembolic complications[14,15]. In a population of 28 patients with prosthetic heart valves receiving warfarin and hospitalized for major hemorrhage who were retrospectively evaluated, discontinuation of OAC therapy for 1 d to > 3 wk (mean duration 15 ± 4 d) was not associated with thromboembolic complications at 6-mo follow-up[14]. In a retrospective, population-based, cohort study evaluating 8450 patients aged > 65 years on warfarin for various reasons and surviving a major trauma, the incidence of stroke at a mean follow-up of 3.3 years did not differ between patients who discontinued warfarin as compared to those who continued warfarin [hazard ratio (HR), 0.99; 95% CI: 0.82-1.21], while the incidence of major hemorrhages was significantly lower (HR, 0.69; 95% CI: 0.54-0.88) and that of venous thromboembolism was significantly higher (HR, 1.59; 95% CI: 1.07-2.36)[15]. Antagonism of the VKA anticoagulation effect is obtained by directly administering vitamin K[16]. Vitamin K can be given orally or intravenously, with the parenteral route having the advantage of a more rapid onset of action[17]. After intravenous administration of vitamin K, the INR will start to drop within 2 h and will be normalized within 12-16 h[18], whereas after oral administration it will take up to 24 h to normalize the INR[19]. While low (1-2.5 mg) to moderate (2.5-5 mg) doses of vitamin K given orally are indicated for the management of non-emergency bleeding, slow intravenous infusion of 10 mg vitamin K should be given in emergency situations[6]. Higher doses of vitamin K are equally effective but may induce resistance to VKAs for more than 1 wk[20], and are therefore not recommended. In emergency situations, immediate correction of high INR should be pursued also by the administration of vitamin K-dependent coagulation factors. These factors are present in fresh frozen plasma, which however is inconvenient to use owing to the very large amount needed, the prolonged time required for administration, and the associated risk of fluid overload[21]. Therefore, prothrombin complex concentrates, most of which contain all vitamin K-dependent coagulation factors, are more useful and should be administered either according to fixed dose schemes or, preferably, by individualized dosing regimens based on INR value and body weight[22].

Table 2 Factors associated with an increased risk of bleeding

Author
Age > 65-70 yr
Female gender
CYP2C9 and/or VKORC1 gene polymorphism
Higher intensity of anticoagulation (i.e., INR > 4.5)
Labile INR (i.e., TTR < 60%)
Early 90 d of anticoagulation
History of bleeding
Comorbidities (i.e., hypertension, malignancy, liver and/or renal and/or cardiac failure)
Comedications (i.e., antiplatelet agents, non-steroidal anti-inflammatory drugs)

INR: International normalized ratio; TTR: Time within the therapeutic range.

RISK FACTORS FOR BLEEDING

Numerous factors, including individual characteristics, intensity, timing and quality of OAC therapy, and use of concomitant medications, have been established as impacting on the risk of bleeding during VKA treatment (Table 2).

Age

In most studies, older age has consistently shown to increase the risk of bleeding[11]. As compared to younger patients, elderly patients have about a 5-fold higher incidence of major and fatal bleeding (3.2% and 0.64% per year *vs* 0.6% and 0.12% per year, respectively)[23]. Importantly, the risk of ICH is particularly increased in subjects of advanced age[24]. In patients aged ≥ 85 years an adjusted odds ratio of 2.5 (95% CI: 2.3-9.4) for ICH has been recently reported in comparison to a reference group of patients of 70-74 years[25]. Elderly patients are at higher risk of bleeding for several reasons, including the lower dose of anticoagulant required for effective an-

ticoagulation (mainly because of reduced metabolic clearance)[26], the higher frequency of pathological changes in cerebral vessels, such as leukoaraiosis and amyloid angiopathy, which may increase the risk of ICH[27,28], and the increased prevalence of diverticulosis, malignancy, angiodysplasias, and ischemic colitis, which in turn may predispose to gastrointestinal bleeding. Additionally, elderly patients have a higher prevalence of comorbid conditions and are more likely to take interacting drugs[29]. Non-compliance to VKAs and lack of a clear understanding of their purpose and actions by older patients[30], who are also prone to mental impairment, are additional factors which may influence the bleeding rate.

Gender

Female gender has been found to be associated with a greater risk of bleeding during OAC therapy with VKAs for atrial fibrillation[31,32], but such an association has not been found in another study which enrolled patients with various indications for VKA anticoagulation[33].

Intensity and quality of anticoagulation

Although bleeding complications are not always related to a high intensity of anticoagulation and may occur even with INR values lower than 2.0, the target intensity of anticoagulation, and especially the actually achieved intensity, have long been recognized as major determinants of anticoagulation-related hemorrhages[11]. The increase in bleeding becomes exponential for INR values > 4.5, while the lowest rate is observed with INR values between 2.0 and 3.0[32]. The risk of death is also related to INR values with a minimum risk at INR 2.2[34]. High INR values are associated with an excess in mortality as well with a 2-fold increase in risk for one unit increase in INR above 2.5[34].

The initiation phase of anticoagulation, and especially the first 90 d of treatment, are associated with a higher incidence of bleeding[32,35]. Factors including the unmasking of occult lesions at the beginning of anticoagulation and/or less adequacy of dose adjustments in that period may account for this finding.

The quality of anticoagulation, as expressed by the time spent within the TTR, is another important variable influencing the likelihood of hemorrhagic complications. A strong relationship between TTR and bleeding, as well as thromboembolic complications, has consistently been reported in different patient populations and different intensity ranges[6]. Both major bleeding and mortality rates have been reported to be significantly higher in patients with TTR < 60% (3.85% and 4.20%, respectively) compared to those with TTR > 75% (1.58% and 1.69%, respectively)[36]. Apart from the application of general measures, like patient information and education and use of coumarin derivatives with a longer half-life, such as warfarin and phenprocoumon[37-39], achievement of good anticoagulation control may be better obtained by monitoring the treatment at specialized coagulation services or by patients themselves[6,40].

Comorbid conditions and comedications

Both as a marker of increased patient frailty and cause of concomitant use of other medications, the presence of comorbidities represents another factor potentially increasing the risk of bleeding during OAC therapy with VKAs. Apart from previous bleeding (especially in the gastrointestinal tract), which is the most potent predictor of recurrent hemorrhagic complications, congestive heart failure, hepatic or renal failure and diabetes have been identified as conditions associated with major bleeding[41,42]. Blood pressure control is also a critical factor for hemorrhagic complications during VKAs therapy. Among anticoagulated patients experiencing bleeding complications, a higher prevalence of history of hypertension has been frequently reported compared to patients with no previous bleeding[43]. Therefore, strict monitoring and control of blood pressure is warranted to reduce the risk of major hemorrhagic complications. More time spent above the intended intensity of OAC and wide and unpredictable fluctuations of the INR have been observed in patients with malignancies, which should also be regarded as risk factors for bleeding during VKA anticoagulation[44].

Among concomitant drugs frequently taken by patients on OAC therapy, antiplatelet agents are the most important because of the additional inhibitory effect on the anticoagulation system. Such an effect is of high clinical relevance because of the frequent coexistence, especially in elderly patients, of conditions such as atrial fibrillation or venous thromboembolism and coronary artery disease, where both VKAs and antiplatelet agents are indicated. Indeed, a relative risk of major bleeding of 2.5 (95% CI: 1.7-3.7) has been reported for the association of VKAs and aspirin[45]. An increasingly important subset of OAC patients potentially at increased bleeding risk is represented by those with an acute coronary syndrome and/or undergoing percutaneous coronary intervention with stent implantation, in whom a course of dual antiplatelet therapy with aspirin and clopidogrel is necessary to prevent stent thrombosis and/or ischemic recurrences. These patients represent 5%-10% of the whole population undergoing percutaneous coronary revascularization and appear exposed to a higher risk of major bleeding, which apparently increases with prolongation of treatment[46,47]. While waiting for solid data on drug combinations, such as VKAs plus clopidogrel[48], in patients on triple therapy of VKA, aspirin and clopidogrel, meticulous care should be exerted (1) to prolong this regimen for as short as possible (therefore avoiding the implantation of drug-eluting stents for which a duration of 6-12 mo of clopidogrel therapy is recommended)[49]; (2) to target an INR at the lower end (i.e., between 2.0 and 2.5) of the TTR; (3) to frequently review the patient and test the INR; and (4) to extensively use gastric protective agents[46,47].

Genetic factors

Recent advances in the pharmacogenetics of VKAs have greatly increased the understanding of their mechanism

Table 3 Most popular bleeding risk prediction scores

Author	Ref.	Calculation	Risk classification
mOBRI	[54]	Age ≥ 65 yr, previous stroke, GI bleed in the last 2 wk, ≥ 1 of the following: recent MI, hematocrit < 30%, creatinine > 1.5 mg/dL, diabetes) 1 point each	Low: 0 points Intermediate: 1-2 points High: ≥ 3 points
HEMORR$_2$HAGES	[55]	Hepatic or renal disease, ethanol abuse, malignancy, older, reduced platelet count/function, re-bleeding, uncontrolled hypertension, anemia, genetic factors, excessive fall risk, and stroke 1 point each and 2 points for previous bleed	Low: 0-1 points Intermediate: 2-3 points High: ≥ 4 points
Shireman *et al*	[56]	(0.49 × age ≥ 70 yr) + (0.32 × female gender) + (0.58 × remote bleed) + (0.62 × recent bleed) + (0.71 × alcohol/drug abuse) + (0.27 × diabetes) + (0.86 × anemia) + (0.32 × antiplatelet therapy) 1 point each	Low: ≤ 1.07 points Intermediate: < 1.07 to < 2.19 points High: ≥ 2.19 points
HAS-BLED	[57]	Hypertension (SBP > 160 mmHg), abnormal renal/liver function, stroke, history of bleeding, labile INR, elderly age (> 65 yr), drugs (antiplatelets/NSAIDs/alcohol) 1 point each	Low: 0-1 points Intermediate: 1-2 points High: ≥ 3 points

GI: Gastrointestinal; MI: Myocardial infarction; SBP: Systolic blood pressure; NSAIDs: Non-steroidal antiinflammatory drugs.

of action and of the known broad inter-individual variability in VKA response. It is now known that at least 30 genes are involved in the metabolism and action of warfarin, and some polymorphism of genes encoding for VKORC1 and CYP2C9 enzymes is present[6,50]. While mutations of VKORC1 are associated with different sensitivities to VKA, polymorphism of CYP2C9 can cause a delayed stabilization of VKA treatment[11]. Indeed, CYP2C9 variants are significantly more frequent among patients with an unstable response to VKAs[30] who achieve a stable dose significantly later, spend significantly more time above the therapeutic INR range in the initial phase of treatment, and have higher risk of having INR values > 5.0 as compared to non-carrier patients[50]. Owing to the reported association between gene variants and risk of bleeding and dose requirements in the initial phase of anticoagulation[51], several dosing algorithms based on VKORC1 and CYP2C9 genotypes have been proposed, although not integrated yet in clinical practice, to assist initiation of VKA treatment[52].

BLEEDING RISK SCORES

Stratification of the individual bleeding risk prior to initiation of OAC therapy with VKAs is another important measure to adopt for prevention of hemorrhagic complications[53]. To assist clinicians in this task, several schemes have been developed (Table 3).

The modified outpatient bleeding risk index (mOBRI) has been prospectively derived and extensively validated in patients with different indications for VKAs[54]. Also, the mOBRI was evaluated in a "real-life" setting of anticoagulation monitoring (i.e., primary care physicians or pharmacist-run anticoagulation clinic) and the assessment of bleeding was blinded[54]. The hepatic or renal disease, ethanol abuse, malignancy, older, reduced platelet count/function, re-bleeding, uncontrolled hypertension, anemia, genetic factors, excessive fall risk, and stroke score has been derived from a retrospective chart review of nationwide registry data of patients with atrial fibrillation[55]. The retrospective design, the inclusion of genetic factors (which are rarely investigated in common practice), and of anemia and platelet data (also infrequently available), limit the usefulness of this score, as well as the lack of inclusion of important factors such as the concomitant use of antiplatelet agents and/or other drugs. The schema by Shireman *et al*[56] is also derived from a retrospective evaluation of nationwide registry data, and incorporates eight risk factors for bleeding. As regards limitations, the follow-up period was relatively short (i.e. 90 d), the outcome assessment was not blinded, and the quality of anticoagulation control and the use of comedications were not reported[56]. Finally, the individual determination of this score requires a complex mathematical calculation, which makes it rather impractical[56]. The hypertension, abnormal liver or renal function, stroke, bleeding, labile INRs, elderly, drugs or alcohol (HAS-BLED) score has been recently developed for patients with atrial fibrillation, based on the prospective Euro Heart Survey on atrial fibrillation[57]. Compared with the previous three scores, the HAS-BLED score was recently demonstrated to have better predictive ability for bleeding among all patients enrolled in the SPORTIF Ⅲ and Ⅴ trials, as well as among warfarin-naïve patients and patients treated with warfarin and aspirin[58]. The HAS-BLED score appears easy and user-friendly for everyday application, owing to the small number of variables to memorize and the common availability of all the information required for risk calculation. Finally, the HAS-BLED score allows for periodical re-assessment of a patient's bleeding risk as it also takes into account the quality of INR control.

When applying the different bleeding scores, a wide variability in the prevalence of patients determined to be at low-, moderate-, and high-risk is observed because of differences in the risk factors comprising each schema, the various definitions of major bleeding, the different lengths of follow-up in the cohorts, and the different populations evaluated in the studies. Furthermore, no data on the impact of these scores on patient outcomes are currently available, so that none of the proposed bleeding risk scores can currently be recommended for widespread clinical use. Nonetheless, it must be empha-

sized that bleeding risk stratification should represent an integral part of the management of OAC therapy, and application of these scores may assist clinicians in their decision-making in everyday clinical practice.

NOVEL ORAL ANTICOAGULANTS

While VKAs are the standard drugs for OAC therapy, they have several major limitations, including the narrow therapeutic window, the cumbersome management, and the wide inter- and intra-individual variability. Therefore, more effective and/or safer and/or easier to use oral anticoagulants have long been sought. Recently, two main classes of new non-VKA oral anticoagulants (i.e. factor Xa-inhibitors and direct thrombin inhibitors) have been developed. These agents can be given in fixed doses, have little interaction with foods and drugs, and do not require regular monitoring of anticoagulation[59].

Apixaban, rivaroxaban and edoxaban are orally active, direct inhibitors of factor Xa. While being currently evaluated in several large, double-blind trials in patients with atrial fibrillation or venous thromboembolism, some evidence about the efficacy and safety of these drugs has already been reported. In the EINSTEIN-DVT and EINSTEIN-Extension studies[1], 3449 patients with acute deep vein thrombosis received, in an open-label manner, rivaroxaban or standard treatment (i.e. initial course of enoxaparin followed by VKAs) for 3, 6 or 12 mo. The 602 patients who had completed 6 to 12 mo of treatment then entered a double-blind study with randomization to rivaroxaban or placebo for an additional 6 or 12 mo. In the whole population, the efficacy of rivaroxaban on recurrent venous thromboembolism was non-inferior to the enoxaparin/VKA regimen (2.1% *vs* 3.0%, $P < 0.001$). The safety, as expressed by the on-treatment occurrence of major bleeding, was identical (8.1% in both groups). In the extended-treatment group, rivaroxaban was significantly more effective (1.3% *vs* 7.1%, $P < 0.001$), however, there was an increased, albeit non significant, incidence of major bleeding (0.7% *vs* 0%). In the AVERROES trial[2] 5599 patients with atrial fibrillation, who were unsuitable for or who were not willing to receive VKAs were randomized to apixaban or aspirin. At the 1.1-year follow-up, the treatment with apixaban was significantly more effective on the incidence of stroke/systemic embolism (1.6% *vs* 3.7%, $P < 0.001$). No differences in the rates of major bleeding were observed between the apixaban and aspirin groups (1.4% *vs* 1.2%, $P = 0.57$). In the double-blind ROCKET-AF trial[3], which enrolled > 14 000 atrial fibrillation patients, and investigated the efficacy (incidence of stroke/systemic embolism) and safety (incidence of bleeding) of rivaroxaban compared to warfarin, rivaroxaban was more effective (1.71% *vs* 2.16%, $P < 0.001$ for non-inferiority), without no significant difference in the rate of major bleeding (3.60% *vs* 3.45%).

Dabigatran is an orally active, direct thrombin inhibitor, which has been tested for the long-term treatment of patients with nonvalvular atrial fibrillation and venous thromboembolism. In the RE-LY trial, 18 113 patients with atrial fibrillation were randomized to two blinded doses of dabigatran against open-label warfarin[4]. At 2-year follow up, the primary outcome of stroke and systemic embolism was lower both with low-dose and high-dose dabigatran compared to warfarin (1.53% and 1.11% *vs* 1.69%, $P < 0.001$ for non-inferiority and $P < 0.001$ for superiority, respectively). The incidence of major bleeding was lower in the low-dose group (2.71% *vs* 3.36%, $P = 0.03$) and similar to warfarin in the high-dose group (3.11% *vs* 3.36%, $P = 0.31$). Among the 2564 patients with acute venous thromboembolism enrolled in the double-blind RE-COVER study, dabigatran was as effective as warfarin for secondary prevention of recurrent venous thromboembolism at 6-mo follow-up (2.4% *vs* 2.1%). The incidence of major bleeding was also comparable in the two groups (1.6% *vs* 1.9%)[5].

In the light of the promising outcomes, as well as of the superior ease of use, the novel non-VKA oral anticoagulants represent an attractive alternative to VKAs for OAC therapy. Nonetheless, additional data on the impact of the lack of a method to monitor the intensity of anticoagulation, lack of a specific antidote, and little information regarding the risk/benefit ratio of their combination with more potent antiplatelet agents, such as the increasingly used prasugrel or ticagrelor, are necessarily awaited before these drugs can be truly considered substitutes for VKAs.

CONCLUSION

OAC therapy with VKAs is the most effective available treatment for prevention of thromboembolic complications in frequent clinical conditions, such as atrial fibrillation, venous thromboembolism, prosthetic heart valves, and cardiogenic stroke. Such efficacy comes at the price of an increased risk of overall, major and ICH bleeding. While novel, non-VKA oral anticoagulants, such as direct thrombin inhibitors and direct factor Xa inhibitors, have been showing promise in the setting of atrial fibrillation and venous thromboembolism, VKA treatment should currently be offered to all patients at high risk of arterial/venous thromboembolism because of the established benefit outweighing the risk. However, meticulous care should be directed towards accurate bleeding risk stratification and minimization and/or control of all the numerous factors known to influence the risk of hemorrhagic complications.

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ORIGINAL ARTICLE

Risk profile and outcomes of aortic valve replacement in octogenarians

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Abstract

AIM: To investigate the patient characteristics, relationship between the Logistic EuroSCORE (LES) and the observed outcomes in octogenarians who underwent surgical aortic valve replacement (AVR).

METHODS: Two hundred and seventy three octogenarians underwent AVR between 1996 and 2008 at Bristol Royal Infirmary. Demographics, acute outcomes, length of hospital stay and mortality were obtained. The LES was calculated to characterize the predicted operative risk. Two groups were defined: LES $\geqslant$ 15 (n = 80) and LES < 15 (n = 193).

RESULTS: In patients with LES $\geqslant$ 15, 30 d mortality was 14% (95% CI: 7%-23%) compared with 4% (95% CI: 2%-8%) in the LES < 15 group (P < 0.007). Despite the increase in number of operations from 1996 to 2008, the average LES did not change. Only 5% of patients had prior bypass surgery. The LES identified a low risk quartile of patients with a very low mortality (4%, n = 8, P < 0.007) at 30 d. The overall surgical results for octogenarians were excellent. The low risk group had an excellent outcome and the high risk group had a poor outcome after surgical AVR.

CONCLUSION: It may be better treated with transcatheter aortic valve implantation.

Key words: Aortic valve replacement; Transcatheter aortic valve implantation; Logistic EuroSCORE; Coronary artery bypass grafting

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INTRODUCTION

Calcific aortic stenosis is the most common structural cardiac disease in an ever growing elderly population. Transcatheter aortic valve implantation (TAVI) has now become a realistic choice for treating high risk, elderly patients and has raised interest in the treatment of aortic valve disease in octogenarians[1-5]. Despite the high mortality and morbidity associated with symptomatic untreated aortic stenosis, a recent survey showed that over 30% of elderly patients did not receive surgical treatment[6,7].

Conventional surgical aortic valve replacement (AVR) can be performed with good success in selected patients[8-10]. However, increasing age is a significant independent predictor of postoperative mortality[11-14]. The perceived risk associated with advanced age and comorbidity may have led clinicians to adopt a conservative approach to treatment of critical aortic stenosis[7,11]. The presence of coronary artery disease requiring coronary artery bypass grafting (CABG) is a risk factor for surgical mortality, when compared with isolated AVR[15]. Frailty is also frequently quoted as a risk factor, but is hard to quantify. Hence, there is a growing need for risk stratification and evaluation of outcomes after surgical AVR and TAVI in octogenarians in the modern era.

Thus, whilst there are reports showing acceptable overall mortality and morbidity for surgical AVR they may still represent a select population[15,16]. Selection criteria for TAVI are clinical and anatomical. With a growing number of TAVI performed worldwide, we considered it important to assess the surgical outcomes of octogenarians undergoing AVR in our institution. We postulated that there would be a subgroup of patients that could be identified as being at high risk for surgery by applying the risk assessment tool currently used for patient selection into our TAVI program. Furthermore, we postulated that some patient subgroups with relative contraindications such as previous cardiac surgery might be under-represented.

MATERIALS AND METHODS

Study design

A retrospective review was performed on patients who underwent isolated, primary AVR and AVR with CABG from 1996 to August 2008 at Bristol Royal Infirmary, Bristol, United Kingdom. Clinical details were obtained from a central cardiac database. Preoperative demographics, predictors of in-hospital mortality and postoperative outcomes were documented. Case records were reviewed and data relevant for the calculation of risk score and outcomes were verified individually.

The selection of patients for cardiac surgery was at the discretion of individual referring physicians, cardiologists and cardiac surgeons. The surgical technique, valve selection and implantation technique were determined by the individual cardiac surgeon. Postoperative care was provided by the intensive care unit, followed by the high dependency unit and the cardiac ward. Duration of stay in the intensive care and high dependency units and perioperative adverse events were documented in the clinical notes.

A Logistic EuroSCORE (LES) of $\geqslant$ 15% is used to define "high risk"[2] in the initial TAVI programs. The patients were separated into LES $\geqslant$ 15% and < 15% for analysis. To further quantify the risk, surgical patients were also analyzed by quartile of risk.

Deaths after hospital discharge were obtained by linking with the NHS Strategic Tracing Service (NSTS).

Definitions

Evidence of elevation of cardiac biomarkers (creatine kinase, CK-MB or troponin elevation above 0.05 μg/L) associated with electrocardiographic changes of ST depression or ST elevation identified a myocardial infarction. An elevated fasting blood glucose value of 6.9 mmol/L was considered sufficient to establish a diagnosis of diabetes mellitus. A serum creatinine value above 200 μmol/L was classified as renal impairment. Pulmonary disease included chronic obstructive pulmonary disease, asthma and emphysema. Previous percutaneous coronary intervention was defined as coronary angioplasty with or without coronary stent insertion prior to AVR.

Patients with previous stroke included patients with a cerebrovascular accident (CVA) or transient ischemic attack (TIA). CVA was diagnosed with imaging evidence of a cerebral infarct with or without a persistent neurological deficit. Persistence of a neurological deficit beyond 24 h was also defined as a CVA. TIA was diagnosed in patients experiencing a transient neurological deficit which resolved in 24 h without any long term neurological sequelae. Patients with documented evidence of claudication pain associated with or without an ankle brachial pressure index of 0.9 were considered to have peripheral vascular disease.

Coronary artery disease was defined as coronary arteries with > 50%. Depending on the number of major coronary arteries involved, patients were classified as having single, double or triple vessel coronary artery disease. Ejection fraction was quantified by biplane Simpson method as a percentage and presented as 3 categories (< 30%, 30%-49%, 50% and above).

The EuroSCORE and LES were calculated with the help of an online risk calculator (http://www.euroscore.org/).

Statistical analysis

Continuous measures are summarized by the mean and standard deviation, or median and interquartile range (IQR) if the distribution was skewed. Categorical data are presented as numbers and percentages. The primary comparisons were made between patients with LES < 15 and those with LES $\geqslant$ 15. Binary outcomes were compared using odds ratios (OR) and 95% CI. Survival and length of stay outcomes were compared using hazard ratios (HR) from the Cox proportional hazards model. For survival, surviving patients were censored at 2 mo prior to the update from NSTS (chosen because the majority

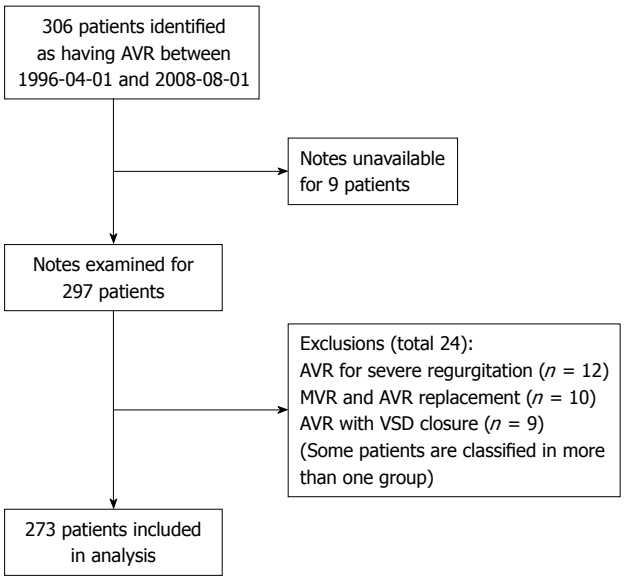

Figure 1 Flow chart of study enrollment. The 9 patients for whom notes are unavailable: 5/9 were male (56%); Mortality-Nil; Age: mean (SD) = 83.9 (3.7), range = 80.2-92.1; EuroSCORE: Median (interquartile range) = 9 (8-10), range = 7 to 11. AVR: Aortic valve replacement; MVR: Mitral valve replacement; VSD: Ventricular septal defect.

of deaths are reported to NSTS within 2 mo). For hospital stay, patients who died before discharge were censored at the date of death. Kaplan-Meier survival curves were also used to illustrate long-term survival.

Mortality was also compared between (1) quartiles of LES; (2) isolated AVR surgery *vs* AVR + CABG surgery; and (3) eras of time (1996-2000, 2001-2004 and 2005-August 2008), with the aim of reflecting the variability in surgical practice and outcomes in the 3 different eras.

The acquired data was anonymized to ensure patient confidentiality. All analyses were performed using Stata version 10.1 (Stata Co., TX, United States).

RESULTS

Study population

Three hundred and six patients underwent surgical AVR between April 1996 and August 2008; 297 case notes were examined as 9 notes were not obtainable. Patients undergoing double valve replacement (mitral and aortic valve) and complex procedures involving AVR with ventricular septal defect closure were excluded from the study (Figure 1). A total of 24 patients were excluded due to categorization of some patients in more than one of these groups. Therefore 273 patients formed the study population, 80 in the group with LES ⩾ 15 and 193 in the group with LES < 15.

The demographics of patients in the LES ⩾ 15 and LES < 15 groups are shown in Table 1. Approximately equal numbers of patients underwent isolated AVR (n = 140) and AVR with CABG (n = 133).

Surgical outcomes

Outcomes by LES group are shown in Table 2. The incidence of postoperative myocardial infarction, CVA, bleeding, infection and the necessity for permanent pacemaker insertion was similar in both groups, although very few patients experienced any of these complications. There was some evidence of increased renal impairment in the LES ⩾ 15 group (n = 18, 23%) compared to the LES < 15 group (n = 26, 14%), although this was not statistically significant at the 5% level (OR, 1.86: 95% CI: 0.96-3.64). Mortality to 30-d was increased for patients with LES ⩾ 15 (n = 11, 14% *vs* n = 8, 4%; OR, 3.69; 95% CI: 1.42-9.55) and fewer patients were discharged home in the LES ⩾ 15 group. Long-term survival was also reduced in the LES ⩾ 15 group (HR, 2.12; 95% CI:

Table 1 Patient demographics n (%)

	All patients (n = 273)	LES < 15 (n = 193)	LES ⩾ 15 (n = 80)	P value
Gender (male)	128 (47)	90 (47)	38 (48)	0.900
Age (mean ± SD, yr)	82.7 ± 2.35	82.4 ± 2.21	83.5 ± 2.53	< 0.001
Surgery				
AVR	140 (51)	103 (53)	37 (46)	0.280
AVR with CABG	133 (49)	90 (47)	43 (54)	
Previous MI				
None	231 (85)	180 (93)	51 (64)	< 0.001
⩽ 90 d	26 (10)	6 (3)	20 (25)	
> 90 d	16 (6)	7 (4)	9 (11)	
Diabetes mellitus	30 (11)	27 (14)	3 (4)	0.014
Renal impairment	11 (4)	4 (2)	7 (9)	0.011
Previous PCI	4 (2)	0	4 (5)	0.002
Pulmonary disease	47 (17)	21 (11)	26 (33)	< 0.001
Prior cardiac surgery	13 (5)	1 (1)	12 (15)	< 0.001
CVA/TIA	42 (15)	28 (15)	14 (18)	0.450
PVD	25 (9)	12 (6)	13 (16)	0.009
CAD				
None	135 (50)	100 (52)	35 (44)	0.590
1 vessel disease	46 (17)	33 (17)	13 (16)	
2 vessel disease	42 (15)	28 (15)	14 (18)	
3 vessel disease	49 (18)	31 (16)	18 (23)	
Pathology				
AS	239 (88)	170 (88)	69 (86)	0.680
AS with mild AR	34 (12)	23 (12)	11 (14)	
Valve				
Mechanical	15 (6)	13 (7)	2 (3)	0.160
Biological	258 (95)	180 (93)	78 (98)	
Cardiogenic shock	4 (2)	0	4 (5)	0.002
Ejection fraction				
< 30%	15 (6)	0	15 (19)	< 0.001
30%-49%	62 (23)	37 (19)	25 (31)	
50% and above	196 (72)	156 (81)	40 (50)	
EuroSCORE, median (IQR)	9 (8-10)	8 (8-9)	11 (10-12)	
LES, median (IQR)	11.1 (8.4-16.6)	9.5 (7.9-11.6)	20.7 (17.4-24.9)	

Prior cardiac surgery - details of types of surgery: Low risk group [Logistic EuroSCORE (LES) < 15] - thoracic surgery (n = 1); High risk group (LES ⩾ 15) - abdominal aortic aneurysm (AAA) repair (n = 1), coronary artery bypass grafting (CABG) (n = 5), peripheral vascular disease (PVD) surgery (n = 2), carotid endarterectomy (n = 1), other (n = 3). Coronary artery disease (CAD) - one patient with missing data (low risk group). P values are for comparisons between LES < 15 and LES ⩾ 15 groups. PCI: Percutaneous coronary intervention; AVR: Aortic valve replacement; MI: Myocardial infarction; CVA: Cerebrovascular accident; TIA: Transient ischemic attack; AS: Aortic stenosis; AR: Atrial regurgitation; IQR: Interquartile range.

Table 2 Perioperative and postoperative outcomes *n* (%)

	All patients (*n* = 273)	LES < 15 (*n* = 193)	LES ⩾ 15 (*n* = 80)	Effect (95% CI)	*P* value
Stroke	13 (5)	8 (4)	5 (6)	OR 1.54 (0.49-4.86)	0.460
MI	3 (1)	3 (2)	0		
Cardiac tamponade	14 (5)	7 (4)	7 (9)	OR 2.55 (0.86.7.52)	0.090
Gastrointestinal bleeding	11 (4)	8 (4)	3 (4)	OR 0.90 (0.23-3.49)	0.880
Infection	22 (8)	15 (8)	7 (9)	OR 1.14 (0.45-2.91)	0.790
Renal impairment	44 (16)	26 (14)	18 (23)	OR 1.86 (0.96-3.64)	0.070
PPM insertion	23 (8)	14 (7)	9 (11)	OR 1.60 (0.66-3.87)	0.290
Mortality					
30 d	19 (7)	8 (4)	11 (14)	OR 3.69 (1.42-9.55)	0.007
⩽ 90 d	31 (11)	16 (8)	15 (19)	OR 2.55 (1.19-5.46)	
> 90 d	22 (8)	10 (5)	12 (15)		0.020
Discharge					
Home	153 (56)	118 (61)	35 (44)		
Other hospital or Ward	97 (36)	64 (33)	33 (41)		
Survival (yr), median (IQR)	6.22 (3.00-10.94)	8.74 (3.54-11.07)	4.19 (1.83-5.94)	HR 2.12 (1.40-3.22)	< 0.001
1 yr postop (95% CI)	87% (82%-90%)	90% (85%-94%)	79% (68%-86%)		
5 yr postop (95% CI)	57% (49%-64%)	64% (54%-72%)	40% (26%-55%)		
ICU stay					
Median (IQR)	1 (1-3)	1 (1-3)	2 (1-3)	HR 0.86 (0.66-1.14)	0.290
Death pre ICU	6 (2)	2 (1)	4 (5)		
HDU stay					
Median (IQR)	3 (1-4)	2 (1-4)	4 (2-5)	HR 0.67 (0.50-0.89)	0.006
Death pre HDU	13 (5)	5 (3)	8 (10)		
Ward stay					
Median (IQR)	6 (4-9)	6 (4-9)	5 (4-8)	HR 1.16 (0.87-1.55)	0.310
Death pre ICU	17 (6)	7 (4)	10 (13)		
Overall, median (IQR)	11 (8-15)	11 (8-15)	11 (8-15)	HR 0.89 (0.67-1.17)	0.400

Effect sizes and *P* values are for comparisons between the Logistic EuroSCORE (LES) < 15 and LES ⩾ 15 groups. Missing data: Discharge destination - low risk (*n* = 1); Pacemaker insertion - low risk (*n* = 2); high dependency unit (HDU) and ward length of stay - low risk (*n* = 2). ICU: Intensive care unit; OR: Odds ratio; HR: Hazard ratio; PPM: Permanent pacemaker; IQR: Interquartile range.

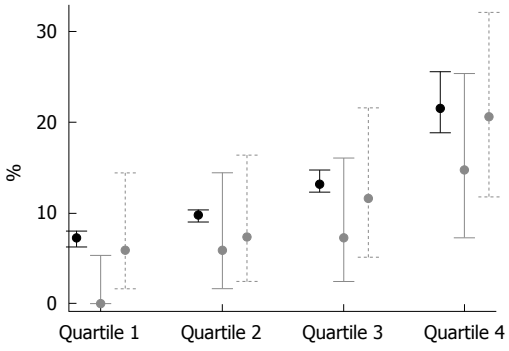

Figure 2 Logistic EuroSCORE, 30- and 90-d mortality by quartiles of Logistic EuroSCORE. Black capped spikes represent median and quartiles of Logistic EuroSCORE (LES) (LES predicted overall mortality for quartiles: 7.8, 9.8, 13.6, 26.5); gray capped spikes represent the percent 30-d (solid) and 90-d (dashed) mortality, with 95% CIs. Tests for trend: 30-d mortality, *P* = 0.001; 90-d mortality, *P* = 0.005. CI: Confidence interval.

1.40-3.22). Median survival time was estimated to be 4.2 years (IQR, 1.8-5.9 years) in the LES ⩾ 15 group and 8.7 years (IQR, 3.5-11.1 years) in the LES < 15 group. The overall duration of hospital stay was similar in the 2 groups, although high dependency unit stay was on average slightly longer in the LES ⩾ 15 group.

The LES distribution and 30-d mortality by LES quartiles is illustrated in Figure 2. As expected, mortality increased with increasing LES. Patients in the highest quartile were at particular risk (30-d mortality 15%; 95% CI: 7%-25%), whilst the lower risk quartiles showed excellent outcomes. The overall mortality in all risk quartiles was below the level predicted by the LES.

Although there were increasing numbers of patients operated over time, the LES and 30-d mortality of patients did not change markedly (Figure 3).

Survival of AVR patients was similar to that of AVR + CABG patients; the 30-d mortality of AVR was 6% (95% CI: 3%-11%), and of AVR + CABG was 8% (95% CI: 4%-14%). One-year survival was estimated to be 91% (95% CI: 85%-95%) in the AVR group compared with 82% (95% CI: 74%-88%) in the AVR + CABG group. Five-year survival was estimated to be 58% (95% CI: 46%-68%) in the AVR group and 57% (95% CI: 45%-67%) in the AVR + CABG group (Figure 4).

DISCUSSION

This analysis of surgical outcomes in octogenarians demonstrated the spectrum of operative risk and identified a low risk cohort with excellent acute and long-term results. Age alone should not be used as selection criteria for alternative non-surgical aortic valve implantation. Whilst the LES did not accurately predict mortality, the preoperative classification into lower or higher risk quartiles matched the incidence of adverse outcomes.

We used our surgical database to identify patients for this study. This database includes every patient operated

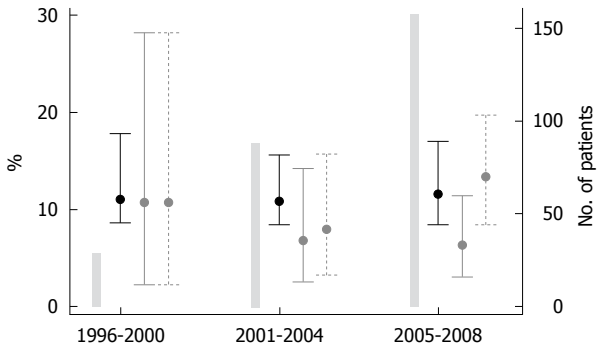

Figure 3 Logistic EuroSCORE, 30-d and 90-d mortality by operative era. Black capped spikes represent median and quartiles of Logistic EuroSCORE; gray capped spikes represent percent 30-d (solid) and 90-d (dashed) mortality, with 95% CIs. Bars represent the number of aortic valve replacement procedures. Tests for trend: 30-d mortality, $P = 0.49$; 90-d mortality, $P = 0.34$.

at our center, so we were able to identify all eligible patients; only 9 patients were excluded due to their notes being unavailable. Using the database and the individual patient case notes we were able to obtain a clinical dataset similar to the dataset collected for our TAVI patients. We were able to use the LES to assess outcomes in patient groups of particular interest: low and high risk for morbidity and mortality.

We identified a subgroup, those in the highest LES risk quartile, with high mortality and morbidity. Outcomes for this subgroup have not been reported previously in the surgical literature. The fact that the LES was able to discriminate between very low risk and very high risk patients prior to surgery, justifies its use in the selection process for the transcatheter programs. Patients in the highest risk quartile had a mortality of 15% (95% CI: 7%-25%). Comparing our high risk cohort with those in TAVI registries adds further support to the argument that this group of high risk patients may benefit from the transcatheter approach. In the PARTNER B trial, the rate of death from any cause was 30.7% with TAVI compared to 50.7% with standard therapy (including balloon aortic valvuloplasty)[5]. The trial concluded that TAVI significantly reduced the rates of death from any cause, despite a higher incidence of major strokes and major vascular events.

We were also able to document excellent results in the lower risk quartiles. In the lowest quartile the surgical outcomes were excellent with no deaths within 30 d (95% CI: 0%-5%). Any enrollment from this patient group into a transcatheter valve program should be done with great caution, as it would be difficult to improve on the results of the conventional approach with the associated known long-term outcome. Hence, age on its own is a poor indicator of surgical risk and age over 80 alone should not be the sole indication for TAVI.

The number of patients treated with AVR in our center increased exponentially over the 12-year study period. The average risk score did not change significantly. This would suggest that while the absolute number of elderly patients with symptomatic aortic stenosis increased, the

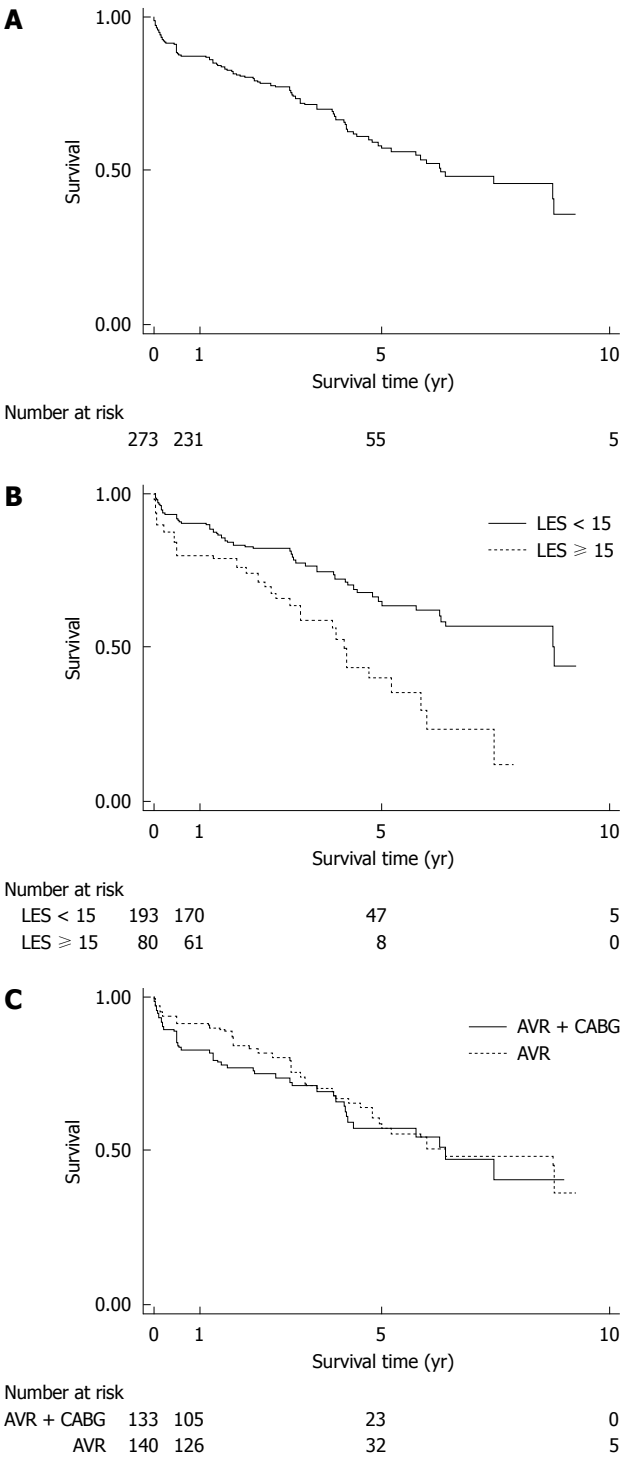

Figure 4 Kaplan-Meier survival curves. A: Overall; B: For Logistic EuroSCORE (LES) < 15/LES ⩾ 15; C: For aortic valve replacement (AVR)/AVR + coronary artery bypass grafting (CABG).

selection criteria for valve surgery did not expand into the very high risk cohort. There was an under-representation of patients with a prior history of CABG or patients with heavily calcified aorta (porcelain aorta). Prior revascularization is considered as a significant risk factor for surgical AVR, hence the under-representation which introduced a selection bias into the study. Whilst the LES was predictive of mortality, the selection of patients for

surgery involved clinical criteria that were not reflected in the LES or any other risk score, such as subjective assessment of frailty.

Previous studies have shown that with good clinical judgment on the part of the surgical and multidisciplinary team selecting patients for surgery, good outcomes for AVR surgery with or without CABG in octogenarians were possible, with previously reported mortality figures of 8%-10%[17,18]. The mortality we report [6% (95% CI: 3%-11%) for AVR and 8% (95% CI: 4%-14%) for AVR and CABG] are consistent with this and are also concordant with previous reports[15]. The surgical results are better than predicted by the LES (predicted mortality 11%), which has been shown previously in other series[13,19].

An LES ≥ 15 is currently used as a criterion for enrollment in the Corevalve registry. In this higher risk surgical cohort, the mortality was 14% (95% CI: 7%-23%) and there was a 6% rate of stroke, a 9% rate of serious infection and 4% incidence of bleeding requiring transfusion, with a median stay in the intensive care unit of 2 d. Only 44% of these patients were then discharged home, and a further 41% went on to recover in district general hospitals or rehabilitation centers. The rate of new pacemaker implantations in this cohort was also higher than previously reported (11%). This could be explained by the selection of patients for the study, which included only the octogenarian population who are more prone for sino-atrial node fibrosis and disease. The median survival in years was 4.19 (range, 1.83-5.94) in the LES ≥ 15 group compared to 8.74 years (range, 3.54-11.07 years) in the LES < 15 group. The 1-year and 5-year survival was 79% (95% CI: 68%-86%) and 40% (95% CI: 26%-55%), respectively, in the LES ≥ 15 group compared to 90% (95% CI: 85%-94%) and 64% (95% CI: 54%-72%), respectively, in the LES < 15 group.

In our study, the LES tended to significantly overestimate the perioperative mortality risk in all quartiles (Figure 2).

Piazza *et al*[2] recently reported on the outcome of the first 646 patients in the Corevalve registry, and Thomas *et al*[6] reported on the SOURCE registry for the Edwards Sapien vlave. In both cohorts, the average LES was over 20. Large proportions of patients included in these registries were not offered surgery and therefore are not comparable with the patients we have presented. Nevertheless, the overall outcomes for TAVI compare favorably with our results in patients with LES ≥ 15, that would now be considered for the transcatheter approach. The SOURCE registry revealed a 1-year survival rate of 81.1% in transfemoral procedures and 72% in transapical procedures. The mortality in both TAVI registries was lower, as was the hospital stay and reported morbidity. The rate of new pacemaker implantation appeared higher in the Corevalve registry than in the Sapiens Edwards series, but the difference compared to our surgical results may not be clinically relevant. The encouraging outcomes add to the evolving body of clinical evidence demonstrating that TAVI is a viable option for this high risk population.

As previously reported, long-term survival after a successful operation was excellent; overall 57% (95% CI: 49%-64%) of patients were alive at 5 years. The median length of stay in hospital was 11 d (IQR, 8-15 d) and 56% (n = 153) of patients were discharged directly to home. The rest were either transferred to a local hospital for recuperation (36%, n = 97) or died prior to hospital discharge (8%, n = 22). Whilst these lengths of stay data are in keeping with other reports[13,18], they are significantly longer than those for younger patients undergoing AVR in our center. This observation, coupled with the increasing number of patients, has implications for intensive care and hospital bed resource planning Economic analyses of TAVI cohorts may show that the benefits of percutaneous procedures may extend to hospital stay.

In the TAVI registries we found a large proportion of patients with previous bypass surgery (20.4%)[2] whilst only 5% of our patients had undergone surgical coronary revascularization. A repeat operation does carry an increased risk, whilst prior bypass surgery has no impact on the technical feasibility or risk of a transcatheter valve implantation. Furthermore, a porcelain (heavily calcified) aorta, present in up to 6.6% in the TAVI series, was not described in any of our patients selected for surgery.

A Canadian study of TAVI identified patient factors that can help in selecting appropriate patients for the procedure and further improve outcomes[20]. The study concluded that the transfemoral or transapical approach did not determine worse outcomes as much as patient factors, such as pulmonary hypertension, severe mitral regurgitation, chronic obstructive pulmonary disease and chronic kidney disease. Patients with a porcelain aorta (18%) or frailty (25%) exhibited acute outcomes similar to the rest of the study population. Porcelain aorta patients tended to have better survival rate at 1-year follow-up. Hence, it underscores the importance of patient selection to improve short- and long-term outcomes after TAVI.

This was a retrospective, single center series spanning 12 years of practice. The results improved with time, and hence surgical results in the modern era may now be better than reported for the whole cohort. No direct statistical analysis was attempted for comparison of this patient cohort with the patients enrolled into TAVI programs. Hence, all discussion and conclusions rely on descriptive parameters.

Whilst risk scoring systems are well developed for coronary artery bypass surgery, the optimal risk scoring system for aortic valve surgery is yet to be defined. Nevertheless, in this cohort, the LES was able to identify a group of patients at high risk of surgical AVR with a less favorable outcome, and a low risk group with an excellent outcome after surgical AVR. New scoring systems that take into account parameters relevant for surgical and transcatheter valve implantation are needed to characterize patients better and to guide selection of the best treatment option There is a clear under-representation of patients with a history of prior CABG or porcelain aorta in our cohort compared to published TAVI registries,

which reflects the surgical selection process in the past and highlights these patient groups as particularly relevant for alternative treatment options The outcomes after successful surgical AVR are good. However, the documented attrition rate in octogenarians is higher than in younger populations and this must be recognized when data from TAVI registries are interpreted.

COMMENTS

Background

Severe aortic stenosis occurs in the aging population, and the definitive treatment for the condition has been surgical aortic valve replacement (AVR) for the past few decades. Technological and scientific advancement has enabled us to perform percutaneous AVR in this era. Two types of percutaneous aortic valves are available: Edward Sapien and CoreValve. The selection criteria need to be robust so that high risk patients who are considered not suitable for surgical AVR can be offered percutaneous AVR. The present article highlights the risk factor profile of these patients by using the Logistic EuroSCORE (LES), which enables us to identify those at high risk and those at low risk.

Research frontiers

Percutaneous AVR is considered a safe alternative to surgical AVR in the octogenarian population with comorbidities. Studies are being conducted on 2 types of valves: Edward Sapien and the CoreValve. The type of approach is also being investigated: transfemoral, transapical, subclavian. Selection criteria and the appropriate imaging techniques before and during implantation are under intense debate.

Innovations and breakthroughs

The major innovations in the past few years have been the size of the CoreValve. Now it is available in 3 sizes. The surgeon can choose the appropriate size depending on the annular dimensions. Technology is advancing so that in future a retrievable percutaneous aortic valve will become available. Expertise in this field will enable us to offer the procedure to even low risk group.

Applications

The present article helps us to identify high risk and low risk patients. The LES is an important scoring system to identify these cases. It is easy to apply in our daily practice.

Terminology

Percutaneous AVR, transcatheter aortic valve implantation: a tissue heart valve is placed on a balloon-mounted catheter and guided *via* the femoral artery into the chambers of the heart and positioned directly over the diseased aortic valve. The balloon is then inflated to secure the valve in place.

Peer review

LES is used as a risk scoring tool to identify high risk group and low risk group. Frequently, it overestimates the predicted mortality. The article clearly shows the difference between the predicted mortality and the observed mortality. Hence patients should not be denied percutaneous aortic valve implantation based on LES alone. Each scoring system has its own pitfalls. The authors have clearly explained the difficulties of using the LES as the only scoring system and additional factors (frailty) need to be taken into account.

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BRIEF ARTICLE

Adequate antiplatelet regimen in patients on chronic anti-vitamin K treatment undergoing percutaneous coronary intervention

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Abstract

AIM: To investigate the impact of dual antiplatelet therapy (DAT) in patients on anti-vitamin K (AVK) regimen requiring percutaneous coronary intervention (PCI).

METHODS: Between February 2006 and February 2008, 138 consecutive patients under chronic AVK treatment were enrolled in this registry. Of them, 122 received bare metal stent implantation and 16 received drug eluting stent implantation. The duration of DAT, on top of AVK treatment, was decided at the discretion of the clinician. Adequate duration of DAT was defined according to type of stent implanted and to its clinical indication.

RESULTS: The baseline clinical characteristics of patients reflect their high risk, with high incidence of comorbid conditions (Charlson score $\geqslant$ 3 in 89% of the patients). At a mean follow-up of 17 ± 11 mo, 22.9% of patients developed a major adverse cardiac event (MACE): 12.6% died from cardiovascular disease and almost 6% had an acute myocardial infarction. Major hemorrhagic events were observed in 7.4%. Adequate DAT was obtained in only 44% of patients. In the multivariate analysis, no adequate DAT and Charlson score were the only independent predictors of MACE (both $P = 0.02$).

CONCLUSION: Patients on chronic AVK therapy represent a high risk population and suffer from a high MACE rate after PCI. An adequate DAT regimen and absence of comorbid conditions are strongly associated with better clinical outcomes.

Key words: Hemorrhagic risk; Anti-vitamin K treatment; Anti-platelet therapy; Percutaneous coronary intervention

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INTRODUCTION

Currently, the optimal antiplatelet regimen after stent implantation consists of a combination of aspirin and ADP-receptor antagonists, such as ticlopidine or clopidogrel, for the prevention of stent thrombosis[1,2]. The recommended duration of dual antiplatelet therapy (DAT) ranges from 4 wk following bare metal stent (BMS) implantation during elective angioplasty to at least 6 to 12 mo after drug eluting stent (DES) implantation. However, in some clinical situations, such as acute coronary syndromes (ACS), it should be extended to up to 12 mo with either BMS or DES[3].

The antiplatelet regimen of patients on long-term anti-vitamin K (AVK) treatment and who receive percutaneous coronary intervention (PCI) remains a challenge for the interventional cardiologist. This group of patients, indeed, includes a rather old population with comorbidities and a high risk of bleeding and cardiovascular events. Moreover, the risk of bleeding in these patients is increased by the addition of DAT but, on the other hand, a temporary discontinuation of anticoagulation may be associated with a high risk of thromboembolism[4].

The aim of this study was to evaluate the outcomes of patients under AVK therapy receiving PCI and to assess the relationship between duration of DAT, in addition to an AVK regimen, and clinical outcomes.

MATERIALS AND METHODS

Study population

Between February 2006 and February 2008 consecutive patients with an absolute indication for AVK treatment and who required PCI were prospectively included in the registry. There were no specific exclusion criteria. Patients were treated at the discretion of the interventional cardiologist, either with BMS or DES. The duration of DAT was variable, according to the clinician's prescription. Those patients who discontinued AVK treatment after index PCI were excluded from the analysis. Clinical and angiographic characteristics of all patients were prospectively recorded. In order to determine comorbidity in the patients, the Charlson score was calculated. Briefly, the Charlson score is the sum of 19 pre-defined comorbidities, that were assigned weights of 1, 2, 3 or 6 (Table 1). Overall, a value ⩾ 3 defines a high level of comorbidity[5].

Table 1 Charlson comorbidity index components and weights

Comorbid condition	Weight
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end-organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	6

AIDS: Acquired immune deficiency syndrome.

Procedure

Stent implantation was performed according to the experience of the interventional cardiologist following standard guidelines. Either direct stent implantation or balloon pre-dilatation was allowed. Glycoprotein Ⅱb/Ⅲa inhibitor administration was left to the interventional cardiologist's discretion. All patients were treated with a therapeutic dose of aspirin at the time of PCI (100 mg daily from at least 5 d before or 500 mg administered intravenously immediately before the procedure). Clopidogrel was administered in a loading 300 mg dose immediately before or after the procedure. As a routine strategy in our center, a radial approach was preferentially used in patients under AVK treatment. AVK therapy was not discontinued as long as the radial artery was patent with good collateral filling of the palmar arch from the ulnar artery (tested by the Allen maneuver or by plethysmography), and the international normalized ratio (INR) was lower than 4.0 at the time of the procedure. No additional anticoagulation was administered during PCI in these patients[6]. In the event that the radial artery could not be used for the above-mentioned reasons, AVK treatment was discontinued and substituted by a weight-adjusted dose of low molecular weight heparin (LMWH). Whenever INR was normalized, the procedure was performed *via* femoral artery. In such patients, PCI was performed under LMWH. AVK treatment was reinitiated within 24 h after the procedure while LMWH was finally discontinued as soon as the INR level rose above 2.0.

Definitions

The outcomes of the patients were assessed by measur-

ing the rates of major adverse cardiac events (MACE), including cardiac death, myocardial infarction or target lesion revascularization. Death was classified as cardiac and non-cardiac. Any death was considered cardiac unless a non-cardiac cause could be adjudicated.

Peri-procedural myocardial infarction was defined as a rise in the troponin T level above the upper reference limit. Acute myocardial infarction was defined as appearance of unequivocal ECG changes together with an increase in creatine kinase levels to at least twice the upper normal limit or an increase in troponin levels[7].

Any revascularization clinically indicated performed on the treated segment was defined as target lesion revascularization. Stent thrombosis was defined and categorized according to Academic Research Consortium, into early (within 30 d), late (more than 30 d to 1 year after stent implantation) and very late (more than 1 year after stent implantation) and into definitive, probable and possible[8].

Cerebrovascular events, including stroke (ischemic or hemorrhagic), cerebrovascular hemorrhage, transient ischemic attack, or reversible ischemic neurological deficits were diagnosed by a neurologist and confirmed by computed tomography scanning.

Bleeding complications were divided into minor and major, according to the TIMI scale[9]. Major bleeding was defined as the occurrence of intracranial or retroperitoneal bleeding, hemorrhage at the vascular access site requiring intervention, a reduction in hemoglobin levels of at least 5 g/dL, reoperation for bleeding or transfusion of a blood product (at least 2 U), or bleeding causing substantial hypotension requiring the use of inotropic agents. All other bleeding events were considered minor (e.g., epistaxis).

To specifically determine the relationship between duration of DAT and outcomes in this high risk population, we defined the adequate duration of DAT, according to the clinical setting and the type of stent implanted, as 1 mo for patients with an elective clinical condition who received a BMS, and 1 year for patients admitted for ACS, regardless of the stent implanted[3,10].

Clinical follow-up

Clinical follow-up was performed by clinical visit or telephone interview. The duration of DAT was specifically investigated by interview with the patient or the doctor who was in charge of the patient. Angiographic follow-up was not mandated unless it was clinically indicated by symptoms or a positive non-invasive test of ischemia.

Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables as counts and percentage. Continuous variables were compared using the independent sample Student *t* test or Mann-Whitney *U* test where appropriate. Categorical variables were compared with the Chi-square or Fisher exact test where appropriate.

Cumulative MACE-free survival was illustrated by the Kaplan-Meier method. We explored the adjusted independent predictors of MACE using Cox regression modeling. We specifically considered, as potential predictors of MACE and thus candidates to enter into the model, the following variables: clinical presentation as ACS, no adequate DAT, Charlson Comorbidity Index and type of stent implanted (BMS or DES). The Charlson Comorbidity Index represents a single aggregate measure of a patient's risk due to comorbid conditions and it has been well validated[11]. The proportional hazards assumption was tested to explore the time-dependence of covariates all at once. The results are presented as hazard ratio (HR) with 95% confidence interval (CI) and *P* value. Statistical significance was accepted for a two-sided value of $P < 0.05$. Analysis was performed with SPSS version 13 (SPSS Inc., Chicago, IL, United States).

RESULTS

Baseline characteristics

Baseline clinical characteristics are summarized in Table 2. During the study period, 138 consecutive patients (178 lesions) on chronic AVK treatment were treated by PCI with either BMS (88%) or DES (12%). All patients were maintained on AVK treatment during follow-up. Mean age was 70.7 ± 9.3 years, 30% of patients were diabetics, almost 22% had renal impairment, 33% had previous acute myocardial infarction and 89% had a Charlson score ⩾ 3. Of the total, 57% were admitted with ACS.

Angiographic and procedural data

Angiographic and procedural data are summarized in Table 3. A total of 178 lesions were treated with 222 stents implanted (196 BMS; 26 DES). Almost 75% of PCI were performed though a radial approach and 25% of stents were implanted without pre-dilatation. No closure devices were used in patients in whom the procedure was performed through a femoral approach. At the time of PCI, the mean INR value was 1.7 ± 0.6.

Compliance with DAT

At follow-up, 62 patients (44%) had adequate duration of DAT (12% of the patients with ACS and 89% of the patients without ACS). Mean duration of DAT was 3.1 ± 6.2 mo (BMS 2.2 ± 4.0 mo, DES 11.1 ± 10.3 mo). Specifically, in patients receiving BMS ($n = 122$) implantation, an adequate DAT regimen was obtained in 53 patients (43%). In the remaining 69 patients, 5 patients did not receive DAT at discharge (2 patients received only aspirin, one patient received clopidogrel alone, and 2 patients did not receive any antiplatelet agent at all) and 64 stopped DAT prematurely. In patients receiving DES implantation ($n = 16$), an adequate DAT regimen was obtained in 9 patients, while the remaining 7 stopped DAT prematurely. Overall, the reasons for stopping DAT prematurely included: medical decision ($n = 55$), clinical event ($n = 8$) and own patient decision ($n = 8$).

In hospital clinical outcomes

During hospitalization, 3 patients (1.7%) died from refractory heart failure related to their baseline clinical condi-

Table 2 Baseline clinical characteristics of the study population (*n* = 138)

	n (%)
Age (mean ± SD, yr)	70.7 ± 9.3
Female	29 (21.0)
Hypertension	95 (68.8)
Diabetes mellitus	44 (31.8)
Dyslipidemia	73 (52.9)
Smoking	34 (24.6)
Renal failure	30 (21.7)
Previous stroke	25 (18.1)
Vasculopathy	22 (15.9)
Previous coronary artery bypass graft	32 (23.1)
Previous percutaneous coronary intervention	21 (15.2)
Previous myocardial infarction	46 (33.3)
Charlson score (mean ± SD)	4.3 ± 1.6
Clinical presentation	
Asymptomatic	12 (8.7)
Stable angina	45 (32.6)
NSTEMI	58 (42.0)
STEMI	21 (15.2)
Indication to AVK treatment	
Atrial fibrillation	93 (67)
CHADS2 0	0 (0)
CHADS2 1	69 (75)
CHADS2 ⩾ 2	24 (25)
Pulmonary emboli	4 (2.9)
Systemic emboli	4 (2.9)
Isolated cardiomyopathy	14 (10.1)
Mechanical valve prosthesis	22 (15.2)
Thrombus in left ventricle	2 (1.4)
Number of diseased vessels	
1	79 (57.2)
2	41 (29.7)
3	16 (11.6)
Number of treated vessels	
1	118 (85.5)
2	20 (14.5)
Vessels diseased	
Left main	13
Left anterior descending	85
Left circumflex	52
Right coronary artery	69
Saphenous vein graft	4

AVK: Anti-vitamin K; NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; CHADS2: Stroke and transient ischemic attack score.

Table 3 Angiographic and procedural characteristics (*n* = 178) *n* (%)

Lesion type classification	
A	40 (23.1)
B	103 (59.5)
C	25 (17.4)
Chronic total occlusion	9 (5.2)
Bifurcation	30 (17.3)
Access site	
Transradial	133 (74.8)
Transfemoral	52 (25.2)
Direct stenting	45 (25.3)
DES	26 (14.6)
Length of implanted stents (mm, mean ± SD)	22.3 ± 11.6
Diameter of implanted stents (mm, mean ± SD)	3.18 ± 1.24
QCA analysis (mean ± SD)	
Reference diameter pre (mm)	2.9 ± 0.67
Reference diameter post (mm)	3.0 ± 0.55
MLD pre (mm)	0.74 ± 0.5
MLD post (mm)	2.6 ± 0.5
% stenosis pre	74.6 ± 16.1
% stenosis post	12.3 ± 8.9
Acute gain (mm)	1.8 ± 0.6

QCA: Quantitative coronary angiography; DES: Drug eluting stent; MLD: Minimal luminal diameter.

Table 4 Long-term clinical outcomes after discharge ([1]*n* = 178)

	n (%)
Major adverse cardiac events	31 (22.9)
Death	21 (15.5)
Cardiac death	17 (12.6)
Non-cardiac death	4 (2.9)
Myocardial infarction	8 (5.9)
Target lesion revascularization	15 (11.1)
Major hemorrhagic event	10 (7.4)
Stroke	
Hemorrhagic stroke	3 (2.2)
Ischemic stroke	2 (1.5)
Definite/probable stent thrombosis	6 (4.4)
Possible stent thrombosis	8 (5.9)

[1]Patients who died during index admission were excluded from this analysis.

tion. One patient (0.07%) suffered from a peri-procedural myocardial infarction, due to occlusion of a side branch. No cases of definitive or probable stent thrombosis were recorded. Five patients (3.6%) suffered from major hemorrhagic events during hospitalization. Specifically, we recorded 2 femoral pseudoaneurysms, 2 gastrointestinal hemorrhages and one patient had red blood cell transfusion for chronic anemia and blood loss during cardiac catheterization. In all these patients a femoral approach was used. No hemorrhagic events were observed in patients with the transradial approach.

Long-term clinical outcomes

Complete follow-up was available for 132 patients (98%). Mean clinical follow-up was 17 ± 11 mo. Long-term outcomes are summarized in Table 4.

Overall, a total of 21 patients (15.5%) died after discharge during clinical follow-up. Of these, cardiovascular death accounted for 17 patients (12.6%). The clinically-driven target lesion revascularization rate was 11.1% and incidence of myocardial infarction was 5.9%. The MACE rate was 3.0% in the first month, 9.8% in the first 3 mo and 14.3% in the first 6 mo after PCI.

We recorded 6 definitive or probable stent thromboses (4.4%). In particular, one of the two definitive stent thrombosies occurred 1 mo after BMS implantation in a patient who was on DAT and AVK treatment. The second definitive stent thrombosis occurred 40 d after the index procedure in a patient who received a BMS and was only on AVK treatment without any antiplatelet agent. The rate of possible stent thrombosis was 5.9%.

After categorizing the entire population by the du-

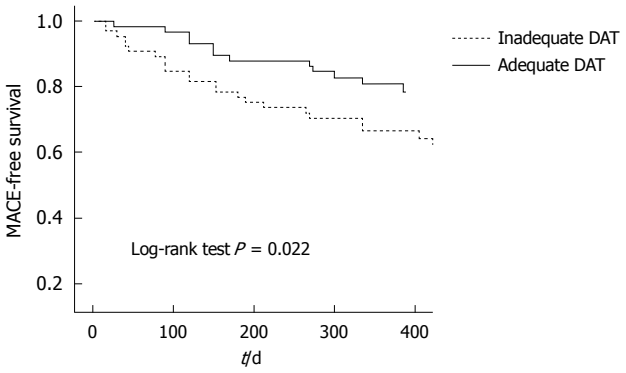

Figure 1 Cumulative Kaplan-Meier curves of major adverse cardiac events-free survival according to clinically adequate dual antiplatelet therapy, adjusted for type of stent and Charlson comorbidity index. MACE: Major adverse cardiac events; DAT: Dual antiplatelet therapy.

ration of DAT, as being adequate or not, the rate of MACE was higher in those patients with no adequate duration of DAT (log-rank test, $P = 0.029$). In the multivariable analysis, the only variables independently associated with MACE were no adequate DAT (HR, 5.30, 95% CI: 1.19-23.55, $P = 0.02$) and Charlson Comorbidity Index (HR, 1.6, 95% CI; 1.06-2.42, $P = 0.02$). Figure 1 presents the cumulative MACE-free survival according to adequate DAT status, adjusted for Charlson Comorbidity Index ($P = 0.022$).

Regarding hemorrhagic events, there were 10 major hemorrhagic episodes (7.4%) during follow-up. In particular, 3 patients died of a hemorrhagic stroke, 3 required red blood cell transfusion, 3 had a gastrointestinal hemorrhage and one had hematuria, requiring red blood cell transfusion. One of the hemorrhagic strokes occurred in a patient who received a BMS, was on aspirin and the INR was above 9. Only half of major hemorrhagic events ($n = 5$) occurred in patients on concomitant treatment with DAT and AVK. No difference was found in hemorrhagic event rates between patients categorized according to adequate DAT or not.

DISCUSSION

The major findings of this analysis are: (1) patients on a chronic anticoagulation regimen represent a highly comorbid population, as shown by a high value of the Charlson score (mean, 4.3) and had a high incidence of MACE after PCI; and (2) no adequate DAT and a high Charlson score seem to be the main independent predictors of events in this population.

Patients who have clear evidence-based indications for long-term AVK treatment represent nearly 10% of patients referred for PCI[12]. This group of patients generally includes a high-risk profile population with comorbid conditions and high risk of ischemic and bleeding events. The Charlson score, an index of their comorbidities, was high in our population (≥ 3 in 89% of the patients) and was one of the independent predictors of MACE at follow-up. The high MACE rate at follow-up (22.9%) was similar to that found by Rogacka *et al*[13] who compared the long-term outcomes in a similar cohort of patients (23.6%). In another study of 426 patients with atrial fibrillation undergoing PCI, Ruiz-Nodar *et al*[14] demonstrated a MACE rate of 36.6% and a major bleeding incidence of 12.3% at 2 years.

DAT on top of AVK treatment in this category of patients is known to increase their risk of bleeding[4]. For this reason, in daily practice, various antithrombotic combinations were used in the past[13-15]. Karjalainen *et al*[12] assessed the safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. The rate of stent thrombosis was highest (15.1%) in patients receiving a warfarin plus aspirin combination without the addition of clopidogrel. This is in agreement with the results of 4 randomized trials (ISAR, FANTASTIC, STARS, and MATTIS) that showed that warfarin plus aspirin combination after PCI is not as effective as DAT in preventing stent thrombosis[16-18]. Recently, Lip *et al*[10] defined a consensus on the "best practice" antiplatelet regimen of patients who are on concomitant treatment with long-term AVK for atrial fibrillation, according to the clinical indication of PCI (ACS or not) and the type of stent implanted (DES or BMS). Our analysis, applying this definition of adequate DAT to a wider population requiring AVK not only for atrial fibrillation, confirms the importance of ensuring a correct DAT according to the clinical scenario of the patient and to the stent implanted. Of note, for those patients with atrial fibrillation and a $CHADS_2$ score of 1, the benefit of AVK treatment *vs* aspirin alone is not well established; a large randomized trial would be required to justify withdrawing of the AVK regimen in these patients when they received a PCI.

Most of the concerns about a prolonged duration of DAT on top of AVK treatment come from the occurrence of hemorrhagic events or local complications at the site of arterial access. A femoral approach has been associated with higher hemorrhagic complications in AVK patients, as was confirmed in our study, while a radial approach is safe[19]. In the series from Orford *et al*[20] and Karjalainen *et al*[12], the incidence of all major bleeding events while on triple therapy (DAT plus warfarin) ranged from 3.1% to 6.6% during follow-up. In our population, the occurrence of major hemorrhagic events during triple therapy was 7.2%, but it could be underestimated due to a lack of complete compliance to DAT.

The type of stent that has to be implanted in a patient on AVK therapy is another important issue to consider; the clinician should weigh the potential bleeding risk derived from prolonged DAT against the risk and consequences of restenosis of a BMS. In many instances, the balance between risk and benefit may lead the clinician to choose a BMS in order to commit the patient to a short course of DAT in addition to warfarin, as reported in our cohort where 88% of the stents implanted were BMS. Ruiz-Nodar *et al*[21] showed that the routine use of DES in patients with atrial fibrillation did not seem to be justified because of the higher risk of major bleeding with

DES in comparison with BMS: an alternative is to implant a DES for treatment of very high-risk lesions and to accept a small-to-moderate risk of bleeding. Sarafoff *et al*[22] also showed that use of some clinical and echocardiographic criteria can help to define the antithrombotic/anticoagulation therapy in patients on chronic AVK undergoing DES implantation.

This was a retrospective study. The sample size of this study did not allow demonstration of differences in efficacy between BMS and DES nor the formulation of reliable recommendations. Thus, conclusions regarding the best stent for restenosis prevention in such a population cannot be drawn from this analysis. The single center registries are often not representative and for this reason we included a real-world population as large as possible.

Due to the period of inclusion of the historical cohort, we could not use the European Society of Cardiology/American Heart Association/American College of Cardiology consensus definition of myocardial infarction[23]. Thus, comparison of myocardial infarction rates between groups was based on the classical World Health Organization definition[7]. This definition, however, has been historically used in most of the studies on AVK patients.

In conclusion, patients on AVK requiring PCI and stent implantation represent a high risk population with a high rate of comorbid conditions. Overall, an appropriate DAT regimen according to the type of stent implanted and to its clinical indication, appears crucial in order to avoid MACE.

COMMENTS

Background

Patients who receive anti-vitamin K (AVK) treatment have a high risk of bleeding and of ischemic events. For these reasons, every time that a percutaneous coronary intervention (PCI) with stent implantation is needed, the interventional cardiologist has to balance the increased risk of bleeding by adding dual antiplatelet therapy (DAT) on top of AVK with the high rate of event recurrence. Normal clinical practice implies, indeed, that patients with a high risk of event recurrence receive a drug-eluting stent instead of a conventional bare metal stent. However, the 1-year duration of DAT that is needed in the case of a drug-eluting stent could expose those patients to a high risk of bleeding events.

Research frontiers

Few recommendations are currently given for PCI in patients under AVK treatment, either for the type of stent to be implanted (drug-eluting or not) or the duration of DAT.

Innovations and breakthroughs

This study represents a real world scenario for the treatment of such patients, where the duration of DAT and the type of stent implanted is left to the discretion of the clinician. No inclusion or exclusion criteria were used. The adequacy of DAT according to the stent implanted and to the baseline clinical condition has been analyzed and related to long-term events.

Applications

The major findings of the study are that patients under long-term AVK treatment represent a highly comorbid population with a high incidence of major adverse cardiac and bleeding events at follow-up. Although it is difficult to specify the duration and quality of DAT associated with an AVK regimen, the absence of adequate DAT according to the stent implanted or to the clinical conditions is the main independent predictor of events and should be keep in mind whenever these patients receive PCI.

Terminology

AVK drugs are a class of drug which inhibit blood coagulation in order to reduce the probability of ischemic events related to thrombi formation. DAT consists of aspirin plus an ADP-inhibitor and is currently prescribed to all patients who receive stent implantation.

Peer review

The limitations of the analysis are related to the small number of the patients and to its retrospective nature. Nevertheless, it adds an important piece of information to the number of studies that already provide some guidance for avoidance of premature DAT discontinuation.

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London, United Kingdom

Februrary 24-26
Abdominal Obesity 2011 - 2nd International Congress on Abdominal Obesity
Buenos Aires, Argentina

Februrary 25-27
CardioRhythm 2011
Hong Kong, China

March 19-26
Cardiology Update: Caribbean Cruise
San Diego, CA, United States

March 25
Cardiology for General Practice
London, United Kingdom

April 1-2
11th Annual Spring Meeting on Cardiovascular Nursing
Brussels, Belgium

April 14-16
EuroPRevent 2011
Genova, Switzerland

April 30-May 4
ATC 2011 - 2011 American Transplant Congress
Philadelphia, United States

May 11-14
3th Radiochemotherapy and Brachitherapy Congress & 6th Medical Physycs Meeting
Córdoba, Argentina

May 15-18
ICNC10 - Nuclear Cardiology and Cardiac CT
Amstedan, The Netherlands

May 19-20
Adult Cardiovascular Pathology
London, United Kingdom

May 20-22
XXIX NATIONAL CARDIOLOGY CONGRESS
Córdoba, Argentina

May 20-22
4th Meeting Uremic Toxins and Cardiovascular Disease
Groningen, The Netherlands

May 21-24
Heart Failure Congress 2011
Gothenburg, Sweden

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Shanghai, China

June 26-29
EHRA EUROPACE 2011
Madrid, Spain

June 29-July 1
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INSTRUCTIONS TO AUTHORS

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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