Risk factors for recurrence of atrial fibrillation in patients undergoing hybrid therapy for antiarrhythmic drug-induced atrial flutter

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\textbf{Aims} Catheter ablation of the inferior vena cava—tricuspid annulus isthmus and continuation of antiarrhythmic drug therapy have been shown to be an effective hybrid therapy for atrial flutter which results from antiarrhythmic drug treatment of atrial fibrillation. The aim of this study was to determine the risk factors for recurrence of atrial fibrillation in patients undergoing hybrid therapy for antiarrhythmic drug-induced atrial flutter.

\textbf{Methods and results} 90 patients with paroxysmal (n=46) or persistent atrial fibrillation (n=44) developed atrial flutter due to the administration of amiodarone (n=48), flecainide (n=22), propafenone (n=14) or sotalol (n=6). Recurrence of atrial fibrillation after ablation was assessed during follow-up on continued antiarrhythmic drug therapy and during long-term follow-up, irrespective of the initial antiarrhythmic medication. During the follow-up on continued antiarrhythmic drug therapy (16±13 months), recurrence of atrial fibrillation was documented in 24 of 90 patients (27%). The presence of accompanying pre-ablation episodes of atrial fibrillation on antiarrhythmic treatment (Odds ratio 7.1, 95% confidence interval 2.3 to 25, p=0.001) and decreased left ventricular ejection fraction (Odds ratio 3.7, 95% confidence interval 1.01 to 12.5, p=0.048) were significant and independent predictors of post-ablation atrial fibrillation. Antiarrhythmic medication was discontinued during long-term follow-up due to adverse drug effects (amiodarone, n=12; flecainide, n=1) in 13 patients (14%). During the long-term follow-up, irrespective of the initial antiarrhythmic medication (21±15 months), stable sinus rhythm was maintained in 60 of 90 patients (67%).

\textbf{Conclusion} Hybrid therapy can be considered as the first line therapy for patients with antiarrhythmic drug-induced atrial flutter but patients should be carefully evaluated for accompanying pre-ablation episodes of atrial fibrillation and possible adverse drug effects before initiation of hybrid therapy.

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\textbf{KEYWORDS} Atrial fibrillation; Atrial flutter; Catheter ablation
Introduction

Typical atrial flutter can be documented following initiation of antiarrhythmic drug treatment in patients with paroxysmal or persistent atrial fibrillation. Catheter ablation of the inferior vena cava — tricuspid annulus isthmus and continuation of antiarrhythmic drug therapy have been shown to be an effective treatment of antiarrhythmic drug-induced atrial flutter.1–4 Although a high initial rate of stable sinus rhythm has been described in patients with hybrid therapy, post-ablation atrial fibrillation can occur during follow-up despite the continuation of antiarrhythmic medication. Several clinical issues remain to be settled with regard to such hybrid therapy. Among these, it has not been clearly defined whether the risk of recurrent atrial fibrillation is influenced by the antiarrhythmic agent used. Secondly, although several clinical variables are known to be associated with atrial fibrillation, the risk factors for the recurrence of atrial fibrillation in patients undergoing hybrid therapy have not been identified. Thirdly, long-term antiarrhythmic drug therapy may be limited by adverse drug effects, but long-term follow-up data after isthmus ablation, with or without continuation of antiarrhythmic drugs, is not available. To address these issues, a study was conducted to determine predictors for the recurrence of atrial fibrillation after ablation of drug-induced atrial flutter. In addition, the long-term post-ablation follow-up of patients with prior antiarrhythmic drug-induced atrial flutter, irrespective of the initial antiarrhythmic drug therapy, was examined.

Methods

Patients

The study population consisted of 90 consecutive patients with typical atrial flutter induced by antiarrhythmic drug therapy for paroxysmal or persistent atrial fibrillation. Typical atrial flutter was defined as an inverted sawtooth pattern in the inferior ECG leads which had not been documented before the initiation of antiarrhythmic drug therapy. All patients underwent non-invasive cardiac examination including M-mode and two-dimensional echocardiography with colour Doppler flow analysis. Left atrial enlargement was diagnosed as a left atrial diameter >40 mm. Definition of structural heart disease included left ventricular fractional shortening (echocardiogram) <30%, left ventricular ejection fraction (angiography) <60%, significant coronary heart disease or valvular heart disease or another congenital or acquired cardiomyopathy. Persistent atrial fibrillation or atrial flutter was diagnosed if it required termination by medical or electrical cardioversion to sinus rhythm.

Electrophysiological study

Written informed consent was obtained from all patients. All patients with persistent atrial flutter had been anticoagulated for at least three weeks before the electrophysiological study, otherwise the existence of thrombi in the left atrium had to be excluded by transesophageal echocardiography. All antiarrhythmic agents except amiodarone were discontinued at the time of the procedure to avoid antiarrhythmic drug-induced depression of atrial conduction velocity which can make the detection of residual trans-isthmus conduction during the ablation procedure in some patients more difficult. Multipolar electrode catheters were positioned in the infero-anterior right atrium, the His bundle region and the coronary sinus ostium. Annular activation during atrial flutter or atrial pacing was assessed by a 20-pole electrode halo catheter (Cordis Webster, 2–7–2 mm intervals). In patients with atrial flutter at the onset of the procedure, mapping, transient entrainment and overdrive stimulation to restore sinus rhythm were performed. In patients presenting with sinus rhythm, induction of atrial flutter was attempted by programmed stimulation with single and double extrastimuli and by atrial burst pacing. Electrophysiological definition of typical atrial flutter was based on the typical activation sequence in counter-clockwise or clockwise direction in the right atrium and by the criteria of entrainment as described by Waldo et al.5 When atrial fibrillation was present at the beginning of the electrophysiologic study or occurred during the procedure, it was terminated by a synchronized direct current shock under brief anaesthesia with propofol. In patients with recurrent atrial fibrillation, only limited attempts were made to induce atrial flutter.

Catheter ablation

Linear lesions between the tricuspid annulus and the inferior vena cava were made by a point-by-point ablation with a 4 mm-tipped ablation catheter (Cordis-Webster, 8F). A 500 kHz ablation unit was used for ablation. The current was initially applied at a power output of 10 W and was increased by 5 W every 5–10 s to a maximum output of 30–40 W and was continued for 60–80 s. Delivery of impulses was guided by impedance control6 and
was immediately stopped if an impedance rise was imminent or if the catheter was displaced. Radiofrequency energy was applied during continuous pacing from the proximal coronary sinus (cycle length 600 ms). Complete bidirectional block was the end-point of the ablation and was said to be present (1) if pacing from the proximal coronary sinus resulted in counter-clockwise activation of the tricuspid annulus with latest activation at the infero-anterior tricuspid annulus, (2) if pacing from the infero-anterior tricuspid annulus resulted in clockwise activation of the tricuspid annulus with latest activation in the proximal coronary sinus, (3) if double potentials were present along the whole ablation line and (4) if typical atrial flutter could no longer be induced by programmed atrial stimulation. All patients received an initial bolus of 5000 IE heparine after the insertion of catheters. All patients underwent electrophysiological re-evaluation 30 min after the catheter ablation and were monitored for at least 24 h in our clinic.

Follow-up

Patients were instructed to continue the antiarrhythmic agent which had initiated the conversion of atrial fibrillation to typical atrial flutter. Most patients received warfarin to maintain INR 2.5–3.5 for at least one month after the ablation. In some patients presenting with sinus rhythm, no indication for systemic anticoagulation existed and they were treated with aspirin 100 mg daily after the ablation. After catheter ablation, each patient was evaluated by a standard 12-lead ECG and trans-thoracic echocardiography. All patients had a close follow-up in our out-patient clinic or by their treating physician. Additionally, all patients were contacted by telephone at the time of writing to confirm their clinical status. Patients with palpitations or symptoms suggestive of atrial fibrillation or atrial flutter underwent ECG and Holter ECG monitoring. Recurrent atrial fibrillation was diagnosed if it was documented by ECG or Holter monitoring. In addition, patients were asked to report whether their clinical situation was improved, unchanged or worsened and whether undesirable effects of the ablation procedure or the drug therapy had occurred. In case of withdrawal or change of the antiarrhythmic drug, the reason for this therapeutic decision was inquired from the patients or their physicians.

Statistical methods

Data are reported as means±SD or as nominal values. Statistical analysis of the variables of the four treatment groups (amiodarone, flecainide, propafenone, sotalol) was performed using multivariate analysis (ANOVA). Univariate analysis of factors associated with the recurrence of atrial fibrillation was performed with the U-test for continuous variables and the Chi² test for nominal variables. Logistic regression analysis was performed to determine independent predictors for recurrence of atrial fibrillation using forward selection with p (inclusion)=0.05 and p (exclusion)=0.10. Univariate analysis of factors associated with early vs late atrial fibrillation was performed using the exact U-test for continuous variables and the exact Fisher-test for nominal variables. The statistical program SPSS version 11.0.1 was used. A p value <0.05 (two-sided) was considered statistically significant.

Results

Study population

Between June 1998 and June 2002, 550 patients with typical atrial flutter underwent isthmus ablation for atrial flutter in the electrophysiological laboratory at our institution. In 90 patients (16%), the paroxysmal or chronic atrial flutter had been initiated by antiarrhythmic drug treatment of paroxysmal or persistent atrial fibrillation (without preexisting atrial flutter). Baseline patient characteristics and variables of drug-induced atrial flutter are summarized in Table 1. At the time of the initiation of atrial flutter, the patients were on therapy with amiodarone (202±38 mg per day; n=48), flecainide (202±24 mg per day; n=22), propafenone (654±182 mg per day; n=14) or sotalol (240±72 mg per day; n=6). Among these four subgroups, no significant differences were found according to age, gender, duration of atrial arrhythmias, presence of arterial hypertension and left atrial enlargement. Persistent (in comparison to paroxysmal) atrial fibrillation before documentation of drug-induced atrial flutter was more frequent in patients on amiodarone treatment compared to patients on flecainide treatment (p<0.05). Presence of structural heart disease and decreased left ventricular function (fractional shortening <30%) were more frequent in amiodarone-treated patients than in patients on therapy with flecainide or propafenone (p<0.05).

Antiarrhythmic drug-induced atrial flutter

After initiation of antiarrhythmic drug therapy, atrial flutter was the only pre-ablation atrial arrhythmia documented in 70 of 90 patients (78%).
Episodes of atrial fibrillation (on antiarrhythmic drug therapy) were additionally found in 20 patients. The rate of accompanying pre-ablation atrial fibrillation was higher in patients on therapy with propafenone or sotalol than in patients on therapy with flecainide or amiodarone (p<0.05) (Table 1). Cycle length of drug-induced atrial flutter and direction of wavefront propagation (counter-clockwise or clockwise) were not significantly different between the four treatment groups (clockwise typical atrial flutter in 7% of patients). Rapid ventricular rate due to atrial flutter with 1:1 conduction to the ventricles was more frequent in patients on treatment with flecainide or propafenone than on amiodarone therapy (p<0.05).

### Entrainment stimulation

At the beginning of the procedure, 32 patients were in ongoing typical atrial flutter. Sinus rhythm or atrial fibrillation was present in 48 and 10 patients, respectively. Atrial flutter was induced or occurred spontaneously during the procedure in 15 patients initially presenting with sinus rhythm or atrial fibrillation. Entrainment manoeuvres confirmed isthmus dependence of atrial flutter in 47 patients (52% of total population). In the remaining 43 patients, typical atrial flutter on antiarrhythmic drug therapy was documented by 12 lead ECG recordings but was not induced during the electrophysiologic study.

### Isthmus ablation

Complete bidirectional isthmus block could be achieved in 85 of 90 patients (94%) in the first ablation procedure and in the remaining five patients in a second ablation procedure. All five patients with incomplete isthmus block after the first procedure had clinical recurrence of typical atrial flutter within the first 2 months after ablation. Recurrence of typical atrial flutter despite successful isthmus ablation was observed in three patients and was due to recurrence of trans-isthmus conduction. Successful re-ablation abolished the atrial flutter in these three patients. One patient developed a transient ischaemic neurological deficit 2 days after the ablation. No other complications associated with the ablation or electrical cardioversion were observed.

### Antiarrhythmic drug therapy after isthmus ablation

All patients continued to receive the antiarrhythmic agent, which had initiated the conversion of atrial fibrillation to atrial flutter, for at least 2 months after the successful ablation. During the long-term follow-up after isthmus ablation, the initial antiarrhythmic medication was discontinued by 27 of 90 patients (30%) (Fig. 1). 14 patients were placed on another antiarrhythmic medication due to non-effectiveness of the initial medication (recurrent atrial fibrillation). In 13 patients, the antiarrhythmic drug therapy was withdrawn due to undesirable or toxic drug effects.

### Post-ablation atrial fibrillation on continued antiarrhythmic medication

Spontaneous atrial fibrillation occurred in 24 of 90 patients (27%) on continued antiarrhythmic drug

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**Table 1** Clinical characteristics and variables of drug-induced atrial flutter

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Amiodarone</th>
<th>Flecainide</th>
<th>Propafenone</th>
<th>Sotalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>48</td>
<td>22</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Age, years±SD</td>
<td>64±9</td>
<td>61±8</td>
<td>63±12</td>
<td>62±10</td>
</tr>
<tr>
<td>Sex, n male</td>
<td>42 (88%)</td>
<td>16 (73%)</td>
<td>10 (71%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Symptom duration, years±SD</td>
<td>4.2±3.7</td>
<td>6.2±5.9</td>
<td>4.1±4.9</td>
<td>2.8±1.6</td>
</tr>
<tr>
<td>Form of atrial fibrillation, n persistent</td>
<td>31 (65%)</td>
<td>4 (18%)a</td>
<td>7 (50%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Structural heart disease, n</td>
<td>29 (60%)</td>
<td>4 (18%)a</td>
<td>2 (14%)a</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Arterial hypertension, n</td>
<td>23 (48%)</td>
<td>8 (36%)</td>
<td>6 (43%)</td>
<td>0</td>
</tr>
<tr>
<td>Left ventricular fractional shortening &lt;30%, n</td>
<td>15 (31%)</td>
<td>0a</td>
<td>0a</td>
<td>0a</td>
</tr>
<tr>
<td>Left atrial enlargement, n</td>
<td>38 (79%)</td>
<td>11 (50%)</td>
<td>9 (64%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Accompanying pre-ablation episodes of atrial fibrillation, n</td>
<td>7 (15%)</td>
<td>4 (18%)a</td>
<td>6 (43%)a</td>
<td>3 (50%)a</td>
</tr>
</tbody>
</table>

**Variables of drug-induced atrial flutter**

| Rapid ventricular rate due to 1: 1 conduction to the ventricle | 2 (4%) | 4 (18%)a | 4 (29%)a | 0 |
| Clockwise atrial flutter | 4 (8%) | 1 (5%) | 0 | 1 (17%) |
| Cycle length, ms±SD | 269±65 | 269±43 | 282±52 | 282±45 |

*a* Significantly different from amiodarone-treated patients, p<0.05.

*b* Significantly different from flecainide-treated patients, p<0.05.
therapy during the follow-up of 16±13 months after ablation. In 15 of the 24 patients with post-ablation atrial fibrillation, the atrial fibrillation occurred within the first month after ablation (early atrial fibrillation) and in the remainder occurred from 2 to 36 months after the procedure (late atrial fibrillation). The post-ablation atrial fibrillation was paroxysmal in 16 patients and persistent in 8 patients. Post-ablation atrial fibrillation occurred in 25% of patients on continued therapy with amiodarone, 18% on flecainide, 36% on propafenone and 50% on sotalol. There was no significant difference in the rate of post-ablation atrial fibrillation between the four treatment groups (Table 2).

Predictors of post-ablation atrial fibrillation

Several pre-ablation clinical variables known to be associated with atrial fibrillation in other populations were tested with regard to their influence on the probability of atrial fibrillation during follow-up (Table 3). By univariate analysis, only a history of accompanying pre-ablation episodes of atrial fibrillation (Odds ratio 7.1, 95% confidence interval 2.3 to 25, p=0.001) and decreased left ventricular ejection fraction (Odds ratio 3.7, 95% confidence interval 1.01 to 12.5, p=0.048) were significant and independent predictors of post-ablation atrial fibrillation on continued antiarrhythmic medication.

The rate of post-ablation atrial fibrillation on continued antiarrhythmic medication was 18%, if atrial flutter was the only atrial arrhythmia on antiarrhythmic drug therapy. In these patients, presenting with drug-induced atrial flutter without accompanying episodes of atrial fibrillation, there was no significant difference between amiodarone (17%) and class IC antiarrhythmic drugs (15%) (Fig. 2).

Adverse effects of antiarrhythmic medication during follow-up

There were no life-threatening adverse drug effects. Antiarrhythmic medication was discontinued due to adverse drug effects in 13 patients (14%). The adverse drug effects were reversible after withdrawal of the antiarrhythmic agent in all patients. Undesirable or toxic drug effects leading to withdrawal of the medication were more frequent in amiodarone-treated patients (n=12) than in patients treated with flecainide (n=1), propafenone (n=0) or sotalol (n=0) (p<0.05). Sinus bradycardia (n=2), hyperthyroidism (n=2), ocular side effects (n=2) and gastrointestinal or neurological disturbances (n=6) were associated with long-term amiodarone therapy. Ventricular pro-arrhythmia occurred in one patient treated with flecainide. Discontinuation of the initial antiarrhythmic medication due to toxic or undesirable side effects was associated with recurrence of paroxysmal or persistent atrial fibrillation in eight of 13 patients.

Change of antiarrhythmic medication

During the long-term follow-up of 21±15 months, the antiarrhythmic medication was changed due to ineffectiveness in 14 patients and due to adverse side effects in 13 patients. After discontinuation of amiodarone therapy, 11 patients were placed on β-blockers and five patients had no antiarrhythmic medication (Fig. 1). Following discontinuation of class IC antiarrhythmic medication in nine patients, four patients were placed on amiodarone, three patients were placed on β-blocker, one patient...
with prior propafenone therapy was placed on flecainide and one patient had no antiarrhythmic medication (Fig. 1). The two patients, in whom sotalol treatment was discontinued, were treated with amiodarone.

**Long-term follow-up after isthmus ablation**

Overall, at the end of the follow-up period, stable sinus rhythm was documented in 60 of 90 patients (67%) and symptomatic improvement was reported from 88% of patients. In patients with amiodarone-induced atrial flutter, 62% of patients (irrespective of the initial amiodarone therapy) remained in stable sinus rhythm and 88% of patients reported symptomatic improvement. In the group of patients who had undergone isthmus ablation for class IC antiarrhythmic drug-induced atrial flutter, stable sinus rhythm was documented in 77% (flecainide) and 64% (propafenone) of patients and symptomatic improvement was reported from 91% and 86% of patients, respectively. Of the six patients with sotalol-induced atrial flutter, three/six remained in stable sinus rhythm and five/six reported symptomatic improvement. The rate of stable sinus rhythm during long-term follow-up and the rate of symptomatic improvement was not significantly different between patients undergoing hybrid therapy with amiodarone, flecainide, propafenone or sotalol (Table 2) (Fig. 3).

**Discussion**

To our knowledge, this is the largest series published thus far of patients undergoing hybrid therapy for antiarrhythmic drug-induced atrial flutter. Recurrence of atrial fibrillation was assessed during follow-up on continued antiarrhythmic drug

| Table 2 | Follow-up after isthmus ablation for drug-induced atrial flutter on continued antiarrhythmic medication and during long-term follow-up |
|------------------|------------------|------------------|------------------|------------------|
|                  | Amiodarone | Flecainide | Propafenone | Sotalol |
| Patients, n      | 48         | 22         | 14          | 6       |
| Follow-up on continued antiarrhythmic medication, months±SD | 17±15 | 16±13 | 13±10 | 11±7 |
| Recurrence of atrial flutter, n | 5 (10%) | 1 (5%) | 2 (14%) | 0 |
| Recurrence of atrial fibrillation on continued antiarrhythmic therapy, n | 12 (25%) | 4 (18%) | 5 (36%) | 3 (50%) |
| Long-term follow-up, irrespective of initial antiarrhythmic medication, months±SD | 23±16 | 18±14 | 16±9 | 14±9 |
| Adverse effects leading to withdrawal of antiarrhythmic therapy during long-term follow-up, n | 12 (25%) | 1 (5%) | 0 | 0 |
| Change of antiarrhythmic medication during long-term follow-up, n | 16 (33%) | 5 (23%) | 4 (29%) | 2 (33%) |
| Recurrence of atrial fibrillation during long-term follow-up, n | 18 (38%) | 5 (23%) | 5 (36%) | 2 (33%) |
| Symptomatic improvement | 42 (88%) | 20 (91%) | 12 (86%) | 5 (83%) |

*a* significantly different from amiodarone-treated patients, *p*<0.05.

| Table 3 | Univariate predictors for the recurrence of atrial fibrillation on continued antiarrhythmic medication |
|------------------|------------------|------------------|
|                  | No atrial fibrillation | Atrial fibrillation |
| Patients, n      | 66         | 24         |
| Age, y±SD        | 64±10 | 61±9 | 0.051 ns* |
| Sex, n male      | 52 (79%) | 21 (88%) | 0.350 ns* |
| Symptom duration, y±SD | 4.1±3.9 | 6.1±5.6 | 0.097 ns* |
| Form of atrial fibrillation, n persistent | 29 (44%) | 15 (63%) | 0.119 ns* |
| Structural heart disease, n | 27 (41%) | 10 (42%) | 0.948 ns* |
| Arterial hypertension, n | 28 (42%) | 9 (38%) | 0.675 ns* |
| Left ventricular shortening fraction <30%, n | 9 (14%) | 6 (25%) | 0.201 ns* |
| Left atrial enlargement, n | 46 (70%) | 16 (67%) | 0.784 ns* |
| Accompanying pre-ablation episodes of atrial fibrillation, n | 9 (14%) | 11 (46%) | 0.001 |
| Class IC vs. III antiarrhythmic drug, n class IC | 27 (41%) | 9 (38%) | 0.770 ns* |
| Follow-up, months±SD | 19±14 | 23±14 | 0.333 ns* |

*a* ns=Not significant.

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**With prior propafenone therapy was placed on flecainide and one patient had no antiarrhythmic medication (Fig. 1). The two patients, in whom sotalol treatment was discontinued, were treated with amiodarone.**

**Long-term follow-up after isthmus ablation**

Overall, at the end of the follow-up period, stable sinus rhythm was documented in 60 of 90 patients (67%) and symptomatic improvement was reported from 88% of patients. In patients with amiodarone-induced atrial flutter, 62% of patients (irrespective of the initial amiodarone therapy) remained in stable sinus rhythm and 88% of patients reported symptomatic improvement. In the group of patients who had undergone isthmus ablation for class IC antiarrhythmic drug-induced atrial flutter, stable sinus rhythm was documented in 77% (flecainide) and 64% (propafenone) of patients and symptomatic improvement was reported from 91% and 86% of patients, respectively. Of the six patients with sotalol-induced atrial flutter, three/six remained in stable sinus rhythm and five/six reported symptomatic improvement. The rate of stable sinus rhythm during long-term follow-up and the rate of symptomatic improvement was not significantly different between patients undergoing hybrid therapy with amiodarone, flecainide, propafenone or sotalol (Table 2) (Fig. 3).

**Discussion**

To our knowledge, this is the largest series published thus far of patients undergoing hybrid therapy for antiarrhythmic drug-induced atrial flutter. Recurrence of atrial fibrillation was assessed during follow-up on continued antiarrhythmic drug
therapy and during long-term follow-up, irrespective of the initial antiarrhythmic medication. Accompanying pre-ablation episodes of atrial fibrillation, decreased left ventricular ejection fraction and adverse drug effects leading to discontinuation of antiarrhythmic medication were identified as risk factors for post-ablation atrial fibrillation.

**Drug-specific effects**

Atrial flutter can be documented in about 15% of patients after initiation of antiarrhythmic drug therapy for atrial fibrillation. The mechanism of conversion of atrial fibrillation to atrial flutter is not completely understood. It has been suggested that the wavefront of activation would be forced by the antiarrhythmic drug therapy to follow one unique pathway which necessarily would be the one with the greatest safety factor of conduction.

Drug-specific differences in the effectiveness of hybrid therapy have not been reported. In this study, there was a trend towards a higher rate of post-ablation atrial fibrillation (on continued antiarrhythmic medication) in patients treated with propafenone (36%) and sotalol (50%) compared to amiodarone (15%) and flecainide (18%). If only those patients were considered, in whom atrial flutter was the only atrial arrhythmia documented on antiarrhythmic medication before ablation, the rate of subsequent atrial fibrillation was very similar in all four treatment groups. These results show that post-ablation atrial fibrillation in patients undergoing hybrid therapy for drug-induced atrial flutter is primarily determined by the presence of accompanying pre-ablation atrial fibrillation rather than by the antiarrhythmic drug per se.

**Determinants of post-ablation atrial fibrillation**

Age, left ventricular dysfunction, structural heart disease and left atrial enlargement have been related to the spontaneous occurrence of atrial fibrillation in epidemiologic studies. In this study, the presence of accompanying pre-ablation episodes of atrial fibrillation and decreased left ventricular function were the only independent and significant predictors for post-ablation atrial fibrillation on continued antiarrhythmic drug therapy. The presence of structural heart disease and left atrial enlargement did not significantly influence the risk of post-ablation atrial fibrillation on continued antiarrhythmic drug treatment. The pre-existence of persistent atrial fibrillation (in
comparison to paroxysmal atrial fibrillation) also
did not reach significance as an independent pre-
dictor of atrial fibrillation following ablation of
drug-induced atrial flutter.

Paydak et al. have recently studied predictors
for the recurrence of atrial fibrillation after abla-
tion of type I atrial flutter.12 Similar to our results,
they found that among 17 clinical and procedural
variables, only a history of spontaneous atrial
fibrillation and left ventricular ejection fraction
<50% were independent predictors of subsequent
atrial fibrillation. The results of our study suggest
that the risk factors for recurrent atrial fibrillation
in patients undergoing hybrid therapy for drug-
induced atrial flutter are very similar to the risk
factors for the occurrence of atrial fibrillation after
ablation of drug-independent atrial flutter.

Role of adverse drug effects
Discontinuation of antiarrhythmic drug therapy due
to toxic or undesirable drug effects is associated
with a high risk for the recurrence of paroxysmal
or persistent atrial fibrillation. Withdrawal of anti-
arrhythmic medication due to adverse drug effects
was an important limitation of hybrid therapy in the
case of amiodarone but played no relevant role
in the case of flecainide, propafenone or sotalol.
Although the rate of adverse drug effects in the
case of amiodarone was high (25%), none of the
adverse effects was irreversible or life-threatening.
It has to be considered that, in addition to drug-
specific effects, different patient characteristics in
the four treatment groups may have contributed to
the different rates of toxic or undesirable drug
effects. The results show that the development of
toxic or undesirable drug effects can be an import-
ant limitation of hybrid therapy, and patients
should be carefully evaluated for adverse drug
effects before initiation of hybrid therapy.

Clinical implications
Catheter ablation targeting the breakthrough of the
left atrium to the pulmonary veins has recently
been shown to be a curative treatment of parox-
ysmal atrial fibrillation with a success rate of about
70%.13,14 However, the effectiveness of pulmonary
vein ablation in patients with persistent atrial
fibrillation is apparently much lower.14,15 In ad-
dition, pulmonary vein stenosis has been reported
to be a potentially harmful complication of cath-
teter ablation targeting the pulmonary veins.16,17
The data of this prospective study indicate that
hybrid therapy consisting of isthmus ablation for
drug-induced atrial flutter and continuation of
antiarrhythmic medication is a safe and effec-
tive therapy allowing the maintenance of stable
sinus rhythm during long-term follow-up in 67% of
patients and symptomatic improvement in 88% of
patients. Hybrid therapy for drug-induced atrial
flutter can also be considered as an effective
approach in patients with persistent atrial fibril-
ation and in patients with structural heart disease.

Fig. 3  Recurrence of atrial fibrillation (a-Fib) during long-term follow-up irrespective of the initial antiarrhythmic drug therapy.
Comparison of amiodarone and class IC antiarrhythmic (AA) drugs (flecainide, propafenone).
If drug-induced atrial flutter was the only atrial arrhythmia on antiarrhythmic drug treatment, the recurrence rate of atrial fibrillation on continued antiarrhythmic drug therapy was even less than 20%. The presence of accompanying pre-ablation episodes of atrial fibrillation is the strongest predictor of post-ablation recurrence of atrial fibrillation, and patients should be carefully evaluated for episodes of accompanying atrial fibrillation before initiation of hybrid therapy.

Limitations

This is an observational study and a randomized evaluation would be more appropriate to answer the question if hybrid therapy is the better treatment for drug-induced atrial flutter. Entrainment manoeuvres to confirm isthmus dependence of atrial flutter were not performed in the entire population. This may explain some recurrences of atrial fibrillation after ablation. Holter and event monitors were only available based on symptomatic recurrences; therefore, it is possible that some asymptomatic recurrences of atrial fibrillation were missed. Because patients were followed by their referring physicians, it was not always possible to control the prescription of antiarrhythmic drugs. Minor undesirable drug effects may have initiated discontinuation or change of the antiarrhythmic medication and the rate of serious undesirable or toxic drug effects may be overestimated. There is a large difference in the number of patients treated with the various antiarrhythmic drugs. It is possible that in larger or more equal groups of patients, drug-specific differences in the recurrence rate of atrial fibrillation may be identified.

Conclusions

Hybrid therapy should be chosen as the first-line therapy for patients with antiarrhythmic drug-induced atrial flutter, at least if atrial flutter is the only or predominant atrial arrhythmia on antiarrhythmic medication and if serious undesirable drug effects are not expected to occur during long-term treatment.

References