Anticoagulant and/or Antiplatelet Treatment in Patients with Atrial Fibrillation after Percutaneous Coronary Intervention
A Single-Center Experience

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia sustained and frequently occurs in patients with coronary heart disease. Thus, a large number of patients requiring percutaneous coronary intervention (PCI) also suffer from AF. An anticoagulant regimen has not been standardized for patients with AF after coronary stent implantation.

Patients and Methods: The authors investigated data from 159 patients with AF who underwent PCI in their department. Baseline variables and incidence of a combined endpoint (stroke, myocardial infarction, cardiovascular death, severe bleeding) were compared in patients receiving clopidogrel and acetylsalicylic acid (ASA; group 1) versus patients receiving the combination of clopidogrel and ASA with low-molecular-weight heparin (LMWH; group 2) versus patients receiving the combination of clopidogrel and ASA with oral anticoagulation (OAC; group 3) at discharge.

Results: Patients discharged with triple therapy including OAC seemed to be at higher risk: patients in group 3 had decreased left ventricular ejection fraction and increased inflammatory state as measured by plasma fibrinogen and C-reactive protein. Moreover, previous OAC treatment and strokes were found more often in this subgroup of patients. In a median follow-up of 1.4 years, two severe bleeding events (both in group 1), four myocardial infarctions (all in group 1), 13 strokes (nine in group 1, four in group 2), and nine cardiovascular deaths (three in group 1, five in group 2, one in group 3) occurred.

Conclusion: In this analysis, no treatment regimen seemed to be clearly superior. It underlines the importance of prospective, randomized trials to investigate the optimal antithrombotic/antiplatelet treatment for patients with AF after PCI.

Key Words: Atrial fibrillation · Percutaneous coronary intervention · Antiplatelet therapy · Anticoagulants

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Atrial fibrillation (AF) is the most common cardiac arrhythmia sustained and frequently occurs in patients with coronary heart disease [1]. Thus, a large number of patients requiring percutaneous coronary intervention (PCI) also suffer from AF. Several clinical trials have shown that combined antiplatelet therapy comprising aspirin and an adenosine diphosphate antagonist (ticlopidine, clopidogrel) given for a minimum of 4 weeks is the most effective pharmacological approach to prevent subacute stent thrombosis after coronary stent implantation, whereas combination of acetylsalicylic acid (ASA) with oral anticoagulation (OAC) increases the risk for subacute stent thrombosis and bleeding events in comparison to combined antiplatelet therapy [2–4]. After coronary implantation of a drug-eluting stent combined antiplatelet therapy is recommended for 6–12 months [5]. In patients with acute coronary syndrome, long-term therapy with ASA and clopidogrel for 12 months is beneficial in reducing major cardiovascular events [6]. However, although the number of patients, who need the combined treatment of clopidogrel and ASA, increases continuously, a standard regimen for the treatment of the subgroup of patients, who also suffer from AF, is lacking.

The ACTIVE trial showed that the combination of ASA and clopidogrel is inferior to OAC in patients with AF with regard to the primary combined endpoint of this trial defined as stroke, non–central nervous system systemic embolism, myocardial infarction, and vascular death [7]. Thus, OAC is recommended in patients with AF and at intermediate or high risk for thromboembolic events due to its superiority.
ZUSAMMENFASSUNG

Einfluss der Antikoagulation und/oder Thrombozytenaggregationshemmung auf das ereignisfreie Überleben bei Patienten mit Vorhofflimmern nach perkutaner Koronarintervention. Ergebnisse einer monozentrischen Studie

Hintergrund: Vorhofflimmern (VHF) ist die häufigste Herzrhythmusstörung und wichtige Komorbidität bei Patienten mit koronarer Herzkrankheit. Welche antithrombotische/antithrombozytäre Therapiestategie bei Patienten mit Vorhofflimmern nach perkutaner Koronarintervention (PCI) verfolgt werden sollte, ist aktuell nicht eindeutig zu beantworten.

Patienten und Methodik: Die Autoren identifizierten retrospektiv 159 Patienten mit VHF, die in ihrer Abteilung in den Jahren 1999–2004 eine PCI erhalten hatten. Die Grunderkrankungen und die Inzidenz eines kombinierten Endpunkts (Schlaganfall, Myokardinfarkt, kardiovaskulär bedingter Tod, schwere Blutung) wurden bei Patienten verglichen, die Clopidogrel und Acetylsalicylsäure (ASS; Gruppe 1), Clopidogrel und ASS in Kombination mit niedermolekularem Heparin (Gruppe 2) sowie Clopidogrel und ASS und zusätzlich orale Antikoagulation erhalten hatten (Gruppe 3).

Ergebnisse: Die Grunderkrankungen der Patienten in den drei Gruppen waren nicht signifikant unterschiedlich. In einem medianen Beobachtungszeitraum von 1,4 Jahren konnten zwei schwere Blutungen (in Gruppe 1), vier Myokardinfarkte (in Gruppe 1), 13 Schlaganfälle (neun in Gruppe 1, vier in Gruppe 2) und neun kardiovaskulär bedingte Todesfälle (drei in Gruppe 1, fünf in Gruppe 2, einer in Gruppe 3) nachgewiesen werden.

Schlussfolgerung: In dieser Untersuchung erwies sich keine Therapiestategie einer anderen gegenüber als eindeutig überlegen. Die erhobenen Daten zeigen, wie wichtig es ist, prospektive, randomisierte Studien bezüglich der antithrombotischen/antithrombozytären Therapie durchzuführen, um Patienten mit AF nach PCI optimal behandeln zu können.

Schlüsselwörter: Vorhofflimmern · Perkutane Koronarintervention · Antithrombozytäre Therapie · Antikoagulation

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All patients had been admitted to the Department of Medicine II of the Johannes Gutenberg University, Mainz, Germany, for diagnostic angiography between 1999 and 2004. All patients underwent PCI including coronary stent implantation. Patients were followed up for a mean of 1.4 years (range from 2 months to 5.7 years). The majority of the patients presented at our clinic for follow-up. The patients had German nationality and the majority were inhabitants of the Rhein-Main area.

Diabetes mellitus was diagnosed in patients who had previously undergone dietary treatment or received additional oral antidiabetic or insulin medication or who had a current fasting blood sugar level ≥ 125 mg/dl. Hypertension was diagnosed in patients who had received antihypertensive treatment or had been diagnosed as hypertensive (blood pressure > 140/90 mmHg); hyperlipoproteinemia was diagnosed in patients who had been given lipid-lowering medication or had a history of total cholesterol levels > 200 mg/dl. Smoking was defined as current smoking. All laboratory markers were detected by methods routinely used at our department.

The study was approved by the ethics committee of the Johannes Gutenberg University.

Statistical Methods

Levels of continuous variables were compared between treatment groups by ANOVA, χ²-tests were used for comparison of categorical variables. Event-free survival rates in the different categories were estimated using the Kaplan–Meier method, and the treatment groups were compared by the log-rank test. In the endpoint analyses, we compared patients receiving clopidogrel and ASA (n = 103, group 1) versus patients receiving the combination of clopidogrel and ASA with LMWH (n = 42, group 2) versus patients receiving the combination of clopidogrel and ASA with OAC (n = 14, group 3) at discharge. Event-free survival was defined as survival until stroke, myocardial infarction, severe bleeding, or cardiovascular death. Data on patients who died of other causes were censored at the time of death. As
Table 1. Baseline characteristics stratified by patients receiving ASA and clopidogrel \( (n = 103\), group 1) versus patients receiving the combination of clopidogrel and ASA with LMWH \( (n = 42\), group 2) versus patients receiving the combination of clopidogrel and ASA with OAC \( (n = 14\), group 3) at discharge. Categorical variables are presented as percentage of patients (number of patients). Continuous variables are presented as mean (SD). \( p\)-values result from ANOVA or \( \chi^2\)-test. ASA: acetylsalicylic acid; BMI: body mass index; CHD: coronary heart disease; CRP: C-reactive protein; LMWH: low-molecular-weight heparin; NSTEMI: non-ST elevation myocardial infarction; OAC: oral anticoagulation; SD: standard deviation; STEMI: ST elevation myocardial infarction.

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel/ASA ( (n = 103) )</th>
<th>LMWH/clopidogrel/ASA ( (n = 42) )</th>
<th>OAC/clopidogrel/ASA ( (n = 14) )</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male (%)</td>
<td>73.5</td>
<td>66.7</td>
<td>78.6</td>
<td>0.603</td>
</tr>
<tr>
<td>BMI (kg/m(^2)), mean (SD)</td>
<td>27.1 ((3.4))</td>
<td>27.5 ((5.1))</td>
<td>27.0 ((3.3))</td>
<td>0.860</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>69.8 ((9.2))</td>
<td>72.1 ((8.5))</td>
<td>68.5 ((10.6))</td>
<td>0.287</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>30.1</td>
<td>33.3</td>
<td>7.1</td>
<td>0.158</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>91.3</td>
<td>78.6</td>
<td>78.6</td>
<td>0.078</td>
</tr>
<tr>
<td>Hyperlipoproteinemia (%)</td>
<td>68.0</td>
<td>54.8</td>
<td>64.3</td>
<td>0.323</td>
</tr>
<tr>
<td>Active smokers (%)</td>
<td>15.5</td>
<td>19.0</td>
<td>28.6</td>
<td>0.466</td>
</tr>
<tr>
<td>Family history for CHD (%)</td>
<td>16.5</td>
<td>11.9</td>
<td>0</td>
<td>0.224</td>
</tr>
<tr>
<td>Clinical manifestation of CHD (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.589</td>
</tr>
<tr>
<td>Stable angina</td>
<td>11.7</td>
<td>14.3</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>43.7</td>
<td>38.1</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>30.1</td>
<td>35.7</td>
<td>35.7</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>14.6</td>
<td>11.9</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Number of affected coronary arteries (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.658</td>
</tr>
<tr>
<td>1</td>
<td>33.0</td>
<td>28.6</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>26.2</td>
<td>33.3</td>
<td>35.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40.8</td>
<td>38.1</td>
<td>35.7</td>
<td></td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>8.7</td>
<td>16.7</td>
<td>21.4</td>
<td>0.213</td>
</tr>
<tr>
<td>Ejection fraction (%), mean (SD)</td>
<td>55.5 ((14.1))</td>
<td>50.0 ((12.7))</td>
<td>47.7 ((19.0))</td>
<td>0.048</td>
</tr>
<tr>
<td>Oral anticoagulation at baseline (%)</td>
<td>11.7</td>
<td>19.0</td>
<td>57.1</td>
<td>(&lt; 0.001)</td>
</tr>
<tr>
<td>CRP (mg/l), mean (SD)</td>
<td>15.5 ((37.1))</td>
<td>28.5 ((62.1))</td>
<td>27.5 ((48.1))</td>
<td>0.271</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl), mean (SD)</td>
<td>363.8 ((113.0))</td>
<td>409.9 ((150.9))</td>
<td>496.6 ((187.4))</td>
<td>0.002</td>
</tr>
</tbody>
</table>

\( p\)-values are not adjusted for multiple testing, they have to be considered descriptive. All computations were carried out with SPSS, version 12.0.

Results

Baseline Characteristics

Baseline characteristics of the patients are shown in Table 1. Relevant differences were found only for fibrinogen, previous stroke, and left ventricular ejection fraction. Patients treated with OAC/clopidogrel/ASA had decreased left ventricular ejection fraction, increased inflammatory state as measured by plasma fibrinogen and C-reactive protein (CRP). Moreover, previous OAC treatment was found more often in this subgroup of patients.

Endpoint Analyses

In a median follow-up of 1.4 years, two severe bleeding events (both severe gastrointestinal bleedings requiring endoscopic interventions and at least three blood transfusions in group 1), four myocardial infarctions (all in group 1), 13 strokes (nine in group 1, four in group 2), and nine cardiovascular deaths (three in group 1, five in group 2, one in group 3) occurred.

The Kaplan–Meier curves (Figure 1) showed a slight increase in the event-free survival rates for patients who received triple therapy with OAC/clopidogrel/ASA in comparison to both other treatment groups. Only one patient died in this subgroup (event rate 7.2%).

In patients solely treated with clopidogrel and ASA, 18 events (two severe bleeding events, four myocardial infarctions, nine strokes, three cardiovascular deaths) were documented (event rate 17.5%), which was a slightly lower event rate in comparison to patients treated with LMWH/clopidogrel/ASA.

In patients receiving triple therapy with LMWH/clopidogrel/ASA, nine events occurred (four strokes, five car-
diovascular deaths), which represented a higher event rate in comparison to other treatment groups (21.4%).

**DISCUSSION**

Oral anticoagulation is recommended in patients with AF and an intermediate or high risk for thromboembolic events due to its superiority to ASA [8, 10]. When patients with AF are submitted for PCI, their management becomes challenging, due to the concurrent indication for antiplatelet therapy. Therefore, ASA and/or clopidogrel should be combined with OAC in patients with AF who are referred for PCI [11].

In the ACC/AHA/ESC guidelines (American College of Cardiology, American Heart Association, European Society of Cardiology) for the management of patients with AF [12], triple therapy consisting of OAC, ASA and clopidogrel is recommended early after PCI. A maintenance regimen of OAC and clopidogrel should then follow for up to 12 months, after which OAC should be continued [12]. Since no prospective trials have evaluated this treatment regimen, recommendations are currently graded IIb with a C level of evidence [11, 12].

However, totally, twelve retrospective studies on the antithrombotic treatment of patients treated with OAC undergoing PCI with stent implantation have been published [13]. Nearly all of the studies are small, retrospective and single-center. The safety outcome of bleeding was evaluated in all of the studies, whereas efficacy outcomes, such as thromboembolic/stroke, stent thrombosis and adverse cardiac events were variably investigated. In only three reports, clinical follow-up included both the periods on and off the multiple-drug regimen prescribed after PCI [14–16].

On the one hand, triple therapy was associated with a variable incidence of major bleedings, which ranged from 0% to 21%. Most bleeding events were gastrointestinal, and often associated with supratherapeutic International Normalized Ratio levels. Moreover, in most patients experiencing major bleeding, other factors may have been contributory, like advanced age, peri-interventional administration of glycoprotein IIb/IIIa inhibitors, and others [17–19]. In three studies, the safety of triple therapy was compared with dual antiplatelet therapy. In these studies, the relative risk of combined major/minor bleeding was fivefold higher [19–21]. Since a minority of patients was treated with the combination of OAC and a single antiplatelet agent (either ASA or clopidogrel) and corresponding individual data are seldom reported, a reliable evaluation of the relative safety of these regimens could not be carried out [11].

On the other hand, triple therapy showed less events than both dual antiplatelet treatment and the combination of OAC and a single antiplatelet agent in preventing thromboembolic events like stroke or myocardial infarction [16, 21, 22]. Stent thrombosis was also rare in the triple-therapy group in comparison to other therapy groups [16, 19, 22]. However, the small number of patients, adverse events and insufficient information about the time of the ongoing treatment when complications occurred, should be taken into account when these results are considered [11].

In our study, only 14 patients received triple therapy with OAC/clopidogrel/ASA. We found only one event in the follow-up period in this subgroup. However, these patients had a higher risk for further cardiovascular events, as presented by decreased left ventricular ejection fraction and increased inflammatory state (measured by plasma fibrinogen and CRP). Moreover, previous OAC treatment and strokes were found more often in this subgroup of patients.

The addition of LMWH to combined antiplatelet therapy increased the 30-day bleeding risks for AF patients after PCI [9]. In the present study, 42 patients received triple therapy with LMWH/clopidogrel/ASA. Due to the retrospective character of our study we were not able to identify the duration of the LMWH treatment in these patients. We found a slight increase of events in this subgroup of patients.
compared to patients solely treated with clopidogrel and ASA, and patients who received triple therapy with OAC/clopidogrel/ASA. Thus, we conclude from our previous and present data that the addition of LMWH to combined antiplatelet therapy may not be beneficial for patients with AF after PCI. Furthermore, in our study dual antiplatelet therapy with clopidogrel and ASA was also not effective in reducing cardiovascular events.

Our investigation is a nonrandomized, retrospective analysis of a single-center registry. Patients with a high risk of bleeding might have predominantly been treated with dual antiplatelet therapy (group 1), which displays the highest rate of bleeding complications despite administration of the least aggressive therapy. Thus, patients well tolerating OAC might have been assorted to group 3 (OAC/clopidogrel/ASA), where the lowest stroke rate was reported. After all, nonrandomized, retrospective trials always incorporate a potential selection bias, which might be present in our study as well. However, large randomized, prospective trials are lacking which investigate the optimal anti-thrombotic/antiplatelet therapy for patients after PCI suffering from AF.

CONCLUSION

The optimal anti-thrombotic treatment for patients with AF who undergo PCI is at present undefined. Based on our and currently available data, triple therapy consisting of the combination of OAC, ASA and clopidogrel appears to offer the best protection against thromboembolic and myocardial ischemic events. Our small retrospective study suggests that combined clopidogrel/ASA ± LMWH seems not to be beneficial for patients with AF after PCI.

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References
