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Ischaemic event or migraine?
Think also patent foramen ovale

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Although the patent foramen ovale (PFO) has been convicted for causing stroke for the better part of 100 years [1], the medical community continues to turn a blind eye to it when finding and eliminating possible causes of stroke. Two recently published, blatant examples of this omission are the reasons for this editorial. In the first, an otherwise insightful and brilliantly described prospective, observational study examining the "one-year risk of stroke after transient ischemic attack or minor stroke", a score was proposed to define the subsequent risk of stroke after an initial event [2]. The authors included about 4700 patients and followed them up for a median of 27 months. At 1 year, 274 events had occurred, whereof strokes accounted for the majority, followed by acute coronary syndromes (>10% of all events). One of the strongest predictors of stroke at 1 year was the finding of multiple acute cerebral infarctions on brain imaging. The presence of atrial fibrillation as a cause of stroke was reported and discussed, but the authors forgot to consider the PFO, and neither did an accompanying editorial [3].

It had been unequivocally shown that closure of the PFO with the Amplatzer technique infers benefit in patients with cerebral events [4–7]. Reduced mortality after PFO closure has even been shown in a comparative trial in which patients with or without device closure were followed up for more than 10 years. [6]. Not closing a PFO after an ischaemic event without a compelling explanation other than the documented PFO increases the risk of a recurrent ischaemic event by about 1% per year. On the basis of the average age of such patients, this extrapolates to >30% for life. All this has to be seen in the light of PFO closure as the simplest and safest procedure in interventional cardiology. Moreover, closing the PFO for stroke prevention confers collateral benefits such as protection against other paradoxical embolisms (myocardial infarction, visceral or systemic ischaemia) and migraine symptoms.

The link between PFO, connecting thrombosis, stroke and myocardial infarction was proved almost 20 years ago in a seminal paper [8]. It showed that the risk of dying in patients who had been admitted to hospital for deep venous thrombosis or pulmonary embolism was almost tripled by the mere presence of a PFO. The risk of simultaneously suffering a stroke was increased sixfold.

An article in the Lancet several years later completely ignored this link between venous thrombosis and PFO-associated events [9]. And, again, so did the accompanying editorial [10]. In this large Danish field study including 163,566 people followed up over 20 years, 25,199 patients with deep venous thrombosis and 16,925 patients with pulmonary embolism were identified. There was a startling incidence of coinciding stroke or myocardial infarction of about 3% in patients with pulmonary embolism (a clot had travelled through the right atrium) and 2% in patients with deep venous thrombosis only (fig. 1). This resulted in first-year risk hazard ratios of 2.2 (confidence interval 1.9–2.6) for stroke and 1.6 (1.4–1.9) for myocardial infarction after provoked venous thromboembolism. The respective risk hazard ratios for unprovoked venous thromboembolisms were 2.9 (2.3–3.7) and 2.6 (2.1–3.1) [9]. The PFO was not mentioned among the various, sometimes farfetched, hypotheses on what could be a common cause of two such grave events happening in close sequence. The PFO is indeed the most likely explanation. It also explains why the hazard ratio in the patients with these combined events never completely receded to normal (fig. 1). Most of them must have a PFO, which engenders an overall increased risk of stroke and myocardial infarction. The authors’ answer to our question

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**Figure 1:** Relative risk for stroke or myocardial infarction in patients admitted for provoked venous thromboembolism.
as to why the PFO was not mentioned in the report was that a few case records had been screened for the mention of a PFO, but these spot checks had yielded nothing. Of course, a PFO will not be mentioned if it has not been looked for specifically. We suggested then that they recontacted the patients with these combined events for a transoesophageal echocardiogram (TOE), on the assumption that the majority of them would have a PFO. However, there allegedly was no money for this. We offered to help with finding a funding source only to learn that it would not be possible, anyhow, to identify and recontact these patients. This was quite surprising only a short while after their outcomes had been published in a reputable journal.

At about the same time, a report on 2040 individuals in the Framingham Offspring Study described silent cerebral infarctions documented by magnetic resonance imaging, irrespective of the gender, in about 7% of people at the age of 30–49 years, 8% at the age of 50–59 years, 10% at the age of 60–69 years and 15% at the age of 70–89 years [11]. Suspected reasons for this observation were presented. The PFO was not among them.

A paper in Neurology about stenoses and occlusions of brain-supplying arteries in young stroke patients examined the status of afferent vessels [12]. A long list of possible problems in these vessels was presented. However, embolic vessel occlusion due to paradoxical embolism through a PFO was not mentioned.

In an article in the New England Journal of Medicine, the risk for thrombotic stroke and myocardial infarction with hormonal contraception was examined in 1626158 Danish women, representing 14251063 person-years of observation [13]. They found a risk increase of up to 1.7 for stroke or myocardial infarction associated with hormonal contraception in otherwise mostly healthy women. Again, a multitude of possible explanations for this were enumerated, but a higher rate of venous thrombosis and paradoxical embolism in the presence of a PFO was scotomised.

The second recent publication prompting this editorial appeared in the British Medical Journal. It dwelt on migraine and the risk of cardiovascular disease in women and reported a prospective cohort study of 115541 participants the Nurses’ Health Study II [14]. They were aged 25–42 years, free of angina or cardiovascular disease, and 15% of them suffered from migraine. They were followed up from 1989 to 2011. Their adjusted cardiovascular hazard ratio compared with the control background without migraine is listed in table 1. Endothelial dysfunction or abnormal vascular reactivity were indicted in an accompanying editorial and the possibility was raised that these women might benefit from preventive therapy with a statin and acetylsalicylic acid, although the latter had proved to increase the overall risk for myocardial infarction in women [15]. The PFO was again left oblivion. It provides a likely explanation for the issue at stake and can be remedied easily, obviating the need for long-term preventive drugs. PFO closure can also improve symptoms, particularly regarding migraine with aura [16].

It has to be kept in mind that a PFO can be sought quite easily with transthoracic echocardiography. TOE has a higher yield, but the small PFOs seen only with TOE may be negligible. A PFO can also be easily closed at the cost of a few 1000 Swiss francs and the procedure is virtually devoid of complications or follow-up problems. This warrants searching for a PFO as an integral part of any work-up after stroke or transient ischaemic attack, myocardial infarction with an aspect of embolic coronary occlusion, embolic visceral or peripheral artery occlusion, and severe migraine, in particular migraine with aura. At worst, preventive PFO closure (also referred to as mechanical vaccination [17]) provides no protection in cases where no events would have happened. At best, it saves the patient’s life or prevents one or several important events during the remainder of the patient’s life, and thereby possible dire sequelae known to many stroke patients. Twenty-seven PFOs needed to be closed to prevent one stroke within 5 years in a randomised trial [5]. With a conservative assumption of a risk reduction with increasing age because of the increasing pressure in the left atrium reducing right to left shunts through a PFO, that would lead to a number needed to treat of five PFO closures in 65-year-old patients, with two PFOs needing to be closed to prevent one stroke in 20-year-old patients. And this does not consider factors aggravating the risk of paradoxical embolism with age, such as the ever increasing risk of venous thrombosis [18] and the enhanced and prolonged Valsalva manoeuvres during defecation and micturition.

Disclosure statement
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References
The full list of references is included in the online version of the article at www.cardiovascmed.ch

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<td>Angina or coronary revascularization</td>
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<td>Cardiovascular mortality</td>
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Based on the lecture held at the Swiss Society of Cardiology Congress 2016 in Lausanne

Review of the 2016 European dyslipidaemia guidelines

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Cardiology Division, Geneva University Hospitals, Switzerland

Summary

In 2016 the European Society of Cardiology (ESC) published guidelines on the prevention of cardiovascular disease (CVD) in clinical practice, with sections addressing global strategies to minimise the burden of CVD at population and individual levels. A few months later in August, the 2016 ESC / European Atherosclerosis Society (EAS) published guidelines for the management of dyslipidaemias, focusing on their evaluation and treatment. The release of these guidelines was a source of great interest among clinicians, as new emergent therapies, such as proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors have been approved for the treatment of dyslipidaemias. Concurrently, the ESC/EAS produced a consensus paper in order to guide clinicians in the appropriate use of PCSK9 inhibitors for patients at high risk of CVD. These papers followed the extremely controversial 2013 American Heart Association guidelines on the treatment of blood cholesterol, in which the indication for statin therapy was extended to the primary prevention setting according to the new recommended Pooled Cohort equations [4]. Furthermore, the concept of a low-density lipoprotein cholesterol target was withdrawn, and the intensity of statin therapy defined according to the patient’s cardiovascular risk. The purpose of this review article is to summarise the key points, as well as the innovations, in the 2016 ESC/EAS guidelines for the management of dyslipidaemias and prevention of CVD. It does not constitute an official recommendation for clinicians, but should be read as a summary selected by the authors from the official ESC documents. The AGLA/GSLA (Swiss Society of Atherosclerosis) recommendations should be used in clinical practice for Swiss patients.

Risk assessment recommended by the 2016 ESC guidelines

The risk assessment of CVD is recommended to guide clinicians in the selection of the most appropriate treatment, especially when a pharmacological therapy is needed in addition to lifestyle counselling. The ESC guidelines continue to recommend the use of the country-adapted SCORE system to assess a patient’s 10-year risk of undergoing a fatal cardiovascular event. The estimate is based on age, gender, total cholesterol (with an optional use of data relating to high-density lipoprotein cholesterol [HDL-C]), smoking status and blood pressure. Screening for CVD should be considered in asymptomatic men >40 years old and in women >50 years old. A repeat CVD risk assessment every 5 years is recommended, more frequently for individuals with risks close to the threshold requiring drug therapy. People at very high risk are by definition those with: (I) documented CVD, defined as acute coronary syndromes (ACS), coronary revascularisation,
stroke or transient ischaemic attack and peripheral artery disease; (2) type 1 or type 2 diabetes; (3) very high levels of individual risk factors, such as familial hypercholesterolaemia or severe hypertension; (4) severe chronic kidney disease (glomerular filtration rate <30 ml/min/1.73 m²); and (5) a calculated SCORE 10% for 10-year risk of fatal CVD. Additional factors that could modify the interpretation of the SCORE risks include social deprivation, obesity, physical inactivity, psychological stress, family history of, or premature occurrence of, CVD, inflammatory disease, atrial fibrillation or left ventricular hypertrophy.

**LDL-C targets recommended by the 2016 ESC guidelines**

The targets for low-density lipoprotein cholesterol (LDL-C) levels are summarised in table 1 and are meant to help clinicians in their choice of a pharmacological lipid-lowering agent when this is needed in addition to lifestyle counselling. The LDL-C target of 1.8 mmol/l (70 mg/dl) is still widely recommended for very high-risk patients who need drug therapy, and a 50% LDL-C reduction is recommended for those patients whose baseline LDL-C ranges between 1.8 and 3.5 mmol/l. The LDL-C target of <2.6 mmol/l is recommended for high-risk patients (SCORE 5–10%), while for patients with a moderate (SCORE 1–5%) or low (SCORE <1%) risk the LDL-C target is <3.0 mmol/l. Triglyceride measurements are indicated for risk estimation (class I, level C). The risk of CVD is increased for fasting triglyceride values >1.7 mmol/l, and drug therapy should be considered when triglyceride values are >2.3 mmol/l in high risk patients (e.g., statin as first-line treatment). HDL-C is not recommended as a therapeutic target, but is a strong independent risk factor when values are <1.0 mmol/l in men and <1.2 mmol/l in women. According to the 2016 ESC dyslipidaemia guidelines, the measurement of lipoprotein(a) [Lp(a)] levels should be considered in selected cases at high risk, such as: (1) premature CVD; (2) familial hypercholesterolaemia; (3) a family history of premature CVD and/or elevated Lp(a); (4) recurrent CVD despite optimal statin treatment; and (5) ≥5% 10-year risk of fatal CVD according to SCORE. The risk is considered significant for Lp(a) ≥50 mg/dl, but no randomised controlled trial has yet demonstrated that the reduction of Lp(a) levels is associated with a reduction of cardiovascular events.

Neither routine assessment of circulation or urinary biomarkers, nor carotid ultrasound for intima media thickness (IMT) screening are recommended for CVD risk assessment stratification [1]. A meta-analysis has suggested that the addition of IMT to the recommended clinical risk score is not relevant for the prediction of future cardiovascular events, including in patients at intermediate risk [5]. Real-practice data will be needed to evaluate whether IMT is overused by clinicians. The use of other imaging methods, such as coronary artery calcium scoring, is more controversial. Atherosclerotic plaque detection by carotid scanning and ankle-brachial index may be considered in cardiovascular risk prediction, especially in patients with an estimated cardiovascular risk between 5 and 10% [1]. However, the documentation of preclinical CVD based on imaging, such as significant plaque on coronary angiography or carotid ultrasound, classifies patients in the very high-risk category, with need of appropriate lipid-lowering therapy [1].

**Table 1: Recommended treatment goals for low-density lipoprotein cholesterol (LDL-C).**

<table>
<thead>
<tr>
<th>Risk categories</th>
<th>LDL-C goal</th>
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<tbody>
<tr>
<td>Very high risk (&gt;10% SCORE risk)</td>
<td>&lt;1.8 mmol/l or a reduction of ≥50% if baseline is between 1.8 and 3.5 mmol/l.</td>
</tr>
<tr>
<td>High risk (5–10% SCORE risk)</td>
<td>&lt;2.6 mmol/l or a reduction of ≥50% if baseline is between 2.5 and 4.9 mmol/l.</td>
</tr>
<tr>
<td>Low [&lt;1% SCORE] or moderate (1–5% SCORE) risk</td>
<td>&lt;3.0 mmol/l</td>
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**Treatment strategies recommended by the ESC guidelines**

**Population-based approach**

For physical activity, smoking and nutrition, recommendations for population-based approaches are characterised by multilevel actions in: (1) governmental restrictions and mandates, (2) media and education, (3) labelling and information, (4) economic incentives, (5) schools, (6) workplace and (7) community.

**Lifestyle**

Several data suggest that a so-called Mediterranean diet is effective in improving the control of cardiovascular risk factors. To control LDL-C levels, the recommended diet favours the consumption of fruit, vegetables, wholegrain cereal products, nuts, fish, poultry and low-fat dairy products. Other recommendations include limiting the consumption of sweets, sugar-sweetened drinks, red meat, dietary saturated fat and trans fats. Bodyweight reduction and physical activity have an effect on LDL-C levels, but also on other CVD risk factors. Regarding the use of functional foods, “nutraceuticals”, no recommendation is available given the absence of strong evidence. Red yeast rice contains monacolin K, the active element of lovastatin, which
has a statin-like lipid-lowering mechanism. However, the long-term safety of red yeast is not documented and its impact on cardiovascular events needs to be clarified [6].

Regarding physical activity, it is recommended for healthy adults of all ages to perform at least 150 minutes a week of moderate physical intensity, or 75 minutes a week of vigorous intensity, aerobic physical activity or an equivalent combination. Regarding smoking, it is recommended to identify smokers and provide advice on aids to stopping the habit (e.g., nicotine replacement, varenicline and bupropion).

**Statins**

Statins inhibit the synthesis of cholesterol in the liver. The reduction in LDL-C levels depends on the statin type and dosage, patient compliance with the treatment and, variations in genes for both cholesterol and statin metabolism. Several randomised controlled trials and meta-analyses have shown that statin is associated with a reduction of CVD morbidity and mortality [7]. In the large Cholesterol Treatment Trialist (CTT) study, for each reduction of LDL-C of 1.0 mmol/l, the relative risk reduction was 10% for all-cause mortality and 20% for CVD mortality. The predicted CVD deaths avoided from reductions in LDL-C with statin treatment differ according to risk: the higher the baseline risk, the higher the number of deaths avoided by appropriate interventions [8]. Table 2 summarises the main steps of the decision algorithm for statin therapy. The ESC guidelines emphasise the involvement of the patient for an individualised approach to risk management and treatment decisions [2]. Statins remain the first-line therapy to lower LDL-C and triglyceride levels and the most effective lipid-lowering therapy for the reduction of CVD mortality. Statins may be responsible for raising HDL-C levels (by ≈10%). For subjects at very high- or high-risk, the recommended decrease of LDL-C should be at least 50% (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg daily) and drug combinations should be considered if the highest tolerable/tolerated statin dose is not sufficient. Statin-associated muscle symptoms are the most frequent side effect, but in the great majority of cases the symptoms do not fulfill criteria for the potential risk of rhabdomyolysis (creatin kinase at least 10 times higher than the upper limit of the reference range) [9].

**Ezetimibe**

Ezetimibe inhibits intestinal uptake of dietary and biliary cholesterol and has the effect of lowering LDL-C levels by 20% in monotherapy or in addition to a statin. In the IMPROVE-IT trial, (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) the addition of ezetimibe to the standard treatment with simvastatin among 18144 patients after ACS significantly reduced the occurrence of cardiovascular events after 5 years (32.7% vs 34.7%, p = 0.016), as well as LDL-C levels (1.8 mmol/l vs 1.4 mmol/l) [10]. The findings from the IMPROVE-IT trial support the use of ezetimibe as a second-line therapy if LDL-C target levels are not reached with maximum tolerated doses of statin.

**PCSK9 inhibitors**

The use of monoclonal antibodies against PCSK9 has reduced LDL-C by 60% compared with standard care (e.g., maximum tolerated statin dosage) [11]. Alirocumab and evolocumab have been approved by Swissmedic for the treatment of primary hypercholesterolaemia. The guidelines recommend that for patients at very high risk and those with familial hypercholesterolaemia who did not reach the recommended LDL-C targets with maximum tolerated dosages of statin, PCSK9 inhibitors may be considered. Although post-hoc analyses suggest that PCSK9 inhibitors might be associated with a reduction in cardiovascular events, more data are needed from appropriately powered randomised controlled trials.

**Familial hypercholesterolaemia**

Familial hypercholesterolaemia is the most common genetic disease (prevalence between 1/200 and 1/500) and a common form of monogenic dyslipidaemia (95% of cases are caused by mutations of the LDL receptor, and others are due to mutations of apolipoprotein B [Apo(B)] and PCSK9) [2]. Familial hypercholesterolaemia is associated with lifelong elevated LDL-C levels causing premature cardiovascular events (≤5 years of age in men and ≤60 years in women), and an estimated 10-fold increased risk of any cardiovascular event. Earlier recognition and treatment of familial hypercholesterolaemia can improve the prognosis. The Dutch Lipid Clinic Network classified subjects into groups with pos-
The score is based on family history of premature CVD or hypercholesterolaemia, and a clinical history of premature cardiovascular events. Clinical investigations include LDL-C levels and DNA analysis. The causal mutations of probable and definite familial hypercholesterolaemia are found in 60–70% of cases. Family cascade screening is recommended when an index case is diagnosed. According to the ESC guidelines, patients with familial hypercholesterolaemia are considered by definition to be at high risk. Treatment to lower LDL-C should be started once the diagnosis is established, since cumulative LDL-C levels increase over time. High-intensity statin therapy should be initiated in combination with ezetimibe to reach the LDL-C target <2.5 mmol/l or, if CVD is present, <1.8 mmol/l. Treatment with PCSK9 inhibitors may be considered in patients with CVD or at very high risk (e.g., high Lp(a) levels). In children with familial hypercholesterolaemia, statin therapy should be considered from 8 to 10 years of age; the LDL-C goal above 10 years is <3.5 mmol/l [2].

### Special populations and conditions specified by the ESC guidelines

#### Gender
ESC guidelines recommend the assessment of CVD for women >50 years old or postmenopausal with no known cardiovascular risk factors, as their risk is deferred by approximately 10 years [1]. Indications for statin therapy and LDL-C are similar to those for men [2]. As safety data covering pregnancy and breastfeeding are lacking, the use of statins and/or other lipid-lowering therapies, except bile acid sequestrants, is not recommended [2].

#### Elderly
The absolute number of cardiovascular events is especially high in individuals older than 65 years. However, evidence for the benefit of statins for patients older than 80 to 85 years is limited and medical decisions should be individualised. Post-hoc analysis of randomised controlled trials with statin treatment did not suggest a correlation between treatment effect and age. Treatment with a statin is recommended for older adults with established CVD in the same way as for younger patients. Main concerns are related to safety and adverse effects due to comorbidities and polypharmacy. Statin dosage should be started at the lowest level and up-titrated to achieve the optimal LDL-C levels

### Diabetes
Dyslipidaemia in the metabolic syndrome is characterised by a cluster of lipid abnormalities including an increase of both fasting and postprandial triglyceride, apo(B) and small dense LDL, with low HDL-C and apo(A1). Trials specifically performed in patients with diabetes or subgroup analyses have shown the benefit of statin therapy on cardiovascular events. In all patients with type 1 diabetes, and in the presence of microalbuminuria and renal disease, statin therapy is recommended to lower LDL-C by at least 30%, irrespective of basal LDL-C levels. In patients with type 2 diabetes and CVD or chronic kidney disease, or those over the age of 40 years with one or more other CVD risk factors, the recommended target for LDL-C is <1.8 mmol/l. In all patients with type 2 diabetes, the recommended target is <2.5 mmol/l.

### Acute coronary syndromes
ACS patients are considered to be very high-risk subjects, and the management of dyslipidaemia should be integrated into global risk factor management and into a well-coordinated and multidisciplinary cardiac rehabilitation programme. The initiation of high doses of statin is recommended early after admission for ACS, regardless of LDL-C values [12]. If the recommended LDL-C target of 1.8 mmol/l is not reached with the highest tolerable/tolerated statin dose, ezetimibe should be considered as an add-on 4 to 6 weeks after ACS. Pretreatment with a high-dose statin should be considered in elective percutaneous coronary intervention or in non-ST segment elevation ACS.

### Chronic kidney disease
Patients with moderate chronic kidney disease (stage 3) are considered as high-risk patients, and those with severe or terminal disease (stage 4–5 or on dialysis) are regarded as very high-risk CVD subjects. The use of statins or a statin plus ezetimibe is recommended for patients with non-dialysis-dependent chronic kidney disease. In patients on dialysis, a statin or statin/ezetimibe should be continued if they were prescribed before dialysis initiation.

### Transplantation
Lipid abnormalities are common in patients after solid organ transplantation, and a global cardiovascular risk management strategy is recommended. Statins are the first-line therapy and should be initiated at low doses with careful up-titration and with caution regarding interactions with ciclosporin. Ezetimibe can be considered if the control of LDL-C is suboptimal with the maximum tolerated dose of statin.
Human immunodeficiency virus and autoimmune diseases
Patients with human immunodeficiency virus (HIV) can have high levels of LDL-C and triglycerides when undergoing highly active antiretroviral treatment. HIV-infected patients have a higher risk of CVD, even after adjustment for traditional risk factors [13]. Lipid-lowering therapy (mostly statin and preferably pravastatin) should be considered for HIV patients in order to achieve an LDL-C goal of <2.5 mmol/l (for high-risk subjects). However, HIV patients have been excluded from large trials and no data are available regarding the impact of statins or ezetimibe on cardiovascular events in this population.

Recommended performance measurement of CVD prevention
It is important that performance measurements are established and followed in practice in order to improve the quality of care. Adherence to the following criteria define specific groups of patients has been recommended in the guidelines:
1. Subjects identified as tobacco users who received smoking cessation intervention
2. Subjects whose sedentary habits have been recorded and who are being counselled to increase physical activity
3. Subjects whose unhealthy diet / nutritional habits have been recorded and who are being counselled to improve their diet
4. Subjects whose weight and body mass index and/or waist circumference is documented as being above normal limits and who are being counselled on weight management
5. Subjects >40 years old with at least one lipid profile performed within the past 5 years
6. Patients <60 years old with hypertension who had a recorded blood pressure reading at their most recent visit <140/90 mm Hg
7. Patients with diabetes mellitus who had a glycated haemoglobin <7.0% at the most recent visit
8. Patients with a cardiovascular event who have been referred to a cardiac rehabilitation programme.

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References
A high-volume single-centre experience

The evolving role of left atrial appendage occlusion

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Summary

Objectives: To report our 5-year single centre experience with percutaneous left atrial appendage occlusion (LAAO).

Background: LAAO evolved rapidly at our institution, as it has worldwide. The procedure requires experience to be safely performed. We evaluated indications, and short- and long-term outcome of LAAO.

Methods: LAAO was performed either (a) under general anaesthesia with transesophageal echocardiographic and fluoroscopic guidance, (b) under local anaesthesia with intracardiac echocardiographic and fluoroscopic guidance, or (c) with fluoroscopic guidance alone, depending on operator preference. A previously detected patent foramen ovale (PFO) or atrial septal defect (ASD) was used for left atrial access by one operator (FN) with Amplatzer devices only; transseptal puncture was routine in the rest. Patients were discharged on acetylsalicylic acid and clopidogrel for 1–6 months; oral anticoagulation (OAC) was stopped the day of the procedure.

Results: From June 2010 to November 2015, LAAO was performed in 284 patients at the University Heart Centre Zurich, of whom 247 were included in the analysis (164 males, 77 ± 8.9 years, CHA2DS2-Vasc-score 4.5 ± 1.4, HAS-BLED-score 3.6 ± 1.1). Devices used were the Amplatzer Cardiac Plug in 107 patients (42.9%), the Amplatzer Amulet in 87 patients (35.2%) and the Watchman device in 53 patients (21.5%). A PFO or ASD was used for left atrial access by one operator (FN) with Amplatzer devices only; transseptal puncture was routine in the rest. Patients were discharged on acetylsalicylic acid and clopidogrel for 1–6 months; oral anticoagulation (OAC) was stopped the day of the procedure.

Conclusions: In over 90% of AF patients, thrombi can be detected in the left atrial appendage (LAA), which is the rationale for LAA occlusion (LAAO) as an alternative therapy for stroke prevention in AF patients. Several devices have been used (fig. 1). The most commonly used percutaneous devices for LAAO are the Amplatzer (St. Jude Medical, St. Paul, MN) and the Watchman (Boston Scientific, Marlborough, MA) devices. Historically, the PLAATO device (ev3 Inc, Plymouth, MN) was the first available percutaneous device for LAAO, but was removed from the market because of economic considerations [5, 6]. The gap was filled by off-label use of nondedicated Amplatzer devices used primarily for the occlusion of patent foramen ovale (PFO), atrial septal defects (ASDs) or ventricular septal defect (VSDs) [7]. These nondedicated devices served the purpose of stroke prevention, but came along with a relatively high embolisation rate (12%) [8]. In 2008, a dedicated Amplatzer device became available (AMPLATZER Cardiac Plug [ACP]), which reduced device embolisations to 2%. Still, given the intricacy of the procedure, the rate of procedural complications remains relatively high (9.8%) and the procedure has a relatively flat learning curve [8–10]. The Watchman device is another widely used dedicated LAA occluder. In a landmark randomised study with this device (PROTECT-AF) [2], patients were randomised to a vitamin K antagonist (VKA) or LAAO. At 1 year, LAAO

Key words: left atrial appendage; atrial fibrillation; interventional closure; device closure; stroke; embolism

Introduction

The prevalence of atrial fibrillation (AF) is increasing owing to the demographics of aging Western societies. In patients below the age of 55 years the prevalence of AF is 0.1%, but this increases to 9% in patients over 80 years of age [1]. Stroke is the most devastating complication of AF and occurs at an annual rate of 5% in non-anticoagulated patients [2]. Hence, stroke prevention is an essential part of the management of AF. Oral anticoagulation (OAC) with either warfarin or non-vitamin K anticoagulants (novel oral anticoagulants: NOACs) reduces the risk of stroke by 65%, but it comes at the price of an annual rate of major bleeding complications of up to 5% [3].

In over 90% of AF patients, thrombi can be detected in the left atrial appendage (LAA), which is the rationale for LAA occlusion (LAAO) as an alternative therapy for stroke prevention in AF patients. Several devices have been used (fig. 1). The most commonly used percutaneous devices for LAAO are the Amplatzer (St. Jude Medical, St. Paul, MN) and the Watchman (Boston Scientific, Marlborough, MA) devices. Historically, the PLAATO device (ev3 Inc, Plymouth, MN) was the first available percutaneous device for LAAO, but was removed from the market because of economic considerations [5, 6]. The gap was filled by off-label use of nondedicated Amplatzer devices used primarily for the occlusion of patent foramen ovale (PFO), atrial septal defects (ASDs) or ventricular septal defect (VSDs) [7]. These nondedicated devices served the purpose of stroke prevention, but came along with a relatively high embolisation rate (12%) [8]. In 2008, a dedicated Amplatzer device became available (AMPLATZER Cardiac Plug [ACP]), which reduced device embolisations to 2%. Still, given the intricacy of the procedure, the rate of procedural complications remains relatively high (9.8%) and the procedure has a relatively flat learning curve [8–10]. The Watchman device is another widely used dedicated LAA occluder. In a landmark randomised study with this device (PROTECT-AF) [2], patients were randomised to a vitamin K antagonist (VKA) or LAAO. At 1 year, LAAO

proved to be noninferior to VKAs for the primary end-point of stroke, cardiovascular or unexpected death and systemic embolism. In the intervention group, adverse safety events were more frequent, mostly procedure-related pericardial tamponade and periprocedural strokes, again underlining the intricacy of the procedure. With increasing operator experience, procedural adverse safety events were considerably reduced [11]. However, it took almost 4 years of follow-up to neutralise the initial procedure-related events by fewer adverse thrombotic events thereafter. This translated into superiority of LAAO over VKAs for stroke, systemic embolism and cardiovascular death. Of note, mortality was significantly reduced by 40% in the LAAO group as compared with VKAs [12]. It can therefore be speculated that with longer follow-up survival curves might further diverge, resulting in an even more pronounced benefit of LAAO. Besides offering an effective treatment option, LAAO proved to be more cost effective than VKAs and even more so than NOACs [13].

We report our institutional experience with LAAO at the University Heart Centre Zurich, Switzerland over a period of more than 5-years, including different operators and different approaches to LAAO.

**Methods**

**Patients**

This was a retrospective single-centre registry study of all patients undergoing LAAO at the University Heart Centre Zurich between June 2010 and November 2015. Indications for LAAO included AF with CHA²DS²-VASc ≥1 and contraindication for OAC, high bleeding risk or patient preference. Written informed consent was obtained from all patients. Data of clinically indicated follow-up procedures and outpatient consultations were collected. From 2015 on, patients who gave a general consent to data collection were additionally included in a prospective registry. Patients who did not give such a general consent were excluded from the registry and from the current analysis. This study was conducted according to the stipulations of the local ethics committee (Ethikkommission des Kantons Zürich, Switzerland).

**Procedure**

Interventions took place (a) in the catheterisation laboratory, if the procedure was performed under local anaesthesia or with intracardiac echocardiographic (ICE) guidance, or (b) in the hybrid operating suite, if general anaesthesia and transoesophageal echocardiography (TEE) guidance was used, or if LAAO was performed in conjunction with transcatheter aortic valve implantation or transcatheter mitral interventions.

LAAO was either a stand-alone procedure or was combined with selective coronary angiography, percutaneous coronary intervention (PCI), transcatheter aortic valve implantation (TAVI), MitraClip implantation, PFO/ASD closure or other interventions.

At the initiation of the procedure a bolus of 5000 units of heparin was given intravenously. If a PFO or ASD had been detected previously, it was used for left atrial access by one operator (FN); transeptal puncture was routine in the remainder. A standard transseptal...
sheath (e.g., Mullins™ transseptal sheath and Brock-enbrough needle, Medtronic Inc., Minneapolis, MN) was used for transseptal puncture. A 0.035 inch support wire (e.g., Meier Backup wire, Boston Scientific, Marlborough, MA) was used to introduce the large bore Amplatzer delivery sheath through the groin and into the left atrium. If a Watchman occluder was selected, a dedicated Watchman sheath was used.

The landing zone, as well as the orifice and the length of the LAA were visualised and the size was estimated with use of contrast injections through the sheath in two angles (typically right anterior oblique [RAO] caudal and RAO cranial). If available, TEE or ICE was used for sizing. An at least 20% oversized device was selected accordingly or a device that best fitted the individual anatomy was used. After deployment of the device, a tug test and contrast injections were performed to confirm a stable device position [14] (fig. 2). Transthoracic echocardiography (TTE) was performed on the day of the procedure or the next morning to confirm a correct device position in the LAA. Patients were discharged on acetylsalicylic acid (ASA) 100 mg and clopidogrel 75 mg for 1–6 months. Oral anticoagulation was permanently stopped the day of the procedure.

**Follow-up**

After 3–6 months, a follow-up TEE was performed to verify correct device position and to exclude relevant residual leaks into the LAA or thrombi on the device. If TEE was not feasible, follow-up TTE or computed tomography (CT) was used instead.

**Endpoints**

Procedural success was defined as a correct device position upon termination of the procedure. Peri-procedural adverse events included a composite endpoint of procedure-related death, stroke, tamponade (need for urgent drainage or surgical bailout), Valve Academic Research Consortium-2 (VARC) major or life-threatening bleeding, VARC kidney injury grade 3 and device embolisation.

Clinical follow-up data included deaths (cardiovascular, other or unknown), cerebrovascular accidents and major bleeding events.

*Figure 2: Device deployment.* (A) Contrast injection to the left atrial appendage through a 14 French TorqVue 45x45 sheath with an outer diameter of 5.4 mm (left metering). Estimated diameter of the landing zone (right metering). (B) Amplatzer Amulet device still attached to the delivery cable. (C) Once a stable position was confirmed, the device was released.
Statistical analysis
Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Between-group comparisons were made using one-way analysis of variance or student’s t-test, as appropriate. Categorical data are presented as frequency (percentages) and were compared with use of the Fisher exact or the chi-square test. All probability values and confidence intervals were two-sided. A probability value of <0.05 was considered significant, and all tests were two-tailed. All analyses were performed with SPSS version 21.0 software (SPSS Inc., Chicago, IL).

Results
Patient characteristics
From June 2010 until November 2015 LAAO was performed in 284 patients suffering from AF, of whom 247 patients (164 [86%] males, age 77 ± 8.9 years), were included in this study. In 2015, 132 LAAOs were performed at the University Heart Centre Zurich, of which 95 (72%) were included; the remaining patients did not give signed informed consent for general data collection and participation in the study.

AF was persistent or permanent in 40.1% (99 patients), and paroxysmal in 56.3% (139 patients); 7.9% (15 patients) suffered from (concomitant) atrial flutter. Mean CHA2DS2-Vasc score was 4.5 ± 1.4; mean HAS-BLED score was 3.6 ± 1.1. Patient baseline characteristics and risk factors are listed in table 1.

Indications for LAAO
The indication for LAAO was high risk of bleeding in 66.4% (164 patients) or previous relevant bleeding in 42.5% (105 patients). Specifically, 23% (44 patients) had a history of intracranial and 19.9% (38 patients) of gastrointestinal (GI) bleeding. 14.2% (35 patients) had a high risk for falls or prior falls, in 14.2% (34 patients) it was difficult to maintain a therapeutic international normalised ratio (INR) and in 19.8% (49 patients) LAAO was performed to avoid triple anticoagulation with adjunctive antiplatelet therapy.

Procedural outcome
Since 2010, a significant increase in the number of procedures was noted, with 5 procedures in 2010 and 132 (95 included in this study) procedures in the first 11 months of 2015 (p = 0.003; fig. 3). The exact numbers of interventions each year are shown in table 2.

Figure 3: Number of LAAOs performed each year. In 2015, 132 LAAOs were performed of which only 95 were included in the study.

Table 1: Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77 ± 8.9</td>
</tr>
<tr>
<td>CHA2DS2-Vasc</td>
<td>4.5 ± 1.4</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>3.6 ± 1.1</td>
</tr>
<tr>
<td>Male</td>
<td>86.0% 164</td>
</tr>
<tr>
<td>Heart failure</td>
<td>19.8% 49</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81.8% 202</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>86.9% 166</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27.5% 68</td>
</tr>
<tr>
<td>History of stroke</td>
<td>33.6% 83</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>16.2% 40</td>
</tr>
<tr>
<td>Liver disease</td>
<td>3.2% 8</td>
</tr>
<tr>
<td>High risk of bleeding</td>
<td>66.4% 164</td>
</tr>
<tr>
<td>Prior relevant bleeding</td>
<td>42.5% 105</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>19.5% 38</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>23.0% 44</td>
</tr>
<tr>
<td>High risk of falls or prior falls</td>
<td>14.2% 35</td>
</tr>
<tr>
<td>Labile INR</td>
<td>14.2% 34</td>
</tr>
<tr>
<td>Avoid triple therapy</td>
<td>19.8% 49</td>
</tr>
<tr>
<td>Rejection of OAC</td>
<td>1.0% 2</td>
</tr>
<tr>
<td>Avoid triple therapy</td>
<td>19.8% 49</td>
</tr>
<tr>
<td>Drugs predisposing to bleeding</td>
<td>85.8% 212</td>
</tr>
<tr>
<td>Alcohol abuse (&gt;8 U/w)</td>
<td>5.7% 14</td>
</tr>
</tbody>
</table>

Table 2: Different devices implanted each year.

<table>
<thead>
<tr>
<th>Year</th>
<th>ACP</th>
<th>Amulet</th>
<th>Watchman</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>2011</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>2012</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>2013</td>
<td>32</td>
<td>10</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td>2014</td>
<td>47</td>
<td>7</td>
<td>26</td>
<td>80</td>
</tr>
<tr>
<td>2015</td>
<td>3</td>
<td>70</td>
<td>22</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>87</td>
<td>53</td>
<td>247</td>
</tr>
</tbody>
</table>
death and seven tamponades (five requiring urgent percutaneous drainage and two requiring surgical bailout), two life-threatening major bleeds (one TEE-induced upper GI bleeding and one pericardial perforation), three VARC kidney injuries grade 3 and four (1.6%) device embolisations. All embolised devices were snared and a second device was implanted successfully, except in one patient where the embolised device was detected only during follow-up and the patient refused implantation of a second device [15].

The one patient with periprocedural death underwent a combined intervention: MitraClip intervention and LAAO were successful, whereas a subsequent anterior mini-thoracotomy for a single coronary bypass revealed a pericardial effusion with haemodynamic instability. The reason for the pericardial tamponade was found to be a perforation of the right ventricle. The reason remains unclear, particularly since the patient was stable throughout the percutaneous interventions. Potential causes might have been manipulations of the transseptal needle or it might have occurred during surgery. Emergency sternotomy was performed and the right ventricular perforation was sutured. After successful bypass surgery, the patient could not be weaned from the heart lung machine. The further course was complicated by clotting of the extra corporal circulation and recurrent bleeding from the right ventricle. The patient died subsequently on the day of surgery.

The most severe complication related to LAAO was LAA perforation during repositioning of the device. The device was found to be in the pericardial space. Acute pericardial tamponade was initially treated with pericardial drainage and release of the device and implantation of a second LAA occluder to seal the entrance of the LAA. Ongoing bleeding with haemodynamic instability made emergency surgical bailout necessary. During surgery, the LAA was clipped with an ATRICURE 35 mm clip, which terminated the bleeding. The postoperative course was complicated by a prolonged intensive care unit stay with acute renal failure and delirium. The patient was finally discharged to rehabilitation and is currently living independently at home without any long-term sequela (recent follow-up was 2 years after the procedure).

Life-threatening major bleeding occurred in a patient undergoing combined MitraClip implantation and LAAO. During the procedure, acute haemorrhagic shock developed. Emergency gastroscopy revealed TEE-related mid-oesophageal bleeding as the cause. Bleeding stopped spontaneously and the patient fully recovered.

Several of the complications of this series were not directly related to LAAO, and can be explained by the very large number of combined interventions, including high-risk interventions. Overall, there was no statistical difference in complications from 2010 to 2015 (p = 0.6).

Indeed, 62% (n = 153) of LAAOs were combined interventions. In 29.1% (72 patients), LAAO was performed after coronary angiography and in 14.6% (36 patients) combined with PCI, in 22.7% (56 patients) with TAVI and in 5.7% (14 patients) with MitraClip. Finally, in 8.1% (20 patients) LAAO was followed by PFO or ASD closure and in 2.4% (6 patients) combined with other interventions (fig. 4).

**LAAO devices**

In almost half of the patients (43.3% or 107 patients), ACP devices were used, whereas the Amplatzer Amulet was used in 35.2% (87 patients) and the Watchman Occluders in 21.5% (53 patients) (fig. 5). The numbers of different devices implanted are listed in table 2.

In 6.5% (16 patients), the initial device size was replaced with a different device (2 [3.8%] Watchman, 8 [76.6%] ACP, 6 [6.9%] Amulet). The reasons for replacing the initial device were anatomical (e.g., funnel-shaped landing...
zone) or mis-sizing. In one patient (0.4%), LAA occlusion could only be achieved after replacing the second device with a third device (ACP).

In 8.2% (20 patients), the LAA was reached using a PFO or ASD, which was subsequently occluded using a PFO or ASD occluder. The PFO and ASD closures were uneventful; the same sheath and delivery system as for the LAA occlusion (TorqVue 45 × 45 sheath) were used.

Mean duration of hospitalisation was 7.4 ± 7.0 days. In patients with isolated LAAO (not combined interventions) median hospitalisation was 3 days; IQR 2–6 days. Seventeen patients (6.9%) were discharged the day of intervention and 57 patients (23.1%) the day after the intervention. For patients referred for isolated LAAO on an elective basis, same day discharge or discharge the day after the procedure is routine at our institution. Patients were discharged on ASA indefinitely (88.3%; 218 patients) and a thienopyridine for either 3 (22.7%; 56 patients), 6 (25.5%; 63 patients) or 12 months (15.8%; 39 patients).

Follow-up

Clinical follow-up was complete in 89.9% (222 patients) after a mean duration of 10 ± 9.6 months. Overall, 9.9% (22 patients) died during follow-up (after a median of 3 months; IQR 1–5 months). The deaths included cardiac deaths of seven patients, which were due to heart failure in three and ventricular tachycardia and/or fibrillation in two, with one each due to stroke or endocarditis (occurring after an Enterococcus faecalis positive urinary tract infection 7 months after the intervention). Ten deaths were non-cardiac in nature, one due to bleeding and five of unknown cause (fig. 6).

Of all deaths, one due to stroke was related to LAAO. In this case the patient died as a result of a cerebrovascular event (major stroke) occurring 2 weeks after successful LAAO in conjunction with transcatheter aortic valve implantation. Upon presentation of the patient with a major stroke, TEE showed mobile thrombus on the disc of the device as the most likely source of embolism. Three cerebrovascular events (1.4%) occurred during follow-up. In two of these patients a control TEE showed no thrombus on the device; the third patient is described above. Major bleeding occurred in 3 (1.4%) patients. Two major bleeds were life-threatening (one traumatic intracerebral bleeding and one GI bleeding with anaemia) and one was not life-threatening (GI bleeding with drop in haemoglobin to 72 g/l). Clinical follow-up data are shown in table 3.

Of the 222 patients who had clinical follow-up, 70.4% (174 patients) had echocardiographic imaging, and one patient underwent a CT scan (at his own request), confirming a correct device position in 99.4%. A relevant residual shunt or leak of ≥5 mm was found in only one (0.6%) patient, and thrombus on the device was detected in 3.4% (six patients) in three of whom the thrombus appeared to be mobile (table 4). In one pa-

Table 3: Clinical follow-up data.

<table>
<thead>
<tr>
<th>n</th>
<th>Death</th>
<th>Cardiac</th>
<th>Non-cardiac</th>
<th>Unknown</th>
<th>Stroke</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>222</td>
<td>22</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>89.9%</td>
<td>9.9%</td>
<td>1.4%</td>
<td>1.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 6: Clinical follow-up data of 222 (89.9%) patients.

Discussion

This study, based on a large single centre experience, demonstrated that percutaneous LAAO is technically
feasible with a high procedural success rate of over 98%, comparing favourably with previous reports of even larger patient populations (e.g., procedural success: 90.9% in the PROTECT-AF trial [16], 94.4% in the CAP registry [14], 95.1% in the PREVAIL trial [11], 98.5% in the EWOLUTION registry [17] and 97.3% in the largest European multicentre registry [18]). However, LAAO is a procedure with a notable complication rate. Indeed, peri-procedural adverse events occurred in 4.9% which was comparable to other reports (e.g., 5.0% in the European registry [18], 7.7% in the PROTECT-AF Trial [16], 3.7% in the CAP study [14], 2.2% in the PREVAIL study [11] and 2.8% in the EWOLUTION registry [17]). The study population comprised patients at high risk for stroke and bleeding. The average CHA2DS2-Vasc score was 4.5 and a HAS-BLED score of 3.6. Assuming a 65% risk reduction in the occurrence of cerebrovascular accidents with VKAs, the stroke rate after 10 months with VKA therapy would be 1.5%, a value comparable to the observed stroke rate in this registry. On the other hand, major bleeding complications were exceedingly infrequent and were reduced 3.8-fold as compared with the expected rate of 5.5% at 10 months (according to the HAS-BLED score) (fig. 7). Combined interventions are routine in our institution and performed in 62% of the patients. As such combined procedures are inherently associated with an increased risk, this fact negatively influenced the overall peri-procedural adverse event rate (table 5). Indeed, combined interventions accounted for 62% of all procedures and 75% of all adverse events with LAAO in this series. Together with a previous report [8], this is one of the highest ever reported percentages of combined interventions in an LAAO registry or trial. In the European registry, LAAO was performed as part of a combined intervention in 20.6%, [18], and no such combined interventions were performed in the PROTECT-AF trial. In spite of a higher complication rate, our data support combination of procedures as this tends to be more patient-friendly, and allows a single hospitalisation and early discharge in most cases. However, there is a disincentive in the Swiss healthcare system (due to the design of disease-related groups[DRGs]) to combine procedures and therefore such procedures are staged in most institutions for economic reasons. As under these conditions individual billing of the insurance companies for each procedure is possible, the overall healthcare costs are considerably higher than with combined procedures. Not only does this policy make the overall healthcare system more expensive and less patient-friendly, but it could even result in more adverse events if patients experience bleeding complications while awaiting LAAO. Such disincentives should be removed (e.g., by creating DRGs for combined interventions), such that institutions continuing to perform combined interventions are not punished by the system. Thrombus formation on the device remains an issue and occurs in 3–4% of patients. If detected early, a short course of VKA, NOAC or low-molecular weight heparin generally resolves the issue [19, 20]. Patients with an absolute contraindication to VKAs may present a dilemma under these conditions, but low-dose oral anticoagulation with an NOAC could be considered. In order to reduce the risk of thrombus formation on the device, a longer course of dual antiplatelet therapy (DAPT) might be preferable, but exposes these fragile patients to a higher bleeding risk. The same is true for the regimen recommended after implantation of the Watchman device: OAC was continued for 6 weeks after device implantation in the PROTECT-AF trial. In patients at very high risk of bleeding, even aspirin monotherapy or no antiplatelet therapy may present an op-

<table>
<thead>
<tr>
<th>Complication rates in the subgroups of patients undergoing isolated LAAO or under going combined interventions.</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>LAAO only</td>
</tr>
<tr>
<td>Combined interventions</td>
</tr>
</tbody>
</table>

**Figure 7:** Incidence of stroke and major bleeding after 10 months follow-up of the study patients (left column). Expected incident of stroke according to CHA2DS2-VASC-Score of 4 or 5. Expected incidence of major bleeding according to HAS-BLED-Score of 3 or 4. Patients in our study showed a mean CHA2DS2-VASC-score of 4.5 ± 1.4 and a mean HAS-BLED of 3.6 ± 1.1. Mean follow-up was 10 ± 9.6 months.
From 1 month (1M) to lifelong (24+ M). In a few patients no antiplatelet therapy (no APT) or only single antiplatelet therapy (MAPT) was prescribed.

Figure 8: Postprocedural anticoagulation regimens. Dual antiplatelet therapy was given from 1 month (1M) to lifelong (24+ M). In a few patients no antiplatelet therapy (no APT) or only single antiplatelet therapy (MAPT) was prescribed.

Conclusion

In experienced, high volume centres LAAO can be performed with a high procedural success rate and a low complication rate. Nevertheless, LAAO is a complex procedure with potentially important complications that can keep at a low level only after an important learning curve. Under these conditions, LAAO is a valuable alternative to oral anticoagulation in stroke prevention. Importantly, the procedure, if successfully performed, markedly reduces the bleeding risk that is associated with any type of oral anticoagulation. Thus, LAAO should therefore specifically be considered as first-line therapy for stroke prevention in patients at high risk of bleeding, on triple anticoagulation and with a high risk of falls, but may also be offered as an option to all patients suffering from atrial fibrillation after proper informed consent.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

References

The full list of references is included in the online article at www.cardiovascmed.ch.

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A new tool to help diagnose patients suffering from paroxysmal palpitations?

A handheld ECG device

Serban Puricel, Marco Mancinetti, Etienne Delacrétaz, Stéphane Cook
University and Hospital Fribourg, Switzerland

Introduction

The detection of paroxysmal arrhythmias in patients suffering from intermittent palpitations remains an important challenge in modern cardiology. Correct diagnosis of the underlying paroxysmal arrhythmia is needed in order to provide state-of-the-art medical care. Current monitoring tools such as 24-hour Holter ECG, continuous 7-day ECG, and external or implantable loop recorders have many disadvantages and a presumably suboptimal sensitivity for the diagnosis of paroxysmal arrhythmias. Handheld ECG devices are an attractive alternative that may mitigate some of the limitations of conventional devices and have the potential to be implemented in routine clinical practice. We describe the case of a 76-year-old male Caucasian suffering from palpitations associated with malaise. In providing the patient with a handheld ECG device (Zenicor ECG), paroxysmal atrial fibrillation was diagnosed after 2 days. The patient was started on oral anticoagulants and referred for radiofrequency ablation. Portable ECG devices reportedly show an excellent efficiency for the detection of significant arrhythmia in hospital and outpatient settings. Given their wide availability and low cost, they could easily be implemented in daily clinical practice.

Case report

A 76-year-old male patient in good physical condition and known for well-controlled arterial hypertension complained of occasional palpitations associated with malaise. He denied chest pain and loss of consciousness. Clinical examination showed a slightly elevated blood pressure. Transthoracic echocardiography showed early hypertensive heart disease with concentric left ventricular hypertrophy, left atrial dilation, and mild diastolic dysfunction but preserved left ventricular systolic function. The symptoms occurred early (<3 weeks) after radiofrequency ablation of a typical right atrial flutter. Given the good haemodynamic tolerance and a high suspicion of atrial fibrillation, we decided to test recording the arrhythmia with a handheld ECG device (Zenicor ECG, fig. 1). We provided the patient with a device and gave instructions pertaining to its use (application of the thumbs of both hands on the sensors for 30 seconds). Patient instruction took no more than 3 minutes and the patient was advised to record whenever he was symptomatic, at the onset of symptoms. Two days later, the patient contacted us because of a recurrence of three short episodes of self-limiting palpitations and malaise that provided three consecutive recordings. The interrogation of the dedicated web-based platform demonstrated atrial fibrillation (fig. 2). The patient was then given oral anticoagulants and referred for radiofrequency ablation of atrial fibrillation.

Discussion

Palpitations are the most common complaint in patients referred to general cardiologists. In most cases, identification of their causes remains challeng-
ing. In the case of high suspicion of symptomatic re-entry tachycardia (sudden beginning and end, post-paroxysmal diuresis, typical symptom localisation) or severity of symptoms (angina, syncope), an invasive electrophysiological study is usually discussed. Otherwise, noninvasive (external loop recorder, 24-hour Holter ECG or continuous 7-day ECG) or invasive (implantable loop recorder) ECG monitoring is usually ad-

Table 1: Available handheld ECG devices.

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Price</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zenicor ECG</td>
<td>Zenicor Medical Systems</td>
<td>1400 CHF</td>
<td><a href="http://www.zenicor.com">www.zenicor.com</a></td>
</tr>
<tr>
<td>Beurer ME 90</td>
<td>Beurer Gmbh</td>
<td>115 CHF</td>
<td><a href="http://www.beurer.com">www.beurer.com</a></td>
</tr>
<tr>
<td>Kardiamobile</td>
<td>AliveCor Inc.</td>
<td>109 USD</td>
<td><a href="http://www.alivecor.com">www.alivecor.com</a></td>
</tr>
<tr>
<td>Blade Micro Ambulatory ECG Recorder</td>
<td>DIMETEK Digital Medical Technologies Ltd</td>
<td>299 USD</td>
<td><a href="http://www.dimetekus.com">www.dimetekus.com</a></td>
</tr>
<tr>
<td>ECG Check</td>
<td>Cardiac Designs</td>
<td>139 USD</td>
<td><a href="http://www.ecgcheck.com">www.ecgcheck.com</a></td>
</tr>
<tr>
<td>HeartCheck ECG PEN</td>
<td>Cardio Comm Solutions Inc.</td>
<td>259 USD</td>
<td><a href="http://www.theheartcheck.com">www.theheartcheck.com</a></td>
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<tr>
<td>InstantCheck</td>
<td>DailyCare Biomedical Inc.</td>
<td>299 USD</td>
<td><a href="http://www.dcbiomed.com">www.dcbiomed.com</a></td>
</tr>
<tr>
<td>MD100E Handheld ECG</td>
<td>ChoiceMMed</td>
<td>166 USD</td>
<td><a href="http://www.choicecmmed.com">www.choicecmmed.com</a></td>
</tr>
<tr>
<td>PC-80B Color</td>
<td>Shenzhen Creative Industry Co., Ltd.</td>
<td>100 USD</td>
<td><a href="http://www.creative-sz.com">www.creative-sz.com</a></td>
</tr>
<tr>
<td>Reka E100</td>
<td>Reka Health</td>
<td>Not available</td>
<td><a href="http://www.rekahealth.com">www.rekahealth.com</a></td>
</tr>
</tbody>
</table>

CHF = Swiss Francs, USD = US Dollars
This is not an exhaustive list. Not all devices may be available in Switzerland. Prices are as indicated on the companies’ websites or as indicated by official distributors.

Figure 2: Web-based ECG strip showing atrial fibrillation in our patient on the Zenicor-ECG Doctor System.
advocated. The main limitation pertaining to external loop recorders or 24-hour Holter ECGs is the limited duration of monitoring, which may result in failure to identify the arrhythmia in patients who do not suffer a paroxysm throughout the observed period. Implantable loop recorders are expensive and their sensitivity and specificity depends on prespecified detection algorithms and patient symptoms.

Handheld ECG recording devices have become widely available. Some devices consist of a larger piece of hardware that directly acquires and transmits data via a mobile internet connection (e.g., Zenicor ECG) while others consist of a light piece of hardware that can conveniently be connected to a smartphone and that acquires and transmits data via a dedicated application (e.g., Kardia, AliveCor Inc., USA). Most possess inbuilt algorithms that facilitate the detection of arrhythmia. In addition to the automated detection algorithms, manual ECG analysis can be performed on mostly high quality ECG strips that are available on web-based platforms or are distributed via e-mail. Table 1 provides information about available handheld ECG devices. Haberman and colleagues reported excellent sensitivity (94%) and specificity (99%) for the detection of atrial fibrillation with a handheld device including an inbuilt algorithm in 381 athletes, healthy adults (first- and second-year medical students) and ambulatory patients of the University of Southern California cardiology clinic, in an outpatient setting [1]. Hendrikx and colleagues screened an asymptomatic outpatient population of 928 patients with CHADS2 ≥1 and found newly diagnosed atrial fibrillation in 3.8% by use of the Zenicor ECG [2].

The performance of the Zenicor ECG compared with standard 24-hour ECG monitoring for the detection of significant arrhythmias in symptomatic patients was assessed in 95 patients referred to a Swedish outpatient clinic for ambiguous palpitations or dizziness/presyncope. The device was used over a period of 28 days and was significantly more effective for the detection of arrhythmias than the standard 24-hour Holter ECG monitoring (p <0.01) [3]. In the hospital setting, handheld ECG devices have been reported to be effective and cost-effective for the detection of atrial fibrillation when implemented by means of a structured screening strategy [4]. To our knowledge, handheld devices are used for this purpose in over 300 clinics in Scandinavia, the UK, Germany and Austria.

The advantages of handheld devices are their price, their ease of use and the extended duration of monitoring. The price of the device used in this case is approximately 1400 CHF, compared with approximately 4800 CHF for implantable loop recorders and 4200 CHF or 2400–3600 CHF for Holter ECG or external loop recorders, respectively. Implantable loop recorders are for single use only and have to be purchased for every patient, whereas external devices can be employed in a multitude of consecutive patients once purchased. The cost of analysing the recordings of external monitoring devices per patient is 350 CHF for a Holter ECG and 160 CHF for external loop recorders. The use of handheld devices may generate additional fees for the transmission of data or the use of the dedicated web-based platform.

On the other hand, portable devices consisting of a larger piece of hardware are less likely to be used during physical exercise – a limitation that is not the case with smartphone-connectable systems. Furthermore, if recording is activated solely during symptomatic episodes, asymptomatic but relevant arrhythmias (such as silent atrial fibrillation) may easily be missed. In addition, the beginning and end of the arrhythmia can be recorded with loop recorders and continuous monitoring, but are normally missed with handheld devices. No recordings can be made during sleep or syncope, and the recording of only one lead may lead to underdetection of atrial flutter because of the difficulty in differentiating between atrial flutter, regular supraventricular re-entry tachycardia and sinus rhythm. The use of hand-held devices requires a good patient compliance and may be biased if friends or family members use the device.

Conclusion

The use of the handheld Zenicor ECG device permitted prompt diagnosis of atrial fibrillation in a patient suffering from palpitations with associated malaise. Handheld ECG devices are reportedly effective for the detection of significant arrhythmia, easy to use and low cost. They constitute a very attractive alternative to conventional methods for the detection and screening of symptomatic and asymptomatic arrhythmia in daily clinical practice, and could be easily implemented in Switzerland given their wide availability and low price.

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References

The full list of references is included in the online version of the article at www.cardiovascmed.ch
**A rare but challenging condition**

Paradoxical coronary spasm after intracoronary nitroglycerin injection

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**Introduction**

Vasospastic angina is a clinical disorder primarily attributable to coronary artery spasm and typically characterised by a history of rest angina that promptly responds to short-acting nitrates [1]. Coronary spasm usually occurs in patients without evidence of coronary atherosclerosis, but can also be superimposed on atherosclerotic lesions [2]. A paradoxical vasospastic response to nitrates in vasospastic angina patients represents a rare but very challenging condition and the best therapeutic approach in this particular subgroup of patients remains unclear [3–4]. We describe the case of a patient affected by vasospastic angina, presenting with asymptomatic transmural ischaemia during a routine exercise stress test and a paradoxical subocclusive coronary spasm, superimposed on a non-significant coronary stenosis, following intracoronary nitroglycerin injection during coronary angiography. Other cases of paradoxical vasospastic response to nitrates during coronary angiography have been already described in literature. However, in these previously described cases, coronary spasm occurred in a portion of the vessel close to the catheter tip or following sublingual nitroglycerin administration, thus making it difficult to clearly assess the possible causative relation between nitrate administration and coronary spasm. This represents, to the best of our knowledge, the first described case of paradoxical coronary spasm occurring few seconds after direct intracoronary nitroglycerin injection and in a portion of the vessel far enough from the catheter tip to exclude late-onset catheter-induced spasm in the absence of any catheter-tip drop-in or deep intubation. A paradoxical vasospastic response to nitrates in vasospastic angina patients represents a rare but very challenging condition. Thus, the best therapeutic approach in this subgroup of patients remains unclear. We describe the case of a patient affected by vasospastic angina, presenting with asymptomatic transmural ischaemia during a routine exercise stress test and a paradoxical subocclusive coronary spasm, superimposed on a non-significant coronary stenosis, following intracoronary nitroglycerin injection during coronary angiography. This represents, to the best of our knowledge, the first described case of paradoxical coronary spasm occurring few seconds after direct intracoronary nitroglycerin injection and in a portion of the vessel far enough from the catheter tip to exclude late-onset catheter-induced spasm in the absence of any catheter-tip drop-in or deep intubation.

**Case description**

A 72-year-old man, known for hypertension and dyslipidaemia, was treated with implantation of a bare metal stent in the proximal portion of the left anterior descending artery 10 years ago. One year ago he experienced a symptomatic very late in-stent restenosis of the left anterior descending artery stent, treated with drug eluting balloon.

A routine 1-year follow-up exercise stress test was performed while the patient was asymptomatic and without interruption of β-blocker therapy. His treatment at the moment of the exercise stress test included aspirin (100 mg 1×/day), lisinopril (20 mg 1×/day), pravastatin (40 mg 1×/day) and atenolol (25 mg 1×/day). During the exercise stress test the patient was pain free. However, as shown in figure 1, significant ST-segment elevation occurred in all inferior leads. This ST-segment elevation appeared during the effort phase and persisted throughout the recovery phase. The patient was then referred for coronary angiography, which showed a non-significant stenosis (less than 50% of the reference vessel diameter) in the proximal-mid portion of the right coronary artery. During diagnostic coronary
Figure 1: Panel A. Basal electrocardiogram (ECG), showing no significant ST-segment modifications. Panel B. ECG recorded during the stress test. A significant ST-segment elevation occurred in inferior leads. These ECG modifications persisted throughout the recovery phase.
angiography, a 1000 µg intracoronary nitroglycerin bolus was administered in order to better assess reference vessel diameter and stenosis severity. A few seconds after intracoronary nitroglycerin injection, asymptomatic paradoxical subocclusive coronary spasm, superimposed on the previously described plaque, was observed (fig. 2), suggesting a diagnosis of vasospastic angina for this patient. Of note, no drop-in of the catheter tip, which is quite common during right coronary artery cannulation and frequently associated with coronary spasm, was observed during coronary angiography. No deep intubation of the right coronary artery occurred. Because of the transmural ischaemia documented on the exercise stress test, a drug-eluting stent was implanted in the right coronary artery. Interestingly, the spasm was sustained and lasted until stent implantation. The clinical evolution was favourable and a 1-month follow-up exercise stress test was clinically and electrically negative. Holter monitoring did not show any transient ST-segment elevation and the patient did not experience any episodes of chest pain during 6 months of follow-up.

**Discussion**

Vasospastic angina is a clinical disorder primarily attributable to coronary artery spasm and typically characterised by a history of rest angina that promptly responds to short-acting nitrates. During chest pain episodes, the electrocardiogram usually shows tran-
sient ST-segment elevation. Ischaemic episodes often occur in the night or early in the morning and are rarely triggered by physical activity[1]. Smoking represents a significant risk factor for vasospastic angina and Asian ethnicity patients seem to have a higher risk of developing vasospastic angina [5]. Hyperventilation represents a common trigger for coronary spasm in vasospastic angina patients [5]. Moreover, coronary spasms seem to be more frequent during the cold season, probably a result of an increase in systemic sympathetic tone [6]. The prognosis of patients with vasospastic angina is favourable. However, complications can occur, including acute myocardial infarction, malignant ventricular arrhythmias, high-grade atrioventricular blocks, syncope and sudden cardiac arrest[5].

The physiopathology of epicardial coronary spasm is complex and multifactorial, the major determinants being endothelial dysfunction and enhanced contractility of vascular smooth muscle. Endothelial dysfunction essentially leads to deficient basal release of nitric oxide, which induces smooth muscle relaxation. Epicardial coronary spasm can be defined as focal when confined within the borders of a coronary segment and diffuse when adjacent coronary segments are involved[2].

Coronary spasm usually occurs (almost 70% of reported cases) in patients without evidence of coronary atherosclerosis. However, as in our case, coronary spasm can be superimposed on atherosclerotic lesions, with a potential risk of plaque rupture and acute myocardial infarction [2]. In clinical practice, provocative tests are usually necessary to confirm the diagnosis of vasospastic angina. The gold standard diagnostic approach involves invasive coronary angiography with intracoronary acetylcholine or ergonovine used as provocative pharmacological stimulus [5]. In our patient, coronary spasm was paradoxically induced by intracoronary nitroglycerin injection, which suggests severe coronary hyperreactivity. Interestingly, hyperventilation, which represents a well-known trigger for coronary spasms in vasospastic angina patients, was not observed during either the exercise stress test or coronary angiography. However, the exercise stress test and coronary angiography were both performed during the cold season; therefore, an influence of meteorological conditions cannot be excluded in the present case.

This paradoxical response to nitroglycerin was surprising, since nitrates usually induce vasodilatation, even in endothelium-deficient coronary arteries, due to their direct effect on smooth muscle cells in the media. However, a paradoxical vasoconstrictor response to nitrates has already been described in literature. A few clinical reports described a paradoxical increase in frequency and intensity of chest pain episodes in vasospastic angina patients treated with long-acting nitrates. Moreover, in these cases, the clinical evolution was favourable after nitrate discontinuation [3–4]. The mechanisms explaining this paradoxical response to nitrates in patients chronically treated with long-acting nitrates are mostly unknown, but are likely to involve the same mechanisms that account for the well-known phenomena of nitrate tolerance and rebound angina [7]. The first cases of paradoxical coronary spasm occurring during coronary angiography following nitrate administration were reported by Feldman et al. They described two focal coronary spasms occurring in the right coronary artery a few minutes after sublingual nitroglycerin administration during diagnostic coronary angiography. However, both epicardial spasms involved the ostial portion of the vessel and coronary angiography was performed with the Sones technique, which is no longer routinely used in the catheterisation laboratory [8]. A few other cases of paradoxical coronary spasm occurring during coronary angiography following nitrates administration were reported in the Judkins era. Once again, the coronary spasm involved a portion of the vessel close to the catheter tip, thus making difficult to exclude late-onset catheter-induced spasm [9–10]. Hamirani et al. recently described the first case of mid-vessel coronary spasm following nitrate administration during diagnostic coronary angiography performed with Judkins technique. In this case, focal coronary spasm, superimposed on a non-significant epicardial stenosis, was observed in the mid-portion of the left anterior descending artery 5 minutes after sublingual administration of nitroglycerin. Of note, a few minutes after the spontaneous resolution of the epicardial coronary spasm, an intracoronary nitroglycerin bolus was administered, but no subsequent coronary spasm was observed [11].

In our patient, coronary spasm occurred a few seconds after direct intracoronary nitroglycerin injection and in a portion of the right coronary artery far enough from the catheter tip to exclude late-onset catheter-induced spasm in the absence of any catheter-tip drop-in or deep intubation during right coronary artery cannulation, thus further strengthening the possible causative relation between nitrate administration and the occurrence of coronary spasm. This represents, to the best of our knowledge, the first described case of paradoxical coronary spasm occurring a few seconds after direct intracoronary nitroglycerin injection and in a portion of the vessel far
enough from catheter tip to exclude a late-onset catheter-induced spasm in the absence of any catheter tip drop in or deep intubation. Mechanisms explaining this paradoxical response to nitrates are mostly unknown. Our patient did not report a history of previous exposure to long-acting nitrates, so the mechanisms that account for the well-known phenomena of nitrate tolerance and rebound angina are unlikely to explain the vasospastic response to nitrates reported in our paper. It could be hypothesised that in the coronary plaque microenvironment (in which endothelial dysfunction is known to occur) and in adjacent coronary segments, rapid-acting vasoconstrictor agents, such as endothelin-1 and acetylcholine (which is known to have a vasoconstrictor effect in the presence of endothelial dysfunction), are released in response to nitroglycerin injection. These vasoconstrictor agents could drive the vasospastic response once levels of nitroglycerin and of its active metabolites in the plaque microenvironment significantly decrease. However, this mechanism is speculative.

Some limitations of the present case should be highlighted. First of all, the dose of the intracoronary nitroglycerin bolus (1000 µg) was high. However, at high doses, nitroglycerin usually shows an enhanced vasodilator effect via both nitric oxide-dependent and nitric oxide-independent pathways [7]. There is no evidence in literature for a dose-dependent paradoxical vasoconstrictor effect of nitroglycerin. Therefore, it is unlikely that the vasospastic response to nitroglycerin observed in our patient is related to the high dose of the intracoronary bolus. Moreover, injectable nitroglycerin preparations contain some excipients, such as alcohol and propylene glycol. Therefore, a hypersensitivity reaction against excipients cannot be formally excluded.

Conclusion

Paradoxical vasospastic response to nitrates in vasospastic angina patients represents a rare but challenging condition. Indeed, rapid acting nitrates are usually effective for a rapid control of anginal episodes, which were proven to be a trigger for trans-mural ischemia in our case. After percutaneous coronary intervention (PCI), the clinical evolution of our patient was favourable, with a 1-month follow-up exercise stress test not showing recurrence of transmural ischaemia and an uneventful 6-month clinical follow-up. Therefore, in this clinical setting and in the presence of focal coronary spasm, PCI may represent an effective treatment strategy. However, stent implantation has been associated with endothelial dysfunction even with second-generation drug eluting stents [12]. Considering that other pharmacological options are available for vasospastic angina patients [5], any firm conclusion about the best treatment strategy in this situation would be speculative.

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

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