

Individualized antithrombotic therapy

T. F. Lüscher¹; J. Steffel²

¹Department of Cardiology, University Heart Center, University Hospital, Zurich, Switzerland;

²Center for Molecular Cardiology, Campus Schlieren, University Zurich, Switzerland

Keywords

Antithrombotic therapy, platelet inhibitors, NOACs, differential therapy

Summary

Clot formation in the circulation is a physiological mechanism preventing bleeding at sites of loss of vascular integrity. Clot formation may also occur intravascularly under pathological conditions, e.g. leading to myocardial infarction, stroke, and critical limb ischaemia. Clot formation involves activation of the coagulation cascade and of platelets eventually leading to an occlusive clot. In the venous circulation, clots are rich in erythrocytes and fibrin, while in the arterial circulation platelets predominate. Accordingly, drugs have been developed to interfere with the activation of the coagulation and/or platelets. As several coagulation factors such as factor VII, VIII, X and thrombin (factor II) are vitamin K-dependent, drugs interfering with the effects of the vitamin (VKAs), i.e. warfarin, marcoumar or sintrom have been used for decades to prevent thromboembolism and embolic stroke. With the advent of selective inhibitors of factor X (apixaban, edoxaban and rivaroxaban) or factor II (dabigatran) the therapeutic spectrum of anti-thrombotic therapy has been expanded. On the other hand, platelet inhibitors such as aspirin

and thienopyridines, i.e. clopidogrel, prasugrel, and ticagrelor have extensively been used to treat arterial disease in the coronary, cerebrovascular and peripheral circulation.

Individualized antithrombotic therapy considers (1) characteristics of the disease and (2) those of the patient. Such a decision tree first separates "arterial" and "venous" thrombi. For the prevention of arterial thrombi that occur in acute myocardial infarction and certain forms of stroke and critical limb ischemia, platelet inhibitors are indicated. The first line drug is aspirin which interferes with thromboxane A₂ (TXA₂) formation and partially inhibits platelet activation. In patients receiving a stent or in acute coronary syndromes (ACS), the combination of aspirin with a thienopyridine is indicated. On the other hand, patients with venous clots should be treated with anticoagulants interfering with the activation of the coagulation cascade. While the longest experiences exist with vitamin K antagonists, the novel oral anticoagulants (NOACs) are at least as effective, but associated with less intracerebral and life-threatening bleeding. VKAs remain the treatment of choice in patients receiving artificial heart valves or with renal failure (in general a GFR of 30 ml/min/KG or less). In the remaining patients, current evidence suggests that NOACs should be preferred. The NOACs are well documented in patients with

thromboembolism and atrial fibrillation. Whether patients with an acute ACS should receive dual antiplatelet drugs plus a low dose NOAC is a matter of debate, although conceptually it is an attractive concept. In patients after stent implantation with atrial fibrillation, in which a triple therapy with dual antiplatelet drugs and an anticoagulant is indicated, bleeding is an issue. Recent data suggest that administering a thienopyridine plus warfarin (or possibly a NOAC), while at the same time skipping aspirin may be an alternative to avoid severe bleeding and to maintain antithrombotic efficacy. **Conclusion:** An extensive therapeutic arsenal to interfere with clot formation requires an individualized approach considering the disease condition and co-morbidities of the patient, the anticoagulants' and patient characteristics. This review builds on and extends previous publications of the authors on this topic.

Schlüsselwörter

Antithrombotische Therapie, Thrombozytenhemmer, NOACs, Differenzialtherapie

Zusammenfassung

Diese Übersicht bespricht die Rolle der Koagulationskaskade und der Thrombozytenaktivierung für die Bildung arterieller und venöser Thromben. Weiter wird die Wirkweise und der differenzielle Einsatz von Gerinnungshemmern und Thrombozytenhemmern bei verschiedenen kardiovaskulären Erkrankungen besprochen.

Correspondence to:

Thomas F. Lüscher, MD, FRCP
 Professor and Chairman of Cardiology
 University Heart Center, University Hospital
 Raemistreet 100, 8091 Zürich, Switzerland

Individuelle antithrombotische Therapie

Hämostaseologie 2016; 36: 26–32
<http://dx.doi.org/10.5482/HAMO-14-12-0080>
 received: December 3, 2014
 accepted: December 5, 2014
 epub ahead of print: January 19, 2015

Thrombus formation

The formation of intravascular thrombi is a crucial event in the development of many diseases of the heart and the circulation such

as venous thrombosis and pulmonary embolism, myocardial infarction, stroke, and critical ischemia of the limbs or other organs.

The formation of thrombi involves the coagulation cascade and platelet activation

(► Fig. 1). Activation of the plasmatic coagulation cascade is central to thrombus formation particularly in the 'low pressure' system of the circulation, i.e. in veins and the heart chambers. The first step consists

of binding of tissue factor to factor VIIa, leading to initiation of the coagulation cascade and formation of active factor X, thrombin and eventually fibrin (1).

Platelets are activated at sites of endothelial damage with reduced formation of prostacyclin and nitric oxide, exposure of collagen and von Willebrand factor among others. Platelet activation involves TXA₂ formation via phospholipase A₂ and cyclooxygenase-1 and the release of adenosine diphosphate (ADP) and serotonin. These mediators activate specific receptors on the platelet surface, eventually leading to the expression of glycoprotein IIb/IIIa receptors, platelet aggregation and (together with fibrin) to formation of a stable clot.

Antithrombotic agents

Antithrombotic agents can either interfere with components of the plasmatic coagulation cascade (anticoagulants) or platelet activation (antithrombotics) (► Tab. 1).

For decades, anticoagulation for the long-term treatment and prophylaxis of thrombo-embolic diseases has been accomplished with VKAs. These compounds are very effective under optimal conditions, in which a stable level of anticoagulation can be obtained. To achieve such optimal conditions, however, is often challenging, since various foods, especially vegetables, but also drugs such as non-steroidal anti-inflammatory drugs among others may alter both the pharmacokinetics and pharmacodynamics of VKAs. Furthermore, numerous drugs, in particular inducers and inhibitors of hepatic P450 isoenzymes that metabolize VKAs, often unpredictably enhance or reduce their anticoagulant effects. Thus, their narrow therapeutic window requires continuous and life-long monitoring, including repetitive dose adaptations. VKAs are associated with a considerable risk of bleeding (with excessive anticoagulation) as well as of a recurrent thrombotic events (with insufficient anticoagulation).

As a result of these limitations, several novel agents have been developed (► Fig. 1) which do not interfere with the synthesis of the inactive forms of the vitamin K-dependent coagulation factors II,

VII, IX, and X, but selectively inhibit the active form of a single coagulation factor, i.e. factor II or X, respectively. Their major advantages are a better practicability (i.e. fixed oral dose, lack of monitoring) and a reduced risk of bleeding with similar or even better efficacy in most indications tested (► Fig. 2) (2).

The first antiplatelet agent was discovered more than 100 years ago by Felix Hoffmann at Bayer laboratories and marketed as a fever remedy. Only in the 1960ies was there antiplatelet effect recognized thanks to Sir John Vane who received the Nobel prize in 1982 for this discovery. Since then, acetylsalicylic acid or Aspirin[®], which acetylates cyclooxygenase-1 and in turn prevents the formation of TXA₂ and platelet aggregation in response to arachidonic acid and collagen, has been increasingly used in many conditions, in particular coronary artery disease (CAD) and myocardial infarction. Later, the thienopyridines which block the purinergic 2Y12 receptor were developed and mainly used

after stenting and acute coronary syndromes (ACS) (► Tab. 1).

Principles of individualized antithrombotic therapy

The following questions have to be addressed when considering an individualized antithrombotic therapy in a given patient:

1. Is a thrombotic process the underlying cause of the condition?
2. Is the thrombus of arterial or venous origin?
3. Is there evidence for the efficacy of an antithrombotic measure?
4. What is the bleeding risk of the patient?
5. Is the patient compliant?
6. Does the patient present with comorbidities that impact on the choice of the antithrombotic agent (renal failure, diabetes, stents in the coronary circulation among others)?
7. What is the best agent and dose for the patients overall condition?

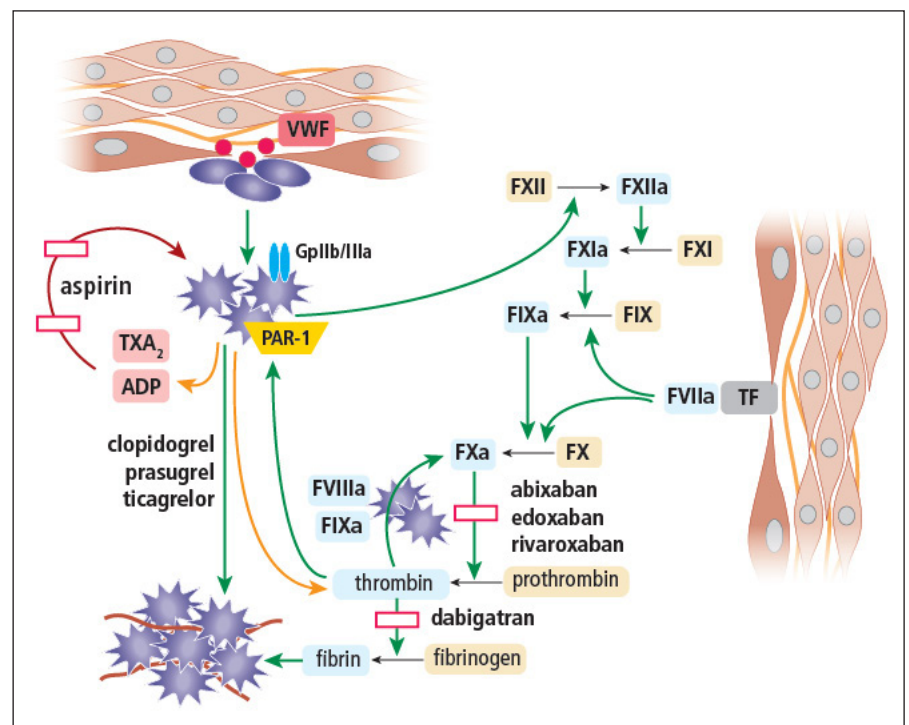


Fig. 1 Mechanisms of clot formation; modified from Steffel & Braunwald (2): Clots form after activation of the coagulation cascade (right) and in parallel with the activation of platelets (left). The coagulation cascade can be inhibited by vitamin K-antagonists (not shown) or the novel oral anticoagulants interfering selectively with either factor X or II (thrombin) which together eventually form and bind fibrin, respectively.

antithrombotic agents		mechanism
antiplatelet agents	1. aspirin 2. others	TXA ² antagonists
	1. ticlopidine 2. clopidogrel 3. prasugrel 4. ticagrelor	thienopyridines
	vorapaxar	PAR-1 inhibitor
anticoagulants	1. warfarin 2. marcoumar 3. sintrom	vitamin-K antagonists
	1. rivaroxaban 2. abixiban 3. edoxaban	factor X inhibitors
	dabigatran	thrombin inhibitor

Tab. 1
Antithrombotic agents and their mechanism of action

ments or spontaneously, venous clots may dislodge and embolize into the right heart and the pulmonary circulation. Large emboli can interfere with the pulmonary circulation and cause hypotension, oxygen desaturation, haemodynamic shock and eventually sudden death.

Venous thromboembolism has traditionally been treated with unfractionated or low molecular weight heparins (LMWH). More recently, clinical trials with factor Xa and factor IIa inhibitors demonstrated similar efficacy and safety both in venous thrombosis as well as pulmonary embolism. Due to the rapid onset of action, NOACs are optimal in the treatment of thromboembolism. In the case of rivaroxaban and apixaban, a higher dose is used for the initial phase of treatment. ..

The conditions in which a thrombus is the underlying cause are venous thromboembolism, stroke, myocardial infarction and critical ischaemia of the legs or other organs (ischaemic colitis among others). If the thrombus is of venous origin (e.g., in venous thromboembolism, embolic stroke), anticoagulants are the preferred treatment, while on the arterial side (e.g., in acute coronary syndromes, certain forms of stroke) antiplatelet agents are the first choice (► Fig. 3).

The bleeding risk of the patient increases with age, a history of gastrointestinal or other bleedings and renal failure among others.

Venous thromboembolism

Thrombus formation in the venous circulation is related to

1. stasis (venous insufficiency, bed rest and other conditions),
2. activation of tissue factor expression and in turn activation of the coagulation (diabetes, inflammation, tumours, genetic mutations of the coagulation cascade among others) and/or
3. endothelial and vascular damage (trauma; Virchow's trias).

Typically venous thrombi form in the veins of the legs and the intestine. During move-

Atrial fibrillation and embolic stroke

Atrial fibrillation (AF) carries a substantial risk of thromboembolism into the brain or other organs. The risk of thromboembolism can be estimated using the CHA2DS2-VASc score which considers age, gender, blood pressure, a history of stroke or TIA, certain vascular diseases, diabetes and cardiac function. The higher the CHA2DS2-VASc Score, the greater the risk of embolism and the stronger the evidence for a benefit of anticoagulants (► Tab. 2) (3). The maximal score is 10. A score of 0 is considered to reflect a low risk of stroke and hence does not require anticoagulation, while with a score of 2–3 anticoagulation is recommended. With a score of 1, anticoagulation is equally recommended (albeit “only” with a IIa recommendation).

Embolic strokes in atrial fibrillation are thought to be mainly due to thrombi originating from the left atrial appendage (► Fig. 4). A large body of evidence derived from many randomized multicenter studies has demonstrated that antiplatelet drugs are not or only marginally effective in AF, while anticoagulants effectively prevent embolic strokes in these patients. In contrast, NOACs are at least equally if not more effective and than VKAs, with a lower risk especially of intracranial as well

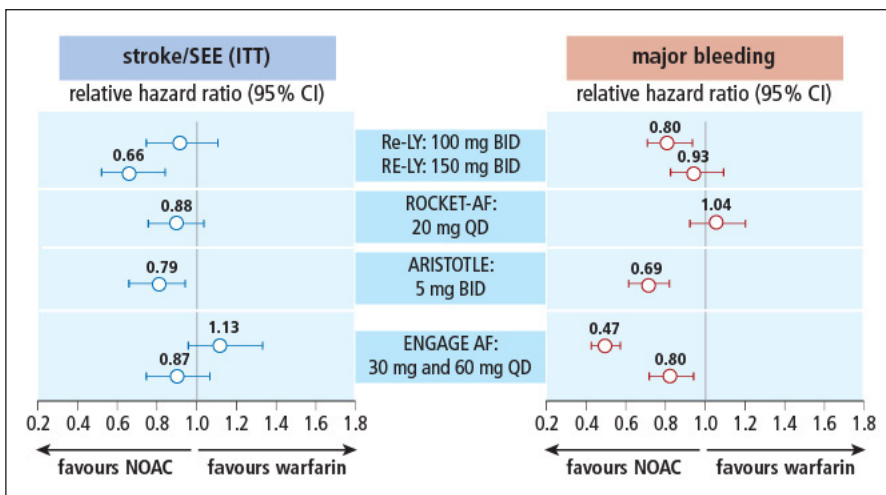


Fig. 2 Overall results of the trials using new oral anticoagulants (NOACs) in patients with atrial fibrillation. **Cave:** For illustrative purpose only! These were not head-to-head trials among the NOACs, hence prohibiting inter-comparison of the effect of the individual NOACs.

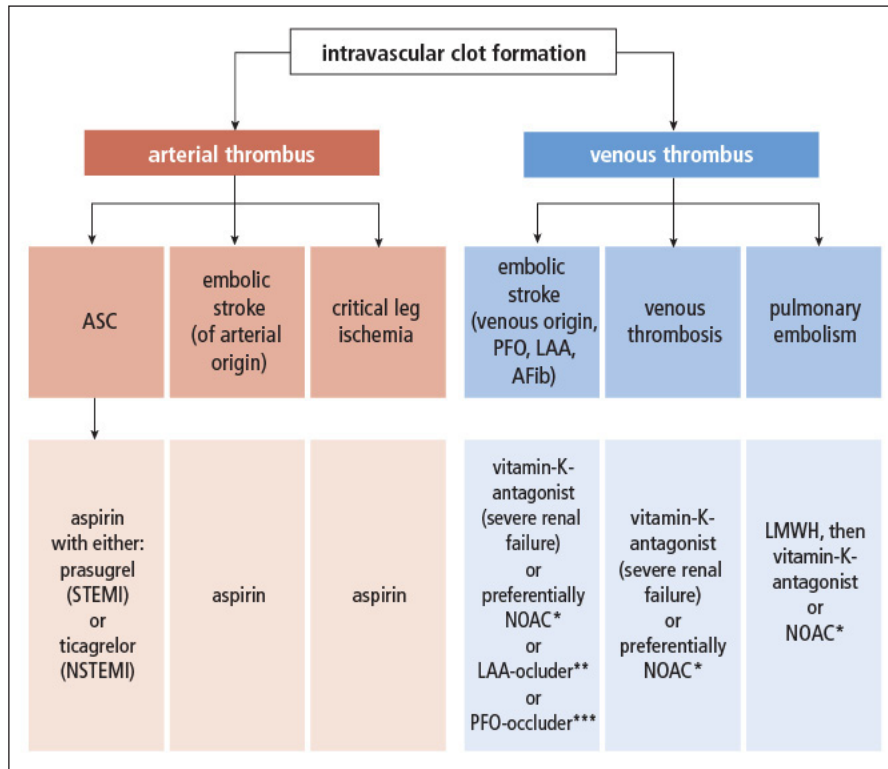


Fig. 3 Algorithm for the management of intravascular clot formation (AFib: atrial fibrillation; LAA: left atrial appendix; LMWH: low molecular weight heparins; NOAC: novel anticoagulant; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; PFO: patent foramen ovale; * contraindicated with a GFR of < 30 ml/min/BSA; ** in patients with contraindication for anticoagulation; *** in patients with likely paradoxical embolism through a PFO

Tab. 2 CHA2DS2-VASc score to determine the risk of cerebrovascular embolisation and in turn transient ischaemic attacks and stroke in patients with atrial fibrillation

condition	point
Congestive heart failure	1
Hypertension	1
Age > 75 years	2
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease*	1
Age 65–74 years	1
Sex category female gender	1

* e. g. peripheral arterial disease (PAD), history of myocardial infarction, severe calcification of aorta or complex aortic plaque

as life-threatening or fatal bleeding (► Fig. 2).

Which anticoagulant should be chosen? The longest experience rests with VKAs, but as outlined above, the NOACs have distinct advantages, which is why they are preferentially recommended according to current ESC guidelines (3). The following algorithm may be used in clinical practice:

1. What is the CHA2DS2-VASc Score of the patient? Decision making see above. In general NOACs are preferred.
2. What is the renal function of the patient? In the presence of a GFR < 30 ml/min/KG, VKAs remain the treatment of choice for the time being, although data from randomized clinical trials are lacking for this patient population for VKA as well. Upcoming trials investigating this challenging patient population are eagerly awaited. With normal or only mildly reduced renal function, NOACs should be preferred.

3. What is the compliance of the patient? In non-compliant patients, VKAs might be preferable as they are better controlled by their physician. If NOACs are chosen, once daily preparations may be preferable (i. e. rivaroxaban). However, it needs to be stated that malcompliant patients carry a worse prognosis independent what they are treated with. It is therefore part of “personalized anticoagulation” to individually speak with every patient requiring anticoagulation, educate about stroke and bleeding risk, educate about compliance and hence actively include the patient in the treatment plan (including responsibility for non-compliance).
4. Are there contraindications for anticoagulation (e.g. history of intracranial haemorrhage, severe gastrointestinal bleeding among others)? In this case, percutaneous implantation of a left atrial appendage occluder should be considered.
5. Also in NOACs, drug-drug interactions do occur. Especially in patients with several co-medications, the EHRA practical guide should be considered to look for potential interactions.

Of note, several studies have shown that patients with paroxysmal atrial fibrillation experience a large number of asymptomatic episodes. Hence, even these patients should receive anticoagulation. Similarly, patients after “successful” AF ablation should be permanently anticoagulated as asymptomatic episodes of atrial fibrillation may still occur even if several Holter recordings are negative.

Other forms of embolic stroke

In certain forms of embolic stroke, the embolus may arise from a patent foramen ovale (PFO), from the aortic valve, aortic plaques and/or the carotid arteries (► Fig. 5). PFOs with paradoxical embolization may be occluded percutaneously. Patients with aortic valve stenosis should either undergo surgical aortic valve replacement (AVR) with or transarterial valve replacement (TAVR). Patients with

TAVR or bioprosthesis typically are anticoagulated only transiently and then receive aspirin only. Patients with AVR and mechanical valves must receive VKAs as NOACs have not been extensively studied in this population (and in fact turned out less effective in preventing stroke and associated with higher bleeding in one phase II study, which is why they are contraindicated in this situation).

Embolic strokes presumed to be due to carotid plaques should receive aspirin as dual antiplatelet therapy is associated with increased rates of cerebral bleeding in this population.

Coronary artery disease

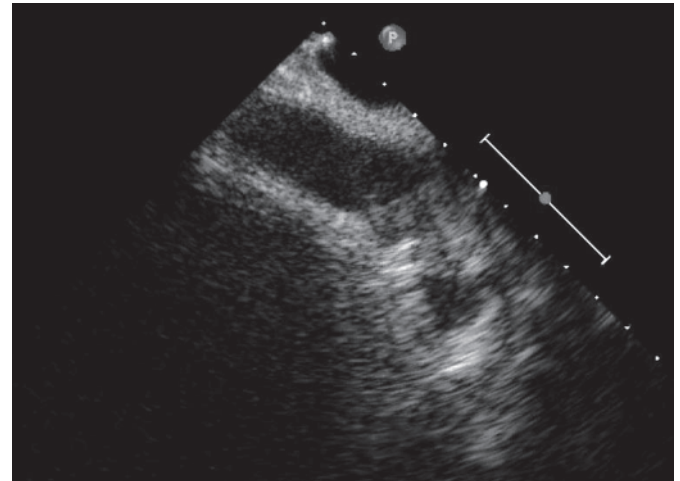
According to current guidelines, all patients with coronary artery disease (CAD) should receive Aspirin^R. If they have undergone percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) is indicated for 6–12 months. Although stent thrombosis rates are currently <1%, the duration of DAPT is controversial, although one trial has shown that 6 months may suffice and prolonged treatment is only associated with more bleeding. On the other hand, in patients after aorto-coronary bypass surgery, DAPT may be beneficial for long-term outcome.

Anticoagulation is only indicated in CAD patients with atrial fibrillation, thromboembolism or mechanical heart valves. In these situations (stable CAD without an event or stenting in the preceding 12 months), aspirin should be omitted and the patient treated only with VKA and/or NOAC (3, 4).

Acute coronary syndromes

Acute coronary syndromes (ACS) are due to a ruptured and/or de-endothelialized plaques in one or more epicardial coronary arteries. Both Aspirin and thienopyridines have documented outcome benefit and therefore all patients undergoing thrombolysis or acute PCI receive Aspirin lifelong and a thienopyridine, possibly prasugrel in ST-segment elevation infarction (STEMI) and ticagrelor in Non-STEMI for 12 months (5, 6)

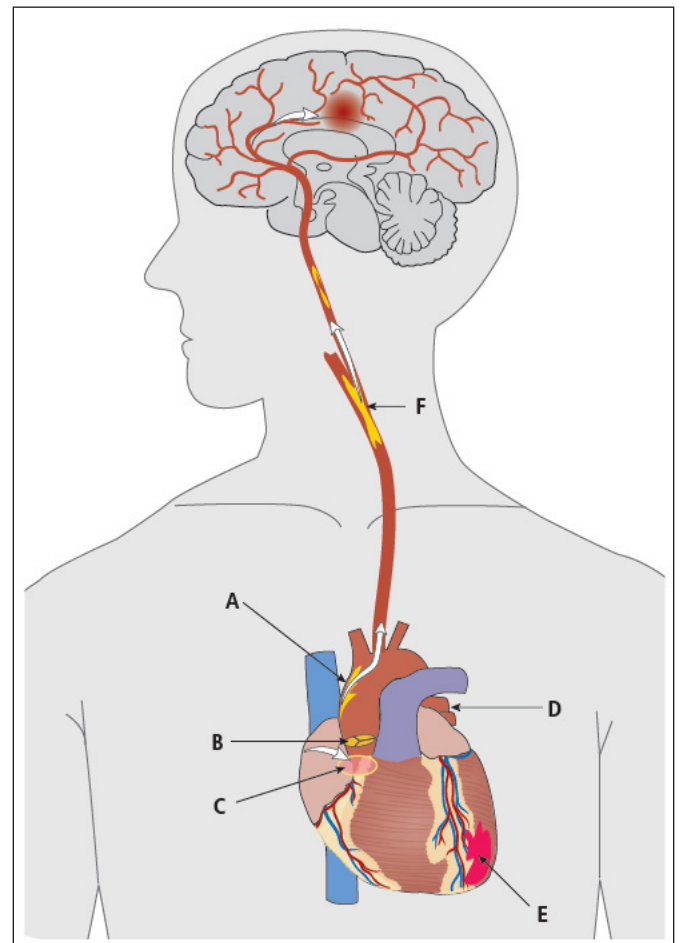
Fig. 4 Thrombus in the left atrium as demonstrated by transoesophageal echocardiography



Patients with an ACS who received a stent and have atrial fibrillation should in principle receive Aspirin, a thienopyridin and anticoagulation. This regimen is indicated to prevent stent thrombosis, future myocardial infarction and death, but also

stroke due to atrial fibrillation (provided the CHADVasc score is ≥ 2). The downside of this approach is a high risk of bleeding that increases with the duration of treatment and is particularly high in elderly patients and those with a history of bleeding.

Fig. 5 Origin of cerebrovascular embolus causing stroke (A: ulcerated aortic plaque; B: aortic valve sclerosis or stenosis; C: patent foramen ovale with paradoxical embolisation; D: left atrial appendage thrombus, typically in atrial fibrillation; E: left ventricular thrombus, typically after myocardial infarction and/or left ventricular aneurysm; F: ulcerated carotid plaque)



To overcome this dilemma, several trials are under way to test alternative regimens. The WOEST study found that the combination of clopidogrel and VKAs might be as effective, but less prone to bleeding in this situation. As indicated above, one year after ACS and/or stenting, VKA and/or NOAC monotherapy without aspirin is indicated in patients with a concomittant indication for anticoagulation (mostly AF). According to a most recent consensus document, NOACs may even be used in the setting of triple anticoagulation following an ACS or stenting, but evidence for NOACs in this scenario is scarce (4).

Peripheral arterial disease

Peripheral arterial disease is and arterial disease that generally is treated like CAD or ACS with Aspirin^R. There is evidence that in these patients with generalized arteriosclerosis, DAPT may be beneficial.

Conclusion

An extensive therapeutic arsenal to interfere with clot formation is available. In

order to maximize patient benefit, an individualized approach is required for every patient, considering the

- patient's disease condition and co-morbidities as well as
- the anticoagulants' characteristics.

Only through this, a reduction in the risk of both thromboembolic as well as bleeding complications can be achieved.

Conflict of interest

TFL has received educational and/or research grants from AstraZeneca, Cham/Switzerland, from Bayer Health Care, Berlin and Zurich, from Boehringer, Ingelheim, Basel, Switzerland, from Eli Lilly Indianapolis, USA to the institution and honoraria for lectures or advisory boards from AstraZeneca, Cham/Switzerland, Boehringer, Ingelheim, Basel, Switzerland, Daiichi Sankyo Japan and Switzerland, Eli Lilly Switzerland and Merck Inc., Rahway, N.J, U.S.A.

JS has received consultant and/or speaker fees from Amgen, Astra-Zeneca, Bayer, Biotronik, Biosense Webster, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi-Sankyo, Cook Medical,

Medtronic, Novartis, Pfizer, Roche, Sanofi-Aventis, Sorin and St. Jude Medical, and is co-director of CorXL LLC.

References

1. Steffel J, Lüscher TF, Tanner FC. Tissue factor in cardiovascular diseases: molecular mechanisms and clinical implications. *Circulation* 2006; 113: 722–731.
2. Steffel J, Braunwald E. Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism. *Eur Heart J* 2011; 32: 1968–1976.
3. Camm AJ, Lip GY, De Caterina R et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2012; 33: 2719–2747.
4. Task Force M, Lip GY, Windecker S et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions. *Eur Heart J* 2014; 35: 3155–3179.
5. Task Force on the management of ST-segment elevation myocardial infarction, Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569–2619.
6. Hamm CW, Bassand JB, Agewall S et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2011; 32: 2999–3054.

Anzeige

