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Přehledový článek | Review article

Antithrombotic therapy in patients after valve surgery with special attention to the combination of anticoagulant and antiplatelet therapy

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ABSTRACT

Patients after implantation of mechanical valves need life-long anticoagulant therapy. Nearly 30% of these patients have also indication for antiplatelet therapy because of concomitant ischemic heart disease or peripheral arterial disease. Combined anticoagulant and dual antiplatelet therapy (so called triple therapy – aspirin, clopidogrel and vitamin K antagonists) is indicated in patients with acute coronary syndrome and after percutaneous coronary intervention (PCI) for a different time according to the type of stent used during the procedure. Triple therapy is substantially more efficacious in reducing the occurrence of cardiovascular events and mortality in patients undergoing PCI with an indication for long-term anticoagulant therapy, compared with dual antiplatelet therapy. On the other hand it carries 3.5 to 4 times higher risk of bleeding in treated patients. Recently new anticoagulants (dabigatran, rivaroxaban, apixaban) and antiplatelet drugs (prasugrel and ticagrelor) came into clinical practice and new studies using these drugs are underway.
The purpose of this review article is to summarize current approach to patients with indication for anticoagulant and antiplatelet therapy after valve surgery.

Klíčová slova:
Antitrombotická léčba
Chirurgie srdečních chlopní
Protidestičková léčba

SOUHRN

Nemocní po implantaci mechanické protézy potřebují celoživotní antikoagulační léčbu. U téměř 30 % z nich je současně indikována také protidestičková léčba pro přidruženou ischemickou chorobu srdeční nebo onemocnění periferních tepen. Kombinovaná antikoagulační a duální protidestičková léčba (tzv. trojitá [triple] léčba – kyselina acetylsalicylová + clopidogrel + antagonista vitaminu K) je indikována u nemocných s akutním koronárním syndromem a u nemocných po perkutánní koronární intervenci po různě dlouhou dobu dle typu implantovaného stentu. Trojitá léčba je v porovnání s duální protidestičkovou léčbou podstatně účinnější ve snížení kardiovaskulárních příhod a mortality u nemocných, kteří podstoupili perkutánní koronární intervenci a u nichž je indikována dlouhodobá antikoagulační léčba. Na druhé straně s sebou tato léčba nese 3,5- až 4krát vyšší riziko krvácení. V poslední době vstoupily do klinické praxe nové antikoagulační (dabigatran, rivaroxaban, apixaban) a protidestičkové léky (prasugrel a ticagrelor) a zároveň probíhají nové studie s těmito léky.
Cílem tohoto přehledového článku je shrnout současný přístup k nemocným s indikací k antikoagulační a protidestičkové léčbě po chirurgické léčbě chlopenních vad.

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Table 1 – Target international normalized ratio (INR) recommended for mechanical prostheses [1].

Prosthesis thrombogenicity	Patient-related risk factors	
	No risk factor	Risk factor ≥ 1
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

Patient-related risk factors: mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; left ventricular ejection fraction < 35%.

Indication of antithrombotic therapy and its intensity

According to the European Society of Cardiology (ESC) and the Czech Society of Cardiology guidelines [1,2] a lifelong anticoagulant therapy is recommended for all patients with mechanical heart prostheses (class of recommendation I, level of evidence B) and for patients with bioprostheses who have other indications for anticoagulation (atrial fibrillation, venous thromboembolism, hypercoagulable state, severely impaired left ventricular function with ejection fraction < 35%) – (class I, level C). Oral anticoagulation should be considered for the first 3 months after implantation of a mitral or tricuspid bioprosthesis and for the first 3 months after mitral or tricuspid valve repair (class IIa, level C).

Warfarin has a narrow therapeutic window and an unpredictable response that requires routine coagulation monitoring and frequent dose adjustment. Despite the disadvantages of warfarin till now there has been no equivalent alternative for this drug. The RE-ALIGN study with dabigatran in patients with mechanical valve prosthesis was stopped because of increased incidence of valve thrombosis and clinical ischemic events (see below).

When anticoagulant therapy is prescribed, the prosthesis thrombogenicity, prosthesis position and patient-related factors should be taken into consideration. Generally Carbomedics, Medtronic Hall, St. Jude Medical or ON-X valves belong to the group of prothesis with low thrombogenicity. Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves belong to the group of prosthesis with high thrombogenicity. Other bileaflet valves not mentioned above constitute a group with medium thrombogenicity. Unfortunately there are insufficient data on valve thrombosis in newly introduced valves. The thrombogenicity of the prosthesis in the aortic position is generally smaller than in the mitral position; the implantation of the mechanical prosthesis into the tricuspid or pulmonary position is exceptional.

Target international normalized ratio (INR) for prosthesis with low thrombogenicity in patient with no risk factor is 2.5, for patient with more than one risk factor 3.0. Target INR for prosthesis with medium thrombogenicity is 3.0 and 3.5 according to presence/absence of risk factors and for prosthesis with high thrombogenicity 3.5 and 4.0 (Table 1). The following conditions are considered patient-related risk factors: mitral or tricuspid valve replacement, previous thromboembolism, atrial fibrillation, mitral stenosis of any degree and left ventricular ejection fraction < 35%.

The most commonly reported anticoagulation regimens had the following rates of early postoperative (30 days) thromboembolism and hemorrhage: oral anticoagulation alone (0.9%, 3.3%); oral anticoagulation with intravenous unfractionated heparin (1.1%, 7.2%); and oral anticoagulation with low molecular weight heparin (0.6%, 4.8%) [3]. After aortic valve replacement, the risk of thromboembolic events falls from 16 per 100 patient years in the early postoperative period to 1.4 per 100 patient years at 5 years. Similarly, after mitral valve replacement, the risk falls from 21 per 100 patient years to 2.5 per 100 patient years. The rate of thromboembolic events after mechanical valve implantation in patients without anticoagulation therapy is estimated to be 8.6% per year. It could be approximated, that patients with prosthetic valves belong to patients with high risk of embolic event according to CHA_2DS_2-VASc score, which was developed for patients with atrial fibrillation (Tables 2 and 3). So the utilization of postoperative warfarin therapy reduces the incidence of major embolism by approximately 75%. Neither single nor dual antiplatelet therapy alone are sufficient in reducing the rate of valve thrombosis [4–6]. Only one study (135 patients) supporting the long-term use of dual antiplatelet therapy (aspirin and clopidogrel) in patients with mechanical aortic valves was published [7]. The incidence of strokes in this study dropped from 2.5%/

Table 3 – CHA_2DS_2-VASc score.

		Points
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥ 75 years	2
D	Diabetes mellitus	1
S	Stroke/TIA/thromboembolism	2
V	Vascular disease	1
A	Age 65–74 years	1
S	Sex category (female sex)	1
		max. 9

Table 2 – The annual risk (%/year) of stroke and systemic embolism by the CHA_2DS_2-VASc score in patients with non-valvular atrial fibrillation. Source: Danish national patient registry, 10-year follow-up rates (n = 73,813). Adapted according LaHaye with permission [34].

Score	0	1	2	3	4	5	6	7	8	9
Reported risk	0.6	1.2	2.6	3.9	6.0	9.4	11.6	13.0	13.2	13.9

Table 4 – The annual risk (%/year) of major bleeding by the HAS-BLED score in patients with non-valvular atrial fibrillation. Source: Danish national patient registry, 1-year incidence (n = 73,813). There were insufficient data to provide a reliable estimate of the risk of bleeding for patients with HAS-BLED scores greater than seven. Adapted according LaHaye with permission [34].

Score	0	1	2	3	4	5	6	7
Reported risk	1.2	3.1	5.4	6.5	9.1	12.8	14.1	15.4

patient/year to 1.0%/patient/year after the use of assays to monitor platelet reactivity. No patient developed valve thrombosis. Five patients had bleeding complications (1.2%/patient/year).

Indication of combined anticoagulant and antiplatelet therapy

According to the guidelines [1,2] the addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease (class IIa, level C) and in patients with a mechanical prosthesis after thromboembolism despite adequate INR (class IIa, level C).

In patients undergoing percutaneous coronary intervention with stent insertion, dual antiplatelet therapy reduces the risk of cardiovascular death or myocardial infarction compared with aspirin alone or aspirin plus warfarin [8]. Dual-antiplatelet therapy (aspirin plus clopidogrel or prasugrel or ticagrelor) is recommended ideally for 1 year in a patient with acute coronary syndrome, for 1 year after the implantation of drug-eluting stent and for minimum of 1 month after the implantation of bare-metal stent [9,10]. In a patient with a mechanical valve triple therapy balancing its benefit and risk should be considered. With some approximation the risk of bleeding could be estimated according to HAS-BLED score which was validated for patients with atrial fibrillation (Tables 4 and 5).

Table 5 – HAS-BLED score

		Points
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g., ≥ 65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		max. 9

Hypertension: systolic blood pressure > 160 mmHg. Abnormal kidney function: chronic dialysis or renal transplantation or creatinine ≥ 200 mmol/l. Abnormal liver function: chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2× upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3× upper limit normal, etc.). Bleeding: previous bleeding history and/or predisposition to bleeding, for example, bleeding diathesis, anaemia, and so forth. Labile INRs: unstable/high INRs or poor time in therapeutic range (e.g., <60%). Drugs/alcohol use: concomitant use of drugs, such as antiplatelet agents, nonsteroidal anti-inflammatory drugs, or alcohol abuse, and so forth
INR – international normalized ratio.

To avoid increased risk of bleeding connected with this therapy, bare-metal stents should be preferred, low level anticoagulation (INR 2.0–2.5) with frequent INR monitoring and low dose of aspirin (75–100 mg) should be used and addition of proton-pump inhibitors or H2-antagonists should be considered. It is necessary to mention that this approach should apply only for patients with modern prosthesis with low thrombogenicity and no risk factors (Table 3). Another possibility to prevent bleeding is to reduce the duration of triple therapy after drug-eluting stents implantation potentially for 3 months after the implantation of limus-eluting stents or for 6 months after implantation of paclitaxel-eluting stents especially in nondiabetics or low-risk patients [11–14]. It might be possible to continue the treatment with warfarin and clopidogrel thereafter till 1 year after implantation of stent with subsequent therapy with warfarin alone. The support for this approach can be found in the results of WOEST study, wherein patients on warfarin therapy undergoing PCI, withdrawing of aspirin was superior to the combination of aspirin and clopidogrel with respect to bleeding without increasing the thrombotic risk [15].

There is no evidence of improved efficacy of a combined therapy with an antiplatelet and anticoagulant agent in a patient with periferal arterial disease even though this combination is frequently used in clinical practice. The rationale for the combined therapy is that warfarin is superior to antiplatelet therapy for the prevention of thromboembolic events in patients with mechanical heart valves whereas antiplatelet therapy is the standard of care for antithrombotic therapy for the secondary prevention of serious vascular events in patients with cardiovascular disease. Because warfarin is also effective for secondary prevention of serious vascular events, it would seem reasonable to discontinue aspirin in patients with stable cardiovascular disease who have a firm indication for warfarin (e.g. patients with mechanical heart valves) [16].

Benefits and risks of combined therapy

A meta-analysis of 2428 subjects compared the efficacy and safety of adding dipyridamole or aspirin to warfarin with respect to warfarin alone in patients with prosthetic heart valves. The combined therapy was shown to reduce thromboembolic events (OR 0.39) and total mortality (OR 0.55), with an increase in major bleeding (OR 1.66). Data were consistent for both aspirin and dipyridamole [17].

Another meta-analysis of 4 randomized controlled trials demonstrated that the antiplatelet therapy plus anticoagulants were more effective than anticoagulants alone for the prevention of thromboembolic events in patients with mechanical heart valves [18]. Among 869 patients treated with warfarin dose-adjusted to achieve an INR of 2–3, aspirin compared with placebo was associated with a 67% reduction in thromboembolic events (3.5% vs. 11.3%, RR 0.33) and a 57% reduction in all-cause mortality (5.4% vs. 7.9%, RR 0.43) at the cost of a 58% increase in bleeding (13.1% vs. 8.1%, RR 1.58). The dose of aspirin in these trials varied from 100 mg daily to 500 mg b.i.d. and follow-up in the studies ranged from 1 to 2.5 years. The benefits of adding aspirin to warfarin were primarily driven by the study by Turpie et al., which included 370 patients and demonstrated a 77% reduction of systemic embolism or cardiovascular death compared to warfarin alone. Most of the benefits occurred in patients with concomitant coronary artery disease [19].

Meschengieser and colleagues randomized 503 patients with mechanical valves who received aspirin 100 mg once daily plus warfarin (target INR 2.5–3.5) or warfarin alone (target INR 3.5–4.5) for a median of 2 years in an open-label fashion. The group randomized to aspirin and warfarin therapy had similar rates of thromboembolic and bleeding events as those that received warfarin alone but the combination significantly reduced all-cause mortality (3.5% vs. 8.6%, RR 0.41) [20].

The meta-analysis data provide clear evidence of a reduction in thromboembolic events and death when aspirin is added to warfarin in patients with mechanical heart valves. However, this summary is based on small trials, and most of these were conducted several decades ago. Furthermore, it appears that the benefits of aspirin were largely seen in patients with coronary artery disease. It is uncertain whether similar efficacy benefits of aspirin would be evident in trials conducted in the modern era with newer valves and better anticoagulant management and in patients without concomitant coronary artery disease [21].

If combined therapy is prescribed it should be taken into account that the mortality rate of a potential intracerebral hemorrhage is reported to be 67% in patients on oral anticoagulant treatment [22].

In meta-analysis of Paikin 2.2% rate of major bleeding at 30 days and 12% at 1 year is reported [23]. Most patients in this meta-analysis were receiving warfarin for atrial fibrillation and dual-antiplatelet therapy for a coronary artery stent. This is in agreement with the results of other studies [24–26]. The risk of bleeding increases up to four- to fivefold at 6 months and five- to eightfold at 12 months as combined antithrombotic therapy is prolonged.

From the study of Lamberts et al. [27] emerges, that both early (within 90 days) and delayed (90–360 days) bleeding risk with triple therapy exposure in relation to warfarin + antiplatelet was increased (hazard ratio 1.47 and 1.36, respectively). No significant difference in thromboembolic risk was observed for triple therapy versus warfarin + antiplatelet (hazard ratio 1.15). The authors conclude, that high risk of bleeding is immediately evident with triple therapy after myocardial infarction/PCI in patients with atrial fibrillation. A continually elevated risk associated with triple therapy indicates no safe therapeutic window.

Table 6 – The risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel and warfarin with aspirin as a reference [28].

Therapy	HR for bleeding
Warfarin	1.23
Clopidogrel	1.33
Aspirin + clopidogrel	1.47
Warfarin + aspirin	1.84
Warfarin + clopidogrel	3.52
Triple therapy	4.05

HR – adjusted hazard ratio.
triple therapy – aspirin + clopidogrel + warfarin.

Detailed data concerning the risk of bleeding in patients with a different combination of aspirin, clopidogrel and vitamin K antagonist are accessible from the Danish registry [28,29]. Sørensen studied the risk of bleeding in patients who had been admitted to hospital with acute myocardial infarction (Table 6). 37.9% of 1852 patients with non-fatal bleeding had recurrent myocardial infarction or died during the study period compared with 18.4% of 38,960 patients without non-fatal bleeding (HR 3.00, $p < 0.0001$). The authors conclude, that the risk of bleeding is proportional to the number of drugs used and that non-fatal bleeding is an independent predictor associated with the increased risk of recurrent myocardial infarction or death. Conclusions of Hansen's study are similar: in patients with atrial fibrillation, all combinations of warfarin, aspirin, and clopidogrel are associated with increased risk of nonfatal and fatal bleeding; dual warfarin and clopidogrel therapy and triple therapy carried a more than 3-fold higher risk than the warfarin monotherapy did (Table 7).

New drugs

The results of 2 studies (APPRAISE-1, ATLAS TIMI-46) comparing the new oral factor Xa inhibitors, apixaban and rivaroxaban, to antiplatelet therapy alone for the

Table 7 – The risk of bleeding with single, dual or triple therapy in patients with atrial fibrillation with warfarin as a reference [29].

Therapy	HR for bleeding
Aspirin	0.93
Clopidogrel	1.06
Aspirin + clopidogrel	1.66
Warfarin + aspirin	1.83
Warfarin + clopidogrel	3.08
Triple therapy	3.7

HR – hazard ratio.
Triple therapy – aspirin + clopidogrel + warfarin.

long-term management of ACS patients are promising. However, both of the new anticoagulants increased bleeding in a dose-dependent manner and were associated with a smaller reduction of ischemic events and a greater increase in bleeding when added to dual antiplatelet therapy compared with when they were added to aspirin alone [30,31]. The third generation of $P2Y_{12}$ antagonists (ticagrelor, prasugrel) increases also the incidence of major bleeding compared to clopidogrel, conceivably limiting their use in triple therapy [32,33]. These drugs have not yet been tested systematically in patients with mechanical heart valves.

The oral factor Xa-inhibitor edoxaban is currently being tested in patients with atrial fibrillation in the ENGAGE AF TIMI 48 study (ClinicalTrials.gov Identifier NCT00781391) as well as in a Chinese study (ClinicalTrials.gov Identifier NCT00806624). Till now we have no data for using this drug in patients with mechanical heart valves.

The efficacy of dabigatran in patients after the implantation of mechanical heart valves (population A – recent surgery group, population B – remote surgery group) was examined in RE-ALIGN study (ClinicalTrials.gov Identifier NCT01505881). Due to a lower than projected exposure together with an excess of clinical ischemic events and valve thrombosis in both groups in patients receiving dabigatran, the study has been recently terminated.

Conclusions

The anticoagulation therapy using vitamin K antagonists is still the cornestone therapy in patients with mechanical heart valves. Currently there is no equivalent alternative to warfarin in this indication. Warfarin substantially decreases the risk of thromboembolism with an acceptable risk of bleeding when optimally managed. The combination of warfarin and aspirin reduces thromboembolic events and total mortality even more at the cost of an increased rate of bleeding. The triple therapy yields the highest rate of bleeding. Every effort should be made to shorten the duration of triple therapy as much as possible (potentially to 3–6 months according to the type of implanted stent) or to modify the number of antithrombotic drugs concomitantly used. Presently there are no sufficient data to recommend new antithrombotic drugs separately or in combination for patients with mechanical heart valves and with indication to combined antithrombotic therapy.

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